MASSACHUSETTS GENERAL HOSPITAL
RHEUMATOLOGY, ALLERGY AND IMMUNOLOGY

Update on Beta-Lactam Allergy

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EAC Annual Conference 2024

RACER

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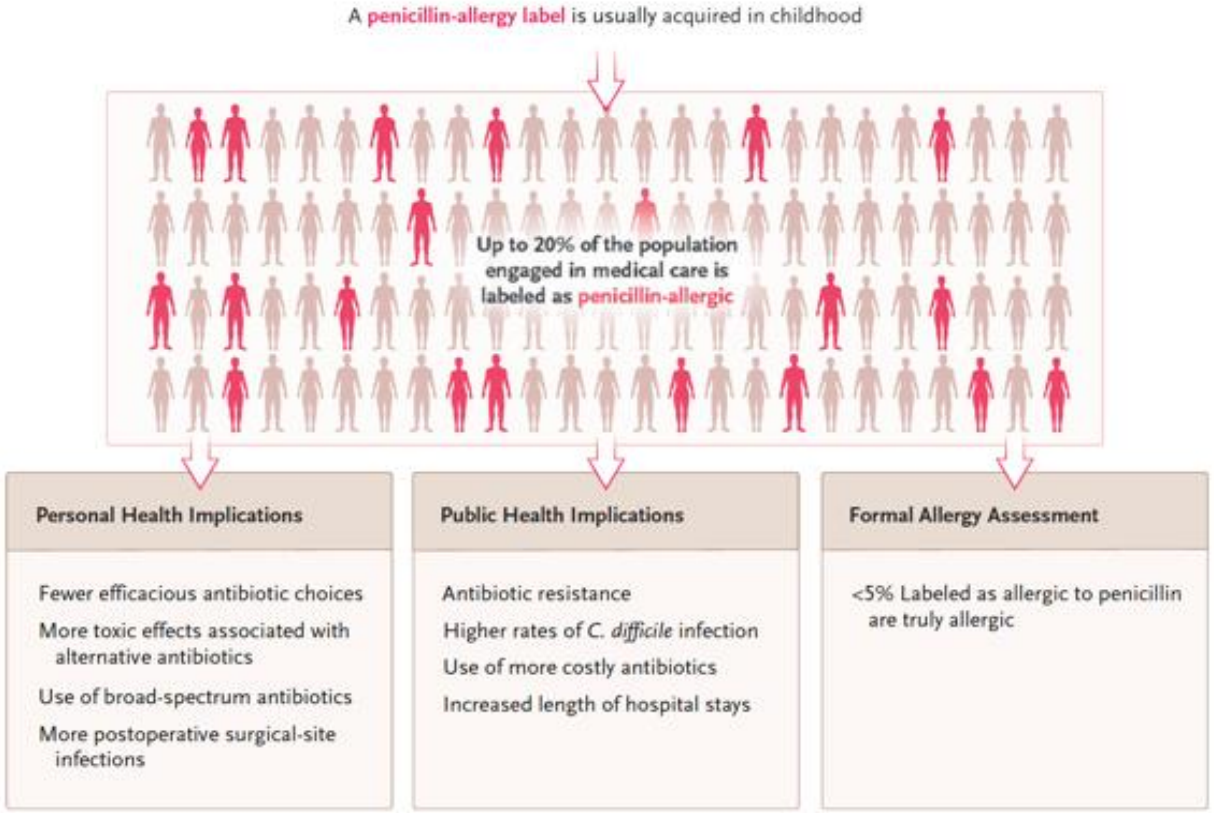
@USdrugallergy

Learning Objectives

- Upon completion of this learning activity, participants should be able to describe the rationale for, and approaches to, beta-lactam allergy evaluation
- Upon completion of this learning activity, participants should be able to address barriers to widespread penicillin allergy de-labeling

Why Penicillin Allergy Labels Matter



Castells *NEJM* 2019

Original Article

The Effect of Penicillin Allergy Testing on Future Health Care Utilization: A Matched Cohort Study

Eric Macy, MD, MS[a], and Yu-Hsiang Shu, MS, PhD[b] *San Diego and Pasadena, Calif*

Beta-Lactam Alternatives	Evaluated (n=308)	Not Evaluated (n=1,251)	P-Value
Cotrimoxazole	21.1	23.7	0.36
Clindamycin	14.6	32.5	<0.001
Macrolide	31.5	41.8	0.001
Tetracycline	24.0	19.2	0.07
Quinolone	31.5	30.7	0.84
Vancomycin	4.5	6.6	0.22
Aminoglycoside	11.0	14.6	0.12

Macy *J Allergy Clin Immunol Pract* 2017

Future Antibiotic Utilization

Beta-Lactams	Evaluated (n=308)	Not Evaluated (n=1,251)	P-Value
Penicillin courses	45.0	2.5	<0.001
1st generation cephalosporin courses	32.5	20.5	<0.001
3rd/4th/5th generation cephalosporin courses	13.3	15.3	0.42
Carbapenems	1.0	0.2	0.10
Monobactam	0.3	1.0	0.33

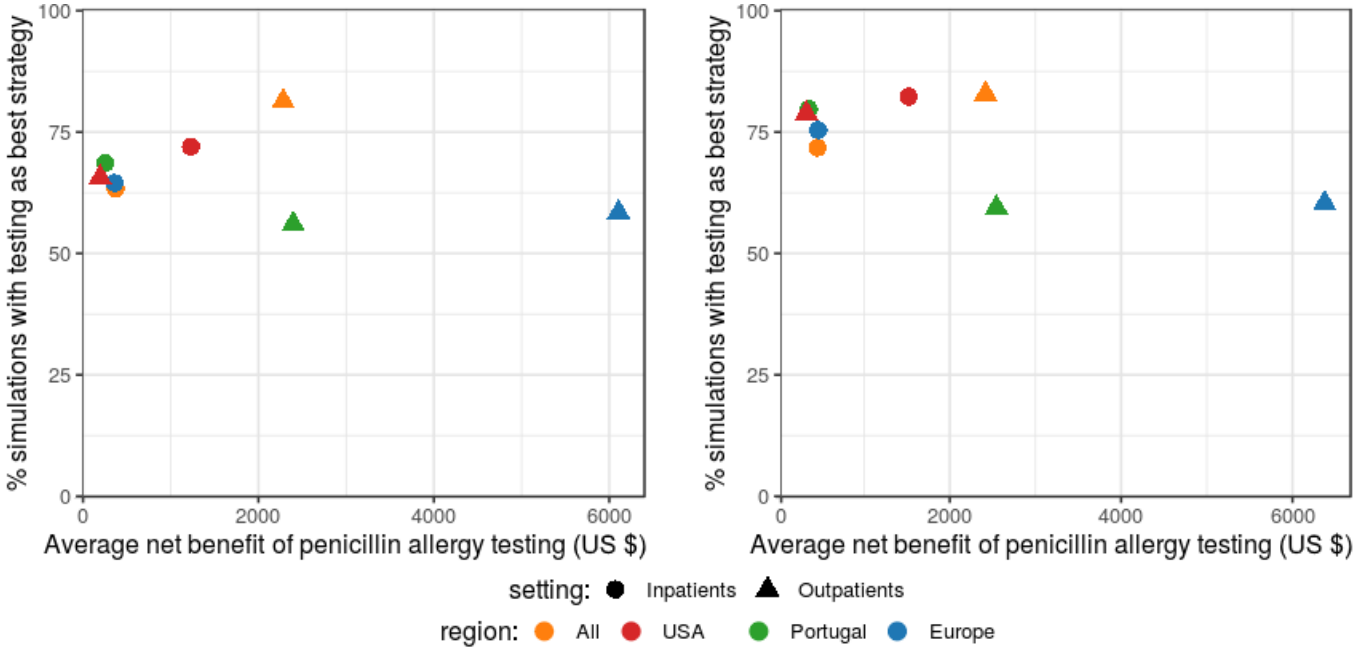
Macy *J Allergy Clin Immunol Pract* 2017

Penicillin Allergy Testing Is Cost-Saving: An Economic Evaluation Study

Bernardo Sousa-Pinto,[1,2,3] Kimberly G. Blumenthal,[4,5] Eric Macy,[6] Ana Margarida Pereira,[1,2] Luís Filipe Azevedo,[1,2] Luís Delgado,[2,3] and João Almeida Fonseca[1,2]

Skin Testing & Drug Challenge Testing:
Savings $554 for inpatients and $2,745 for outpatients

Drug Challenge Testing Alone:
Savings of $616 for inpatients and $3,051 for outpatients



Sousa-Pinto *Clin Infect Dis* 2020

Support for Penicillin Allergy Assessments

10

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

While about 10 percent of the population reports a history of penicillin allergy, studies show that 90 percent on more of these patients are not allergic to penicillins and are able to take these antibiotics safely. The main reason for this observation is that penicillin allergy is often misdiagnosed and when present wanes over time in most (but not all) individuals. Patients labeled penicillin-allergic are more likely to be treated with alternative antibiotics (such as vancomycin and quinolones), have higher medical costs, experience longer hospital stays, and are more likely to develop complications such as infections with vancomycin-resistant enterococcus (VRE) and Clostridium difficile.

Evaluation for specific IgE to penicillin can be carried out by skin testing. Ideally, penicillin skin testing should be performed with both major and minor determinants. The negative predictive value of penicillin skin testing for immediate reactions approaches 100 percent, whereas the positive predictive value is between 40 and 100 percent. The usefulness of in vitro tests for penicillin-specific IgE is limited by their uncertain predictive value. They are not suitable substitutes for penicillin skin testing.

By identifying the overwhelming majority of individuals who can safely receive penicillin and penicillin-like drugs, we can improve the appropriateness of antibiotic therapy and clinical care outcomes.

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In patients with a history of β-lactam allergy, we suggest that ASPs promote allergy assessments and penicillin (PCN) skin testing when appropriate

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Is it Really a Penicillin Allergy?

Assessing penicillin allergy: About 15% of hospitalized patients report an allergy to penicillin[68]. However, less than 1% of the US population has a serious penicillin allergy that would preclude treatment with a beta-lactam antibiotic[69]. There are several effective approaches to properly assess penicillin allergies, including history and physical examination, challenge doses, and skin testing[69, 71]. Nurses may be able to play an important role in improving penicillin allergy assessments[27].

American College of Allergy, Asthma & Immunology

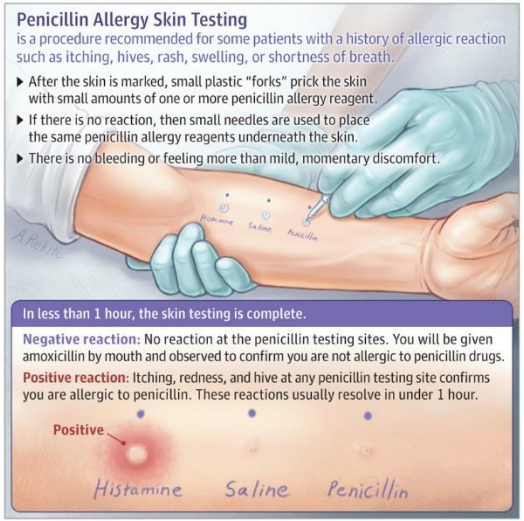
IDSA
Infectious Diseases Society of America

Consensus-Based Statement

Consensus-Based Statement	Strength of Recommendation	Certainty of Evidence
We recommend a proactive effort to de-label a penicillin allergy, if appropriate.	Strong	Moderate

Khan *J Allergy Clin Immunol* 2022

Penicillin Allergy Diagnostic Testing

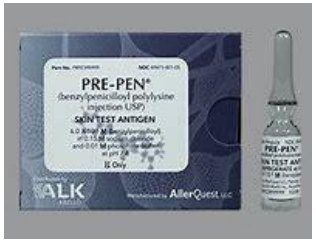


Studies (N)	Sensitivity	Specificity
27	30.7% (18.9-45.9%)	96.8% (94.2-98.3%)

Sousa-Pinto *J Allergy Clin Immunol* 2021

Penicillin Skin Testing Reagents

Reagent	% positive skin test patterns among subjects
	With positive skin test result (N = 63)
PRE-PEN only	3
Minor determinant only	38
Amoxicillin only	6
PRE-PEN + MDM	8
PRE-PEN + amoxicillin	0
MDM + amoxicillin	21
PRE-PEN + MDM + amoxicillin	24



ABBREVIATIONS

PRE-PEN, benzylpenicilloyl polylysine

MDM, minor determinant

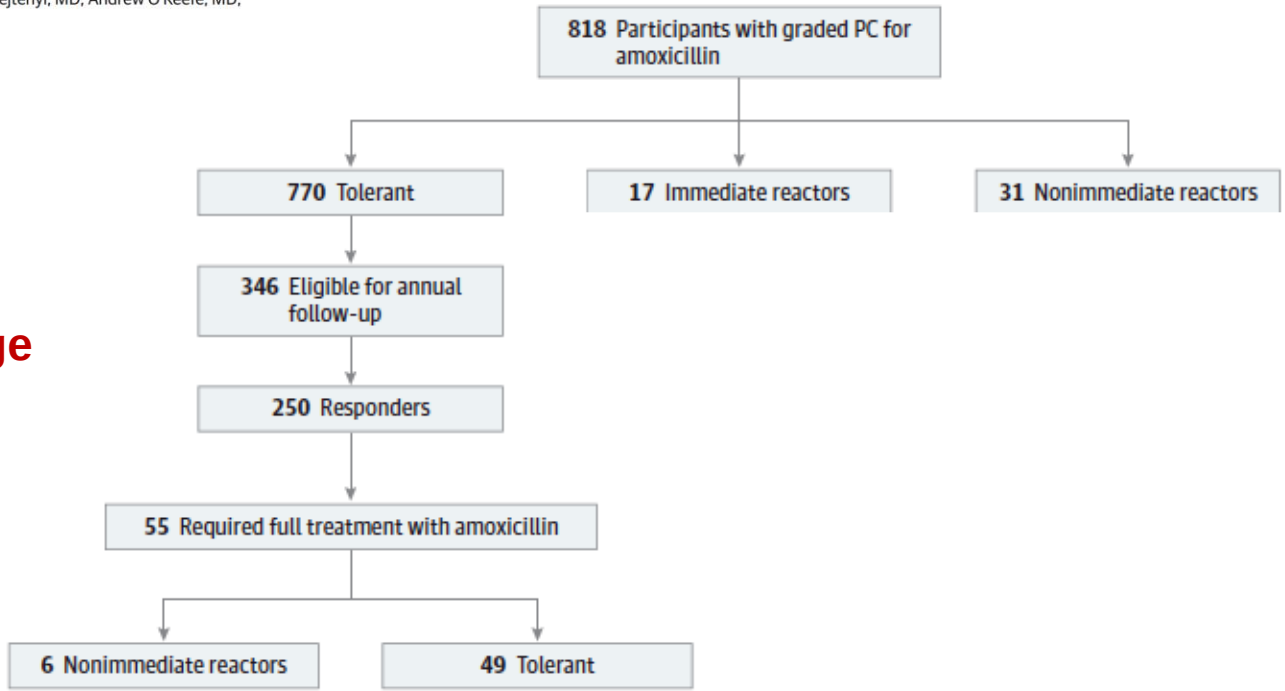
Solensky *J Allergy Clin Immunol Pract* 2019

Original Investigation

Assessing the Diagnostic Properties of a Graded Oral Provocation Challenge for the Diagnosis of Immediate and Nonimmediate Reactions to Amoxicillin in Children

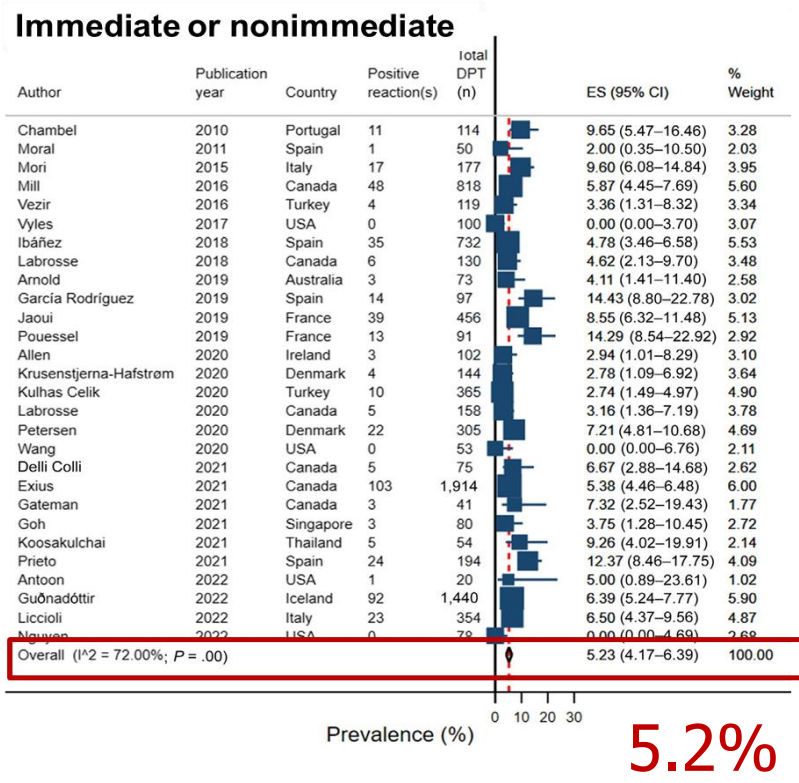
Christopher Mill, MPH; Marie-Noël Primeau, MD; Elaine Medoff, MD; Christine Lejtenyi, MD; Andrew O'Keefe, MD; Elena Netchiporouk, MD; Alizee Dery, BSc; Moshe Ben-Shoshan, MD, MSc

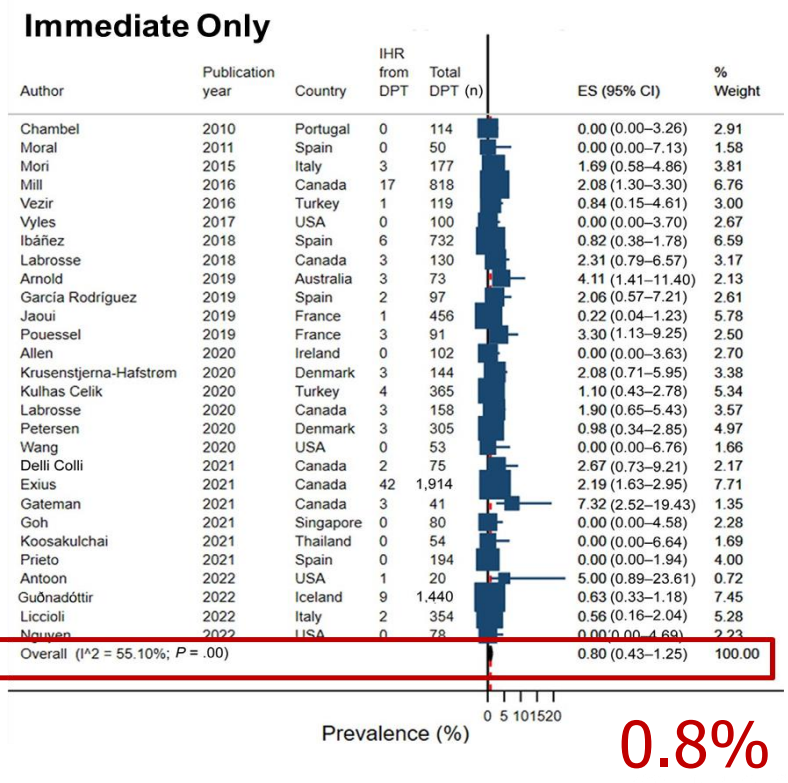
94% passed challenge



Mill *JAMA Pediatr* 2016

Meta-Analysis: 28 Studies in Children





Srisuwatchari *J Allergy Clin Immunol Pract* 2023

CME Review

Who needs penicillin allergy testing?

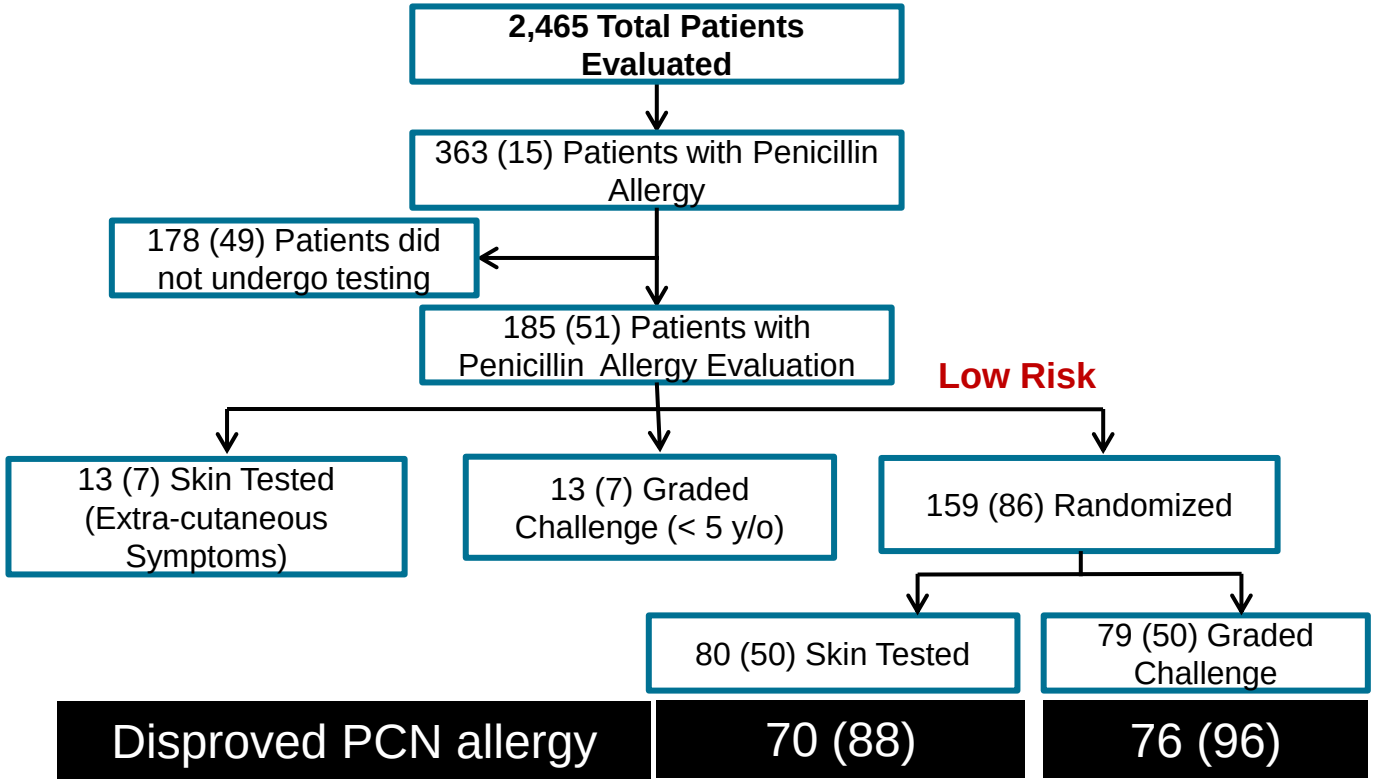
Eric Macy, MD, MS*; David Vyles, DO, MS†

No. of Patients	Age Groups	Country	Immediate-Onset Positive	Delayed-Onset Positive
818	Children	Canada	17 (2.1%)	31 (3.5%)
328	Adults	United States	5 (1.5%)	0 (0%)
130	Children	Canada	3 (2.3%)	5 (3.8%)
155	Children and adults	United States	1 (0.6%)	3 (1.9%)
732	Children	Spain	6 (0.8%)	29 (4.0%)
617	Children (n=435) and adults (n=207)	Israel	9 (1.5%)	1 day: 24 (19.0%); 5 day: 30 (6.1%)
519	Children and adults	United States	1 (0.2%)	8 (1.6%)
3,299			**42 (1.3%; 95%CI 0.9-1.7%)**	**130 (3.9%; 95% CI 3.3-4.7%)**

Macy *Ann Allergy Asthma Immunol* 2018

Original Article

Comparing Direct Challenge to Penicillin Skin Testing for the Outpatient Evaluation of Penicillin Allergy: A Randomized Controlled Trial



Mustafa *J Allergy Clin Immunol Pract* 2019

Defining “Low Risk”: Prediction Models

	Anaphylaxis	SCAR*	Index drug	Reaction onset time	Required treatment	Elapsed time since reaction	Recall of index drug	Multiple reactions	Demographics
Chiriac et al.	+	–	+	+	?	+	?	+	–
Siew et al.	+	×	+	?	?	+	+	?	–
Stevenson et al.	+	×	×	?	?	+	?	?	–
Trubiano et al.	+	+	×	?	+	+	?	?	–
Moreno et al.	+	?	+	+	?	+	?	?	–

+ Associated
– Not associated
? Unknown/Not considered
× Excluded

† Excluded cephalosporins, index penicillin was not significant

* SCAR is difficult to denote because studies differ in how it is used or grouped with other symptoms. Angioedema likewise difficult, but not excluded by any studies

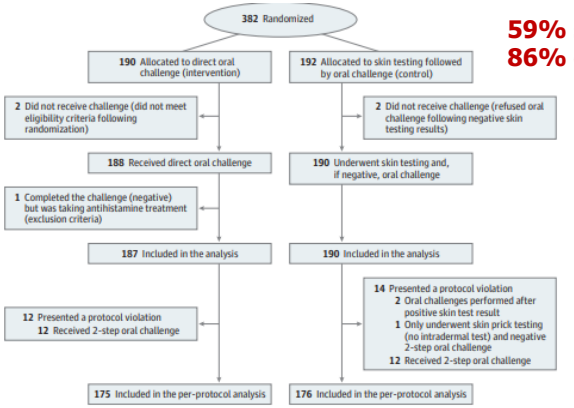
Plager *Curr Opin Allergy Clin Immunol* 2021

PEN-FAST Risk Stratification

PEN	Penicillin allergy reported by patient	If yes, proceed with assessment
F	Five years or less since reaction[a]	2 points
A	Anaphylaxis or angioedema	
OR		2 points
S	Severe cutaneous adverse reaction[b]	
T	Treatment required for reaction[a]	1 point
		Total points

Interpretation	
Points	
0	**Very low risk** of positive penicillin allergy test <1% (<1 in 100 patients reporting penicillin allergy)
1-2	**Low risk** of positive penicillin allergy test 5% (1 in 20 patients)
3	**Moderate risk** of positive penicillin allergy test 20% (1 in 5 patients)
4-5	**High risk** of positive penicillin allergy test 50% (1 in 2 patients)

[a] Includes unknown.
[b] Forms of severe delayed reactions include potential SJS, TEN, DRESS and AGEP. Patients with a severe delayed rash with mucosal involvement should be considered to have a severe cutaneous adverse reaction. Acute interstitial nephritis, drug induced liver injury, serum sickness and isolated drug fever were excluded phenotypes from the derivation and validation cohorts.

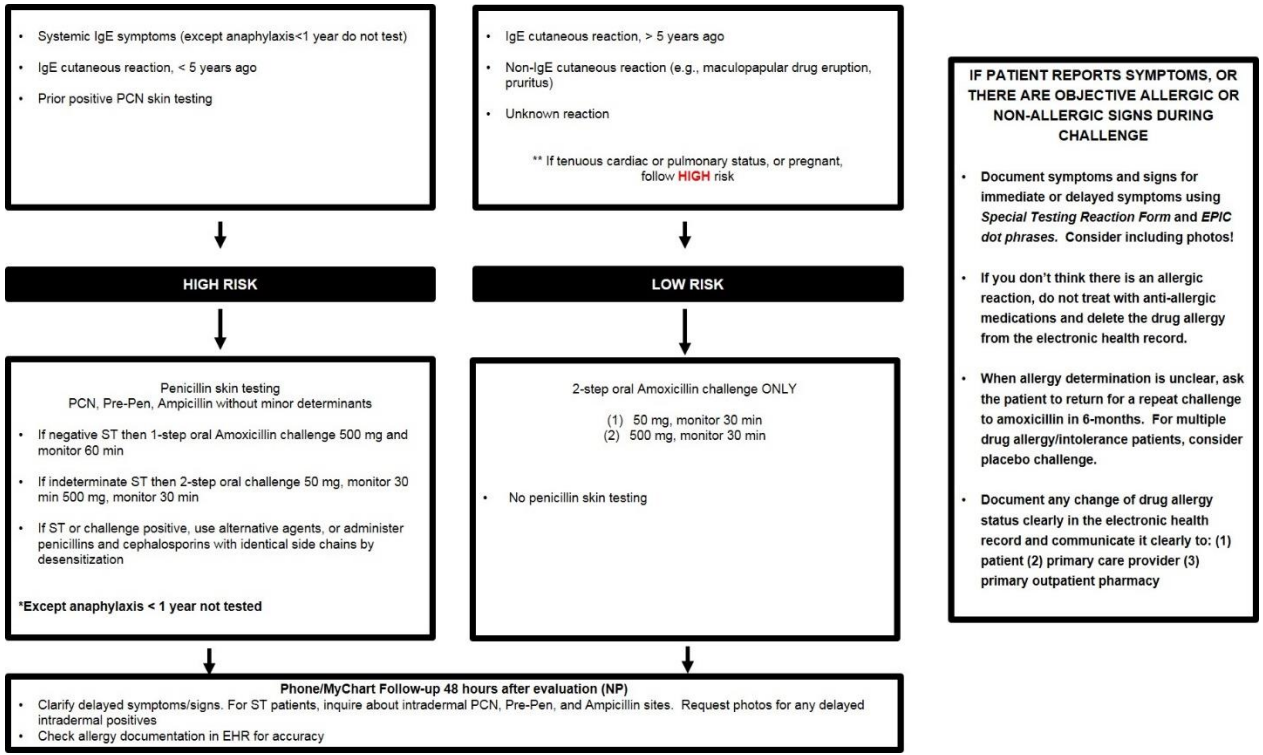


59% screened
86% eligible

	Direct Challenge	Skin Test	Risk Difference
Positive immune-mediated penicillin challenge	1 (0.5%)	1 (0.5%)	RD of 0.0084 pp (90% CI, −1.22 to 1.24 pp
Immune-mediated adverse events	9	10	RD, −0.45 pp; 95% CI, −4.87 to 3.96 pp

Copaescu *JAMA Intern Med* 2023; Trubiano *JAMA Intern Med* 2020

Defining “Low Risk”: MGH Allergy



Blumenthal *J Allergy Clin Immunol Pract* 2019

Consensus-Based Statement

Consensus-Based Statement	Strength of Recommendation	Certainty of Evidence
We recommend against testing inpatients with a history inconsistent with penicillin allergy (such as headache or family history of penicillin allergy), but a 1-step amoxicillin challenge may be offered to patients who are anxious or request additional reassurance to accept the removal of a penicillin allergy label.	Strong	Moderate
We suggest penicillin skin testing for patients with a history of anaphylaxis or a recent reaction suspected to be IgE-mediated.	Conditional	Low

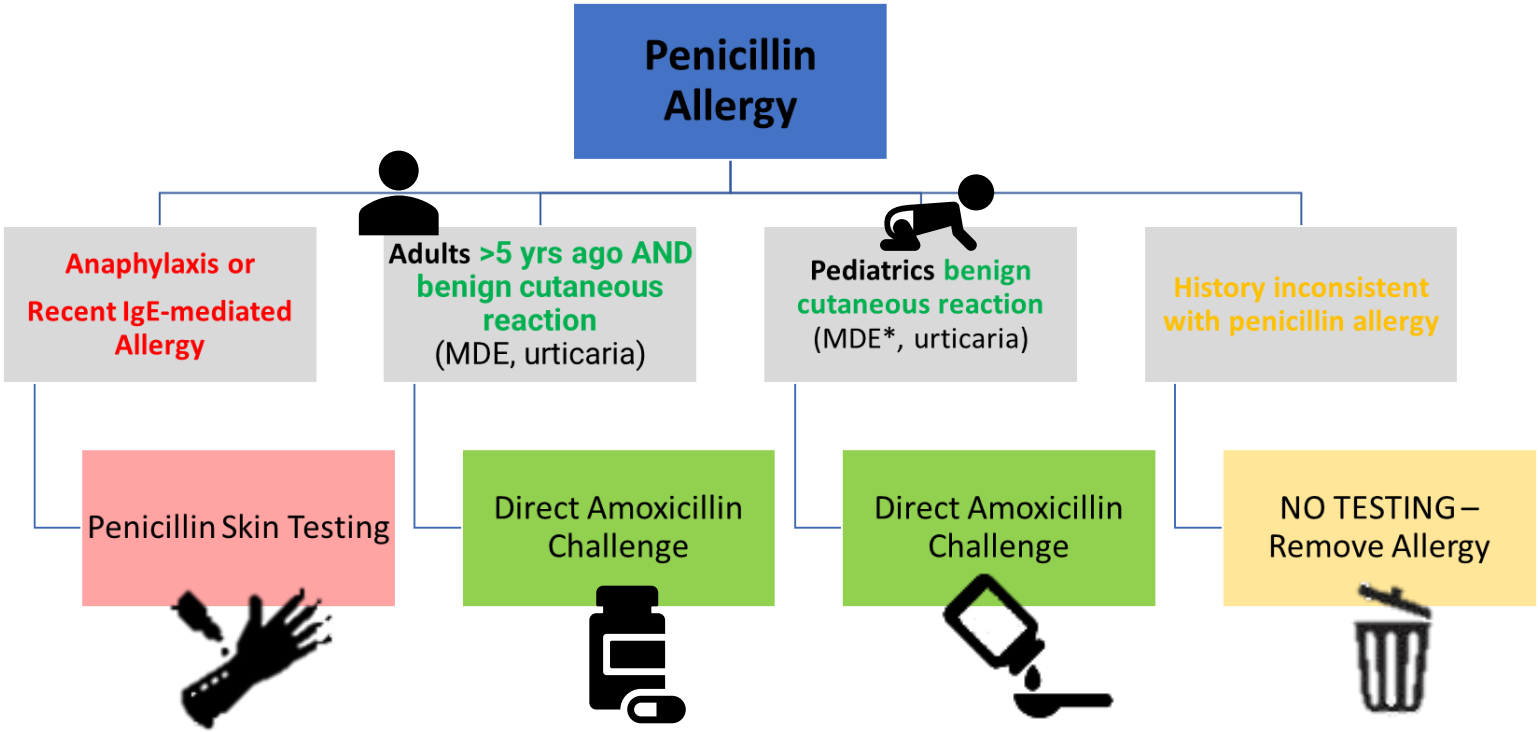
Khan *J Allergy Clin Immunol* 2022

Consensus-Based Statement

Consensus Based Statement	Strength of Recommendation	Certainty of Evidence
We recommend against penicillin skin testing prior to direct amoxicillin challenge in pediatric patients with a history of benign cutaneous reaction (such as maculopapular rashes and urticaria).	Strong	Moderate
We suggest that direct amoxicillin challenge be considered in adults with distant and benign cutaneous reaction histories (such as maculopapular rashes and urticaria).	Conditional	Low

Khan *J Allergy Clin Immunol* 2022

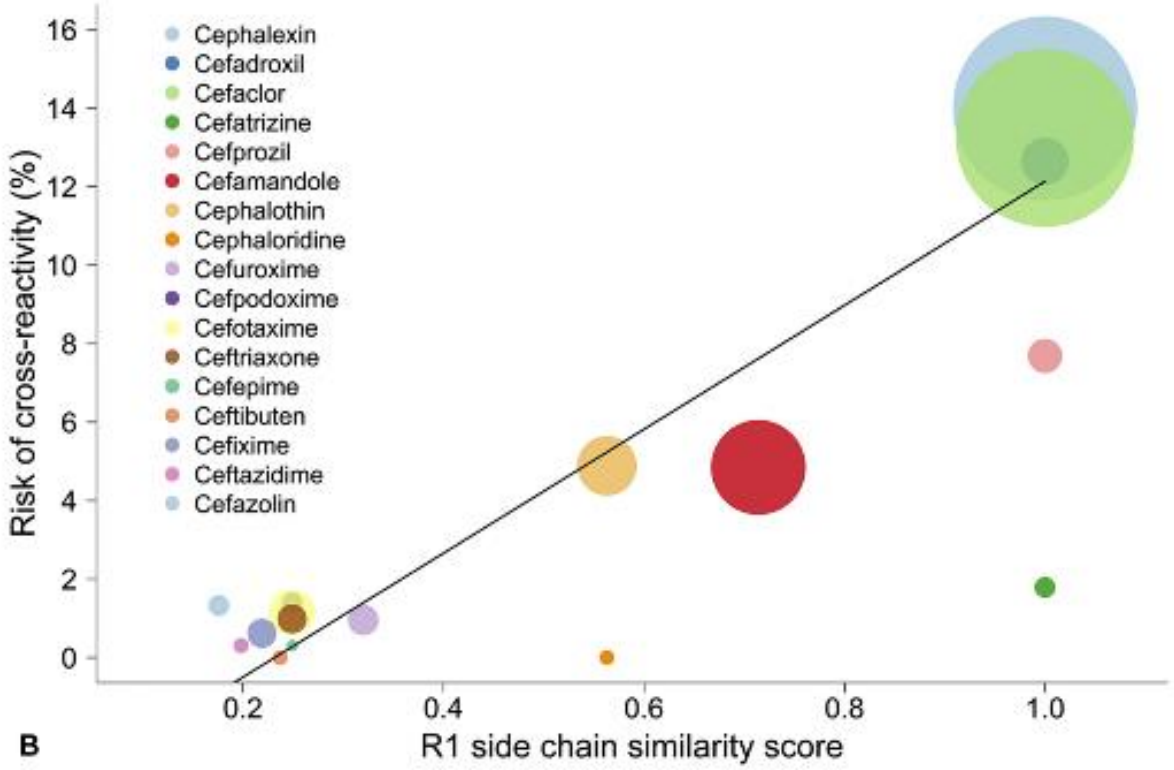
Penicillin Allergy: Summary



Khan *JACI* 2022 (adapted by Deanna McDanel, PharmD)

Original Article

Cross-Reactivity to Cephalosporins and Carbapenems in Penicillin-Allergic Patients: Two Systematic Reviews and Meta-Analyses



Picard *JACI In Practice* 2019

Original Article

Cross-Reactivity to Cephalosporins and Carbapenems in Penicillin-Allergic Patients: Two Systematic Reviews and Meta-Analyses

Generation	Name	No. of studies	n/N	AR in % (95% CI)
First	Cephalexin	8	97/693	14.00 (11.61-16.79)
	Cefadroxil	6	95/557	12.65 (5.85-25.26)
	Cephalothin	3	9/184	4.89 (2.56-9.13)
	Cefazolin	3	1/75	1.33 (0.19-8.86)
	Cefatrizine	2	1/56	1.79 (0.25-11.61)
	Cephaloridine	1	0/17	0.0 (0.0-19.5)
Second	Cefamandole	6	23/474	4.85 (3.25-7.20)
	Cefaclor	7	90/679	13.25 (10.91-16.02)
	Cefuroxime	14	16/984	0.96 (0.26-3.51)
	Cefprozil	1	3/39	7.69 (1.62-20.87)
Third	Cefpodoxime	1	1/71	1.4 (0.0-7.6)
	Ceftazidime	4	2/433	0.31 (0.02-4.72)
	Cefotaxime	4	5/436	1.15 (0.48-2.72)
	Cefixime	7	2/324	0.62 (0.15-2.43)
	Ceftriaxone	9	13/843	0.99 (0.25-3.87)
	Ceftibuten	3	0/153	0.0 (0.0-2.4)
Fourth	Cefepime	2	1/285	0.31 (0.01-10.32)

Picard *JACI In Practice* 2019

JAMA Surgery | Original Investigation

Assessment of the Frequency of Dual Allergy to Penicillins and Cefazolin

A Systematic Review and Meta-analysis

Dual Allergy Results

	Cohort	Surgical Patients	Penicillin Allergy History
Index penicillin allergy	0.7% n=6001	0.7% n=3884	Self-reported 0.6% n=5487
Index cefazolin allergy	3% n=146	4.4% n=104	Confirmed 3% n=514

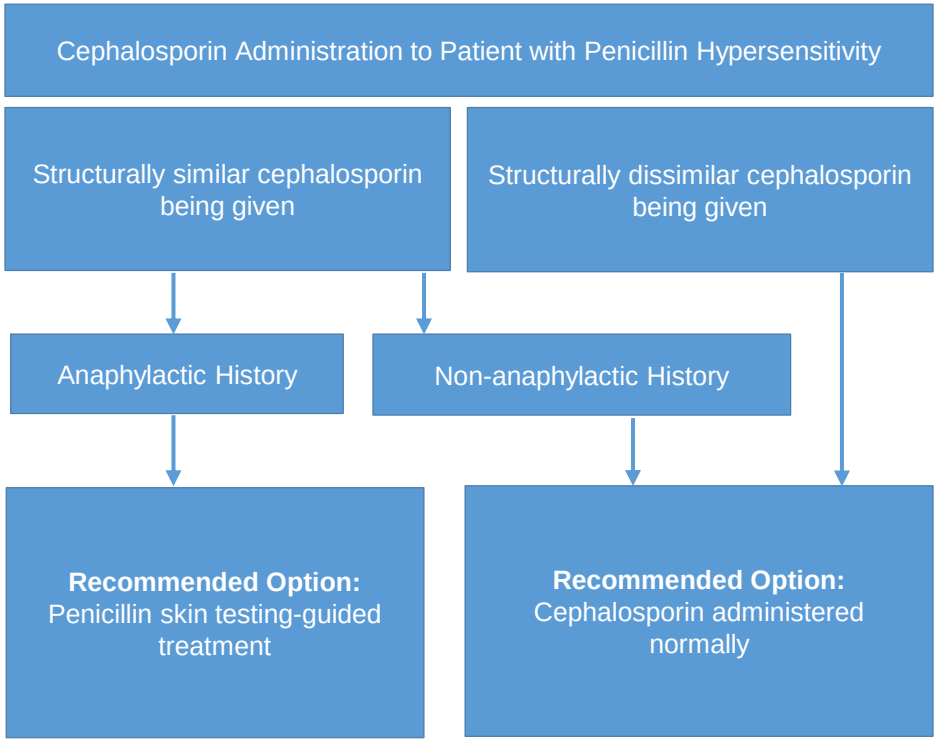
Sousa-Pinto *JAMA Surg* 2020

Use of Cephalosporins in Penicillin Allergy

Consensus-Based Statement	Strength of Recommendation	Certainty of Evidence
We suggest that for patients with an unverified, non-anaphylactic, penicillin allergy, a cephalosporin can be administered without testing or additional precautions.	Conditional	Moderate
We suggest that for patients with a history of anaphylaxis to penicillin, a non-cross–reactive cephalosporin can be administered without prior testing.	Conditional	Moderate

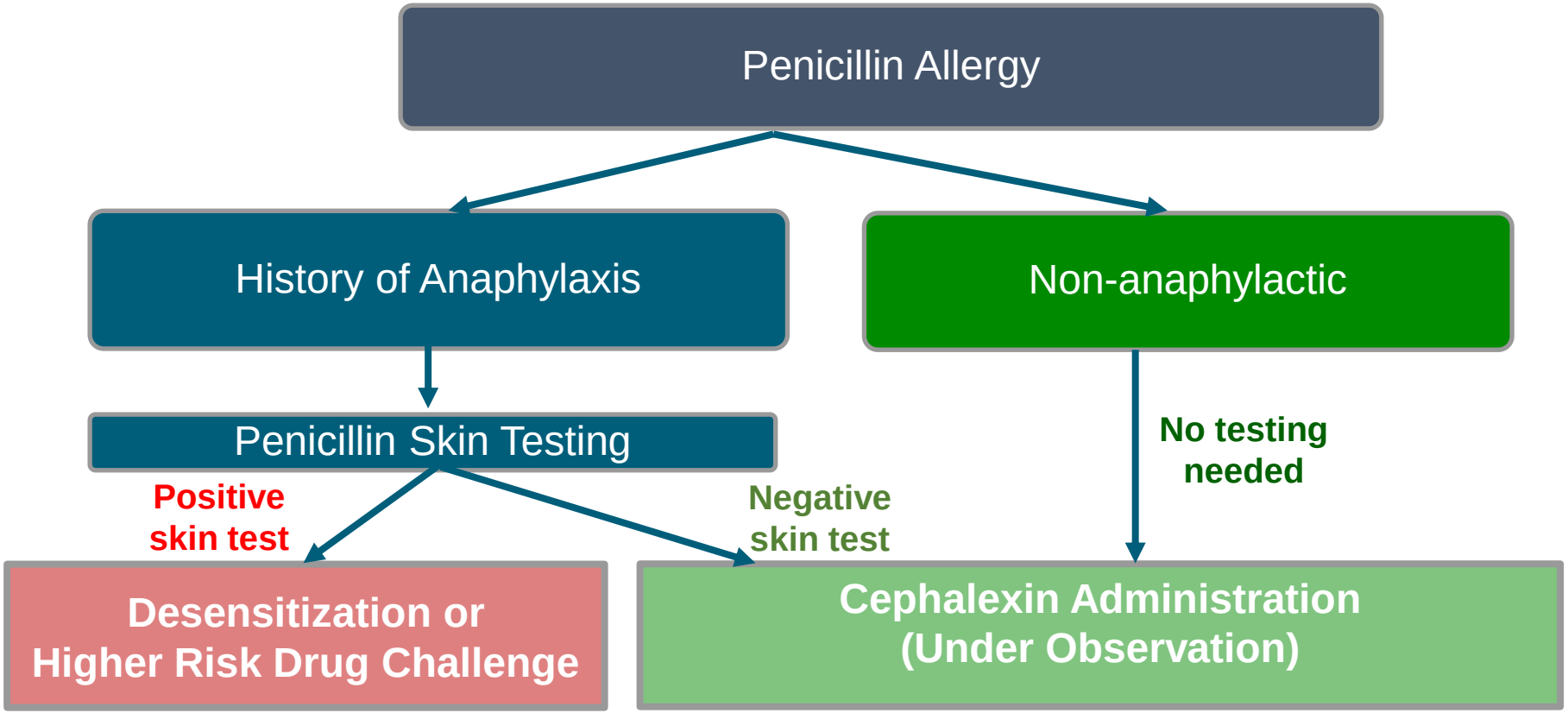
Khan *J Allergy Clin Immunol* 2022

Cephalosporins Administration in Penicillin Allergy



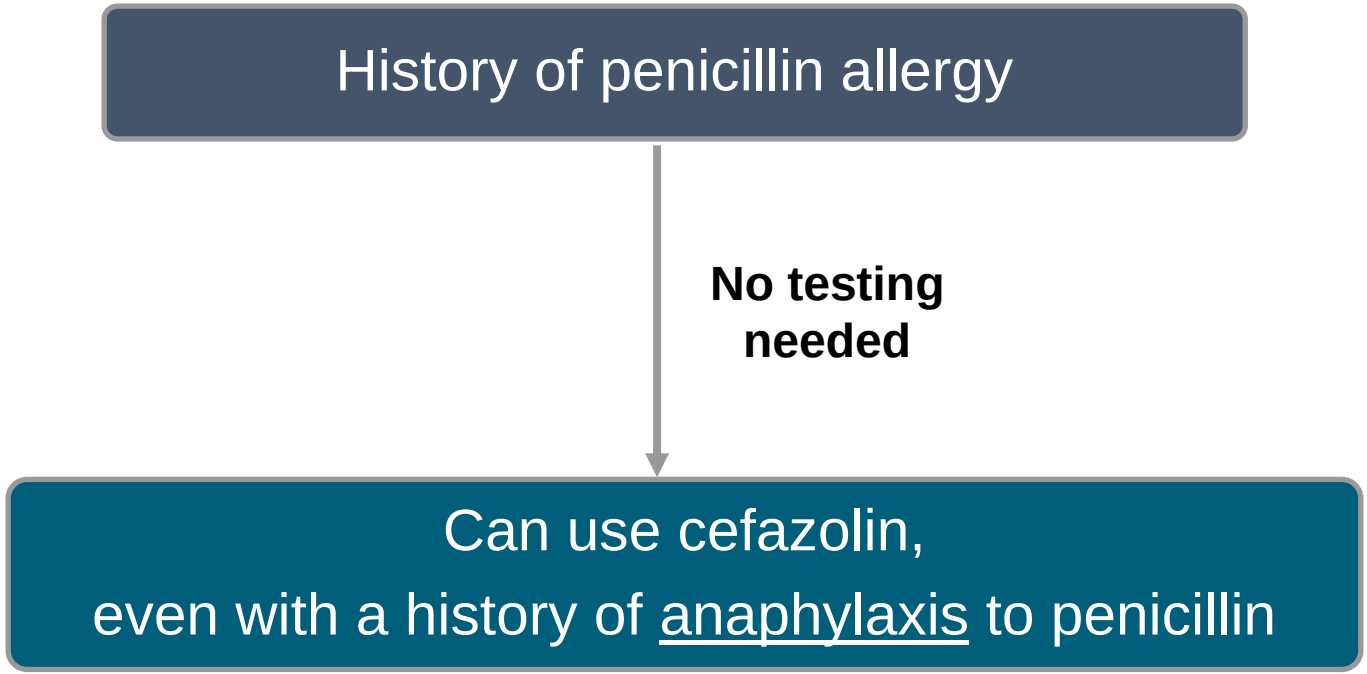
Khan *J Allergy Clin Immunol* 2022

Using Cephalexin in Penicillin Allergy



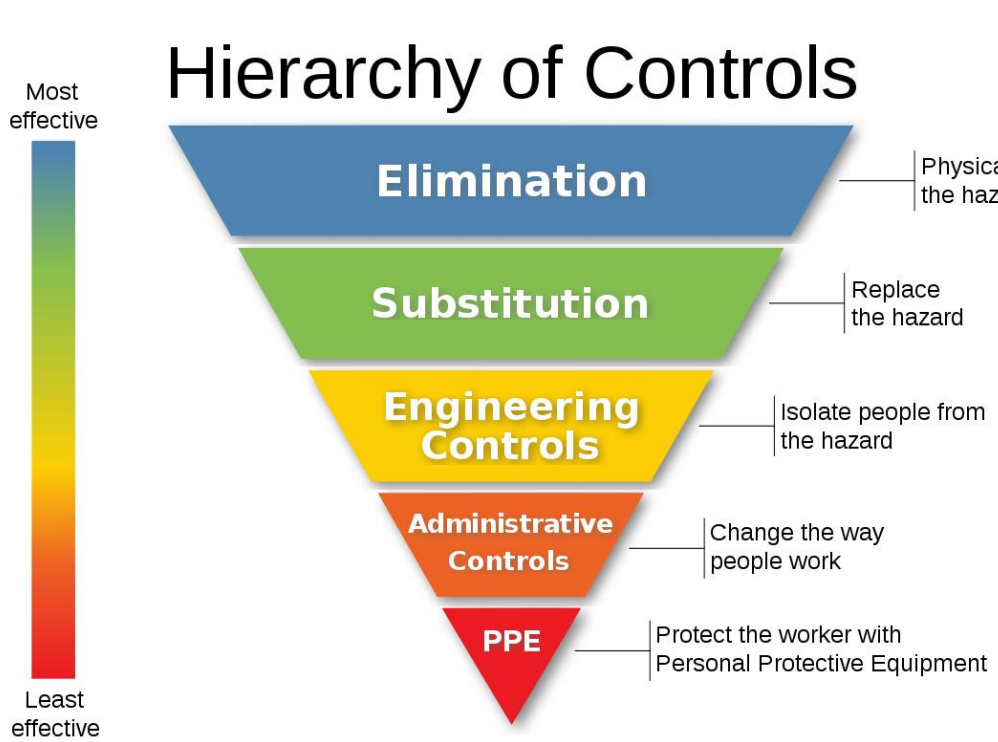
Khan *JACI* 2022 (adapted by Deanna McDanel, PharmD)

Using Cefazolin in Penicillin Allergy



Khan *JACI* 2022 (adapted by Deanna McDanel, PharmD)

Cefazolin in Penicillin Allergy Patients



27-fold increased odd of first line beta-lactam for c section or group b strep [95%CI 6.32, 114.3]

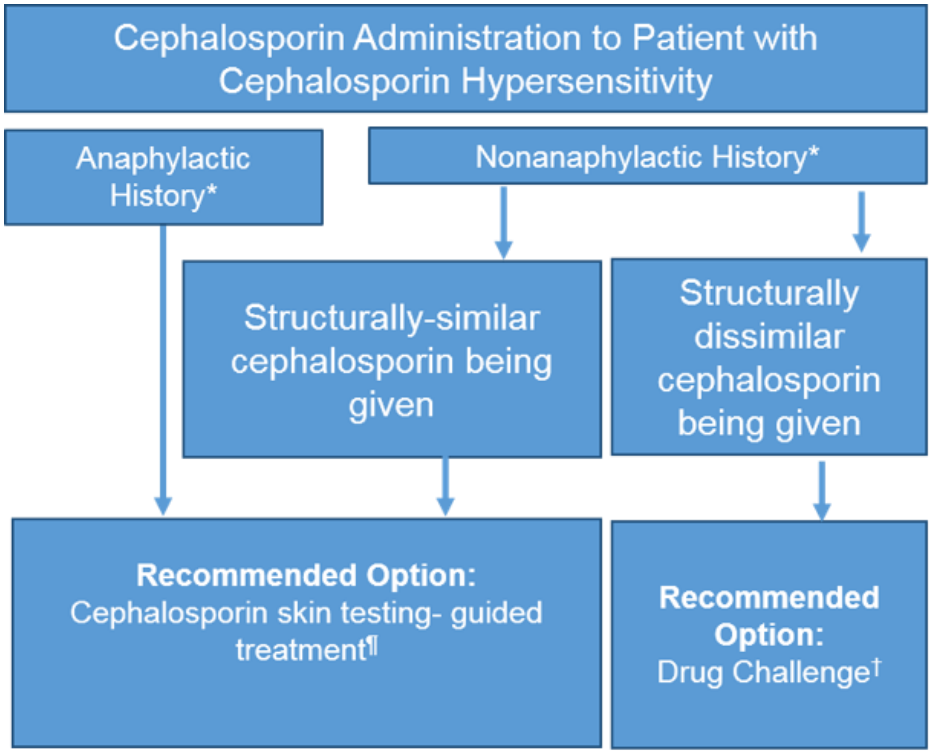
2-fold increased odd of first line beta-lactam [95%CI 1.06, 3.52]

Plager *Ann Allergy Asthma Immunol* 2020; Wolfson *J Allergy Clin Immunol Pract* 2020

Cephalosporin and Penicillin Administration in Cephalosporin Allergy

Consensus-Based Statement	Strength of Recommendation	Certainty of Evidence
We suggest that for patients with a history of non-anaphylactic cephalosporin allergy, direct challenges (without prior skin test) to cephalosporins with dissimilar side chains be performed to determine tolerance.	Conditional	Moderate
We suggest that for patients with a history of anaphylaxis to a cephalosporin, a negative cephalosporin skin test should be confirmed prior to administration of a parenteral cephalosporin with a non-identical R1 side chain.	Conditional	Low

Cephalosporin Administration in Cephalosporin Allergy

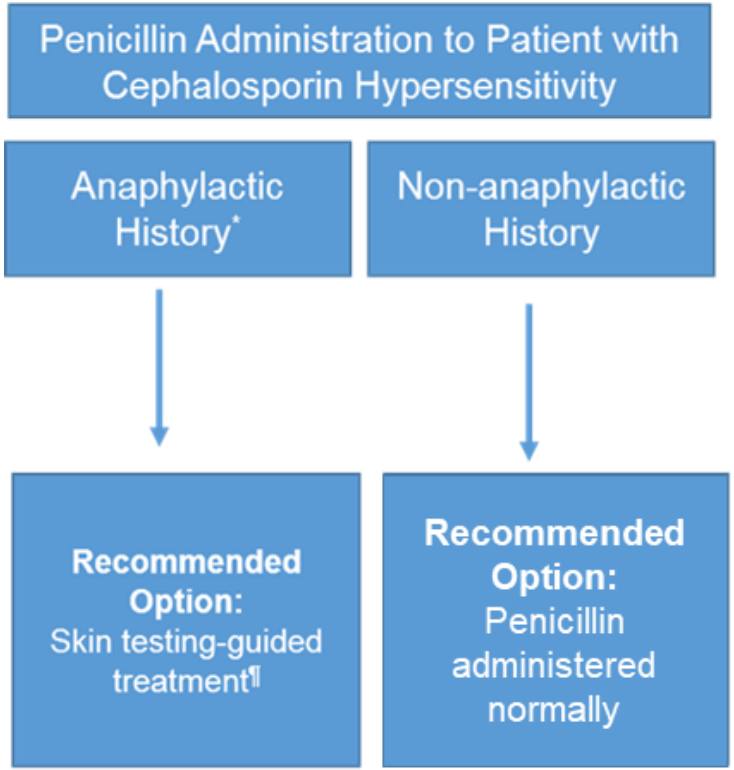


Romano *J Allergy Clin Immunol* 2015

Penicillin Administration in Cephalosporin Allergy

Consensus-Based Statement	Strength of Recommendation	Certainty of Evidence
We suggest against penicillin skin testing in patients with a non-anaphylactic history to cephalosporins prior to administration of penicillin therapy.	Conditional	Low
We suggest that in patients with a history of anaphylaxis to cephalosporins, penicillin skin testing and drug challenge should be performed prior to administration of penicillin therapy.	Conditional	Low

Penicillin Administration in Cephalosporin Allergy



Beta-Lactam Allergy Summary

	Drug to be Administered	History of a Penicillin Allergy/Hypersensitivity	History of Cephalosporin Allergy/Hypersensitivity
Nona-naphylactic Benign Cutaneous Reaction (>5 Years Ago)	Penicillin Derivative	Amoxicillin drug challenge	Administer penicillin normally (no testing is needed)
	Cephalosporin Derivative	Administer cephalosporin normally (no testing is needed)	*Structurally Similar* **Cephalosporin skin testing** (when available) followed by cephalosporin drug challenge **OR** **Cephalosporin drug challenge** only in low-risk patients
			Structurally Dissimilar **Cephalosporin drug challenge**
Anaphylactic Reaction OR Recent Ig-E Mediated Reaction (<5 years Ago)	Penicillin Derivative	**Penicillin skin testing** followed by amoxicillin drug challenge	**Penicillin skin testing** followed by amoxicillin drug challenge **OR** **Cephalosporin skin testing** (when available)
	Cephalosporin Derivative	*Structurally Similar* **Penicillin skin testing** followed by amoxicillin drug challenge and **Administer cephalosporin normally**	**Cephalosporin skin testing** (when available) followed by cephalosporin drug challenge
		Structurally Dissimilar **Administer cephalosporin normally (no testing is needed)**	

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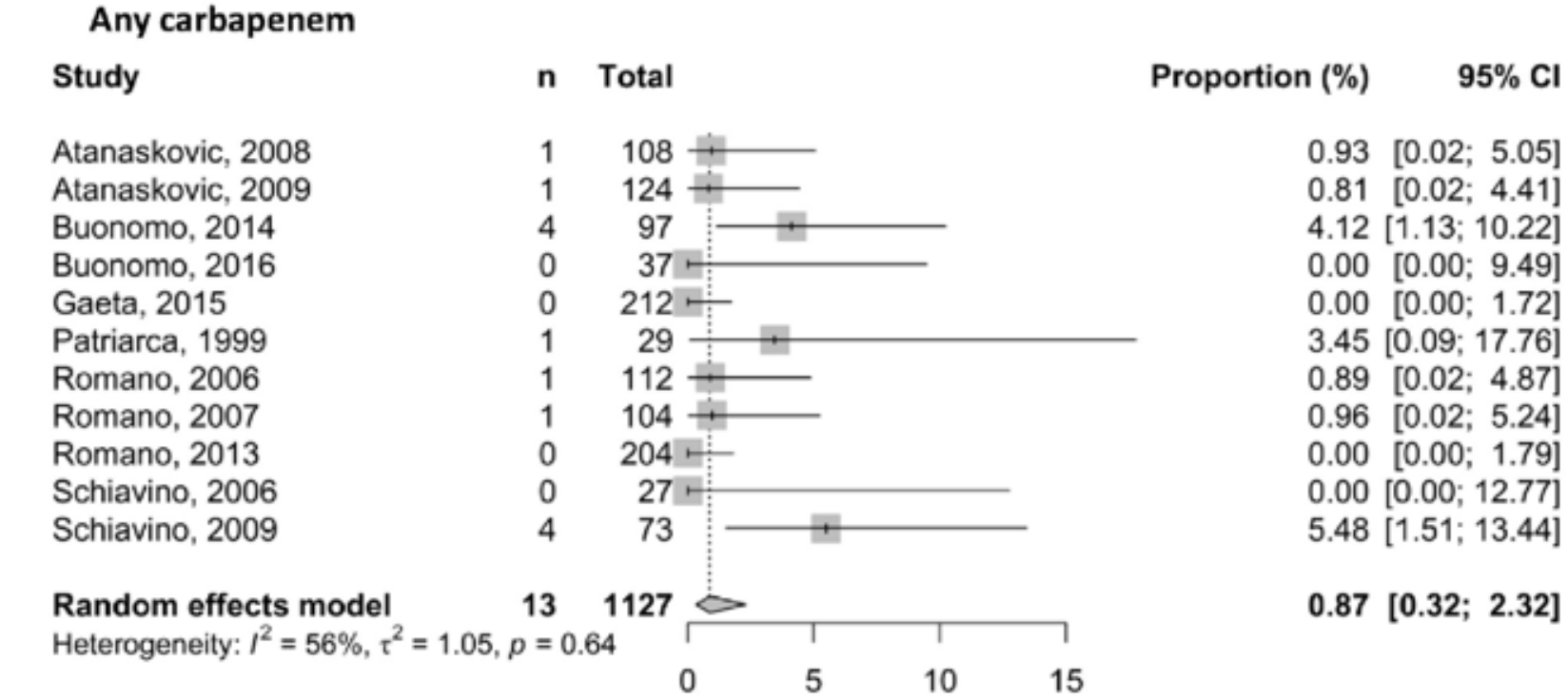

Picard *JACI In Practice* 2019

Carbapenem Administration in Penicillin or Cephalosporin Allergy

Consensus-Based Statement	Strength of Recommendation	Certainty of Evidence
We recommend that in patients with a history of penicillin or cephalosporin allergy, a carbapenem may be administered without testing or additional precautions.	Strong	Moderate

Picard *JACI In Practice* 2019

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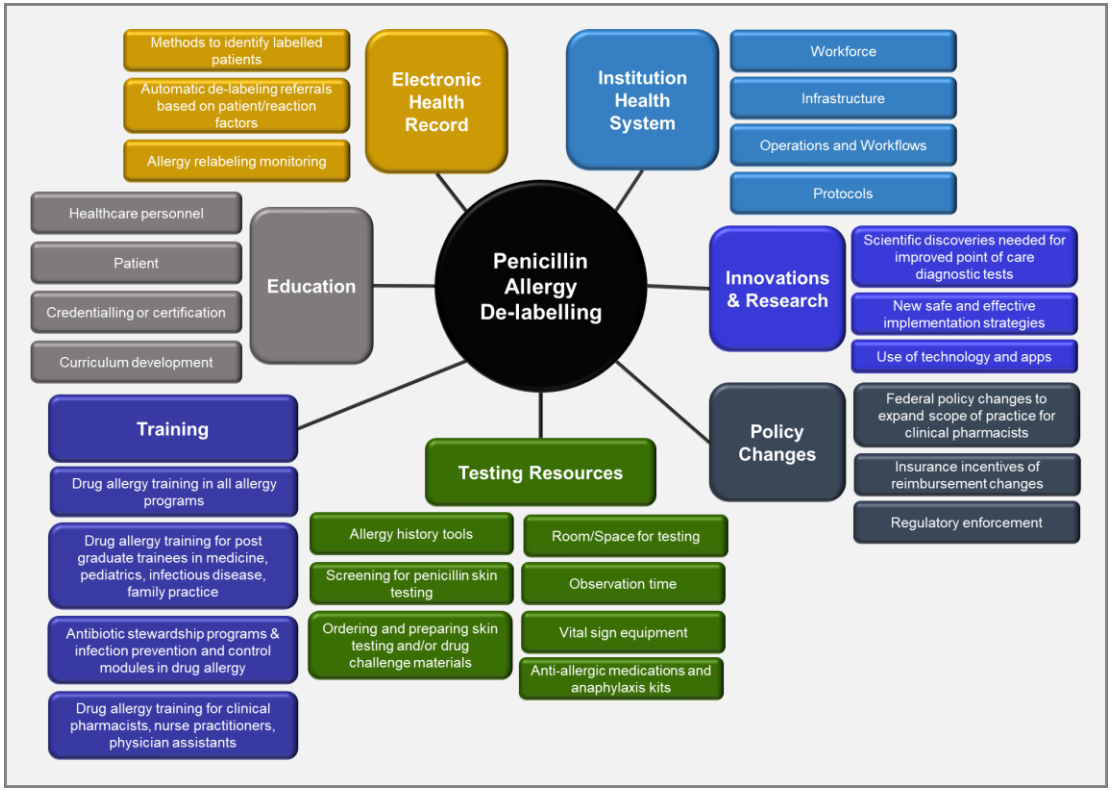
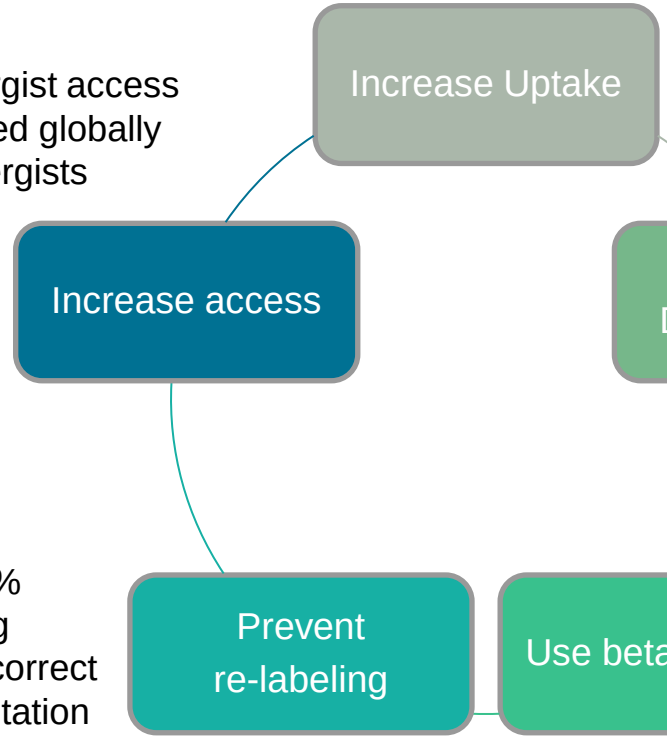
Infectious Diseases Society of America

De-labeling Considerations



Samarakoon *Ann Allergy Asthma Immunol* 2023

De-Labeling Challenges Ahead



- 67-88% interested in evaluation
- Education for patients, clinicians, communities

- Up to 52%
- Tools to correct documentation

- 23-81% use of beta-lactams after negative assessment
- Understand barriers

- Up to 36% relabeling
- Tools to correct documentation

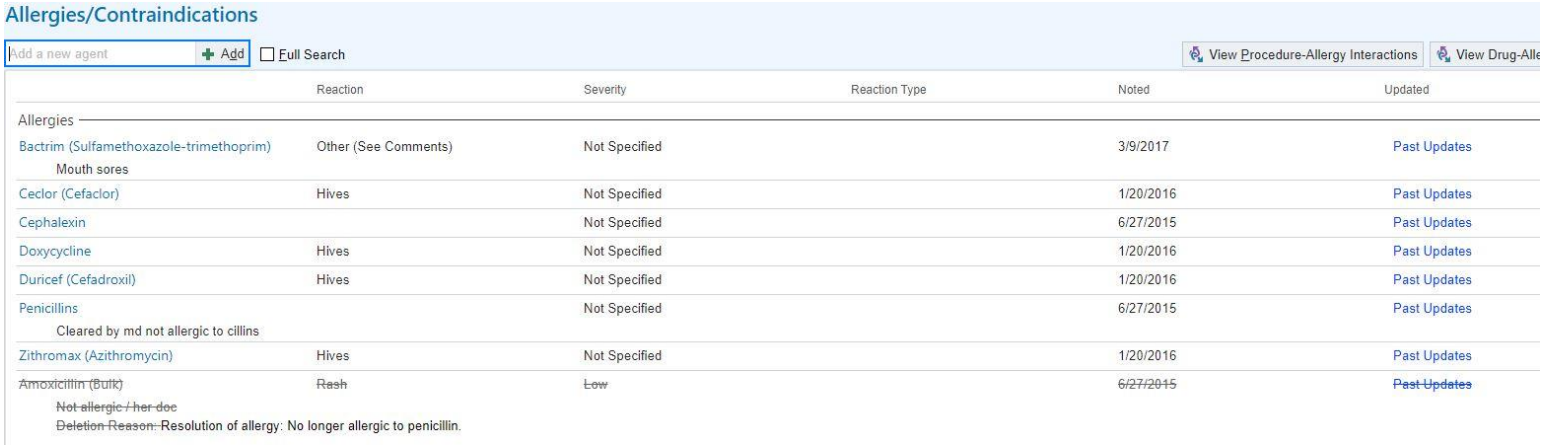
- 44%: hospital allergist access
- Access more limited globally
- Spread to non-allergists

Mancini *Clin Infect Dis* 2020; Blumenthal *JACI* 2017; Harada *Allergy Asthma Proc* 2012; Macy *JACI Pract* 2017; Gerace *JACI Pract* 2015; Rimawi *J Hosp Med* 2013

Barriers and Facilitators

Ngassa *Ann Allergy Asthma Immunol* 2024

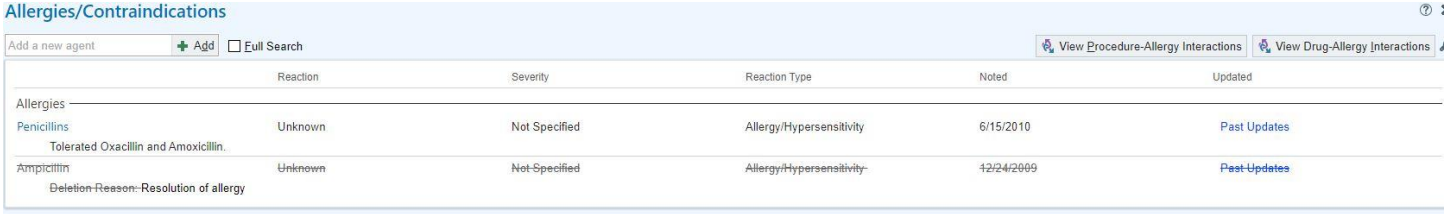
Penicillin Allergy De-Labeling



Allergies/Contraindications

Add a new agent | Add | Full Search | View Procedure-Allergy Interactions | View Drug-Alle

	Reaction	Severity	Reaction Type	Noted	Updated
Allergies					
Bactrim (Sulfamethoxazole-trimethoprim)	Other (See Comments)	Not Specified		3/9/2017	Past Updates
Mouth sores					
Ceclor (Cefaclor)	Hives	Not Specified		1/20/2016	Past Updates
Cephalexin		Not Specified		6/27/2015	Past Updates
Doxycycline	Hives	Not Specified		1/20/2016	Past Updates
Duricef (Cefadroxil)	Hives	Not Specified		1/20/2016	Past Updates
Penicillins		Not Specified		6/27/2015	Past Updates
Cleared by md not allergic to cillins					
Zithromax (Azithromycin)	Hives	Not Specified		1/20/2016	Past Updates
~~Amoxicillin (Bulk)~~	~~Rash~~	~~Low~~		~~6/27/2015~~	~~Past Updates~~
~~Not allergic / her doc~~					
~~Deletion Reason:~~ Resolution of allergy: No longer allergic to penicillin.					



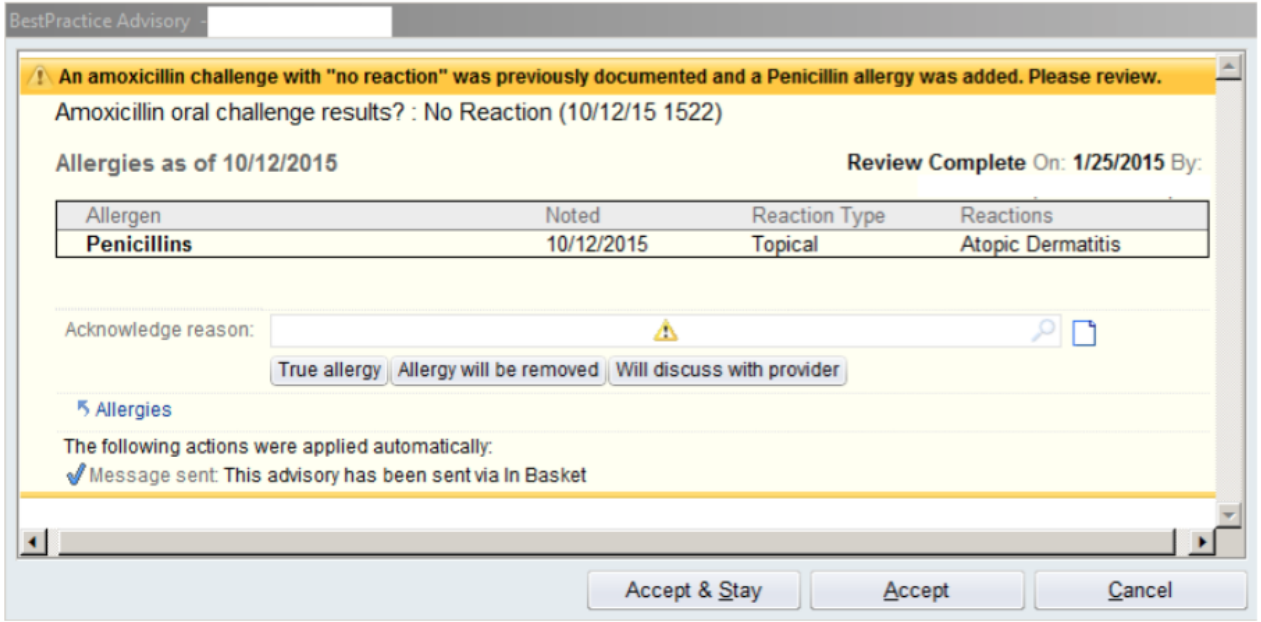
Allergies/Contraindications

Add a new agent | Add | Full Search | View Procedure-Allergy Interactions | View Drug-Allergy Interactions

	Reaction	Severity	Reaction Type	Noted	Updated
Allergies					
Penicillins	Unknown	Not Specified	Allergy/Hypersensitivity	6/15/2010	Past Updates
Tolerated Oxacillin and Amoxicillin.					
~~Ampicillin~~	~~Unknown~~	~~Not Specified~~	~~Allergy/Hypersensitivity~~	~~12/24/2009~~	~~Past Updates~~
~~Deletion Reason:~~ Resolution of allergy					

References

Preventing Re-labeling



- BPA + pharmacist counseling x 2 + wallet card + chart review → “re-labeling” reduction from 12.9% to 2.5%

Lutfeali *J Allergy Clin Immunol Pract* 2021

Acknowledgements

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