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IN MEDICINE

April 4th, 2023

Exciting Penicillin allergy updates

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Cases

Objectives

- Review penicillin allergy natural history, evaluation and management options
- Review exciting drug allergy updates for the following patient populations:
 - Pts with penicillin allergy label who need a cephalosporin or beta-lactam

How common is a pen allergy?

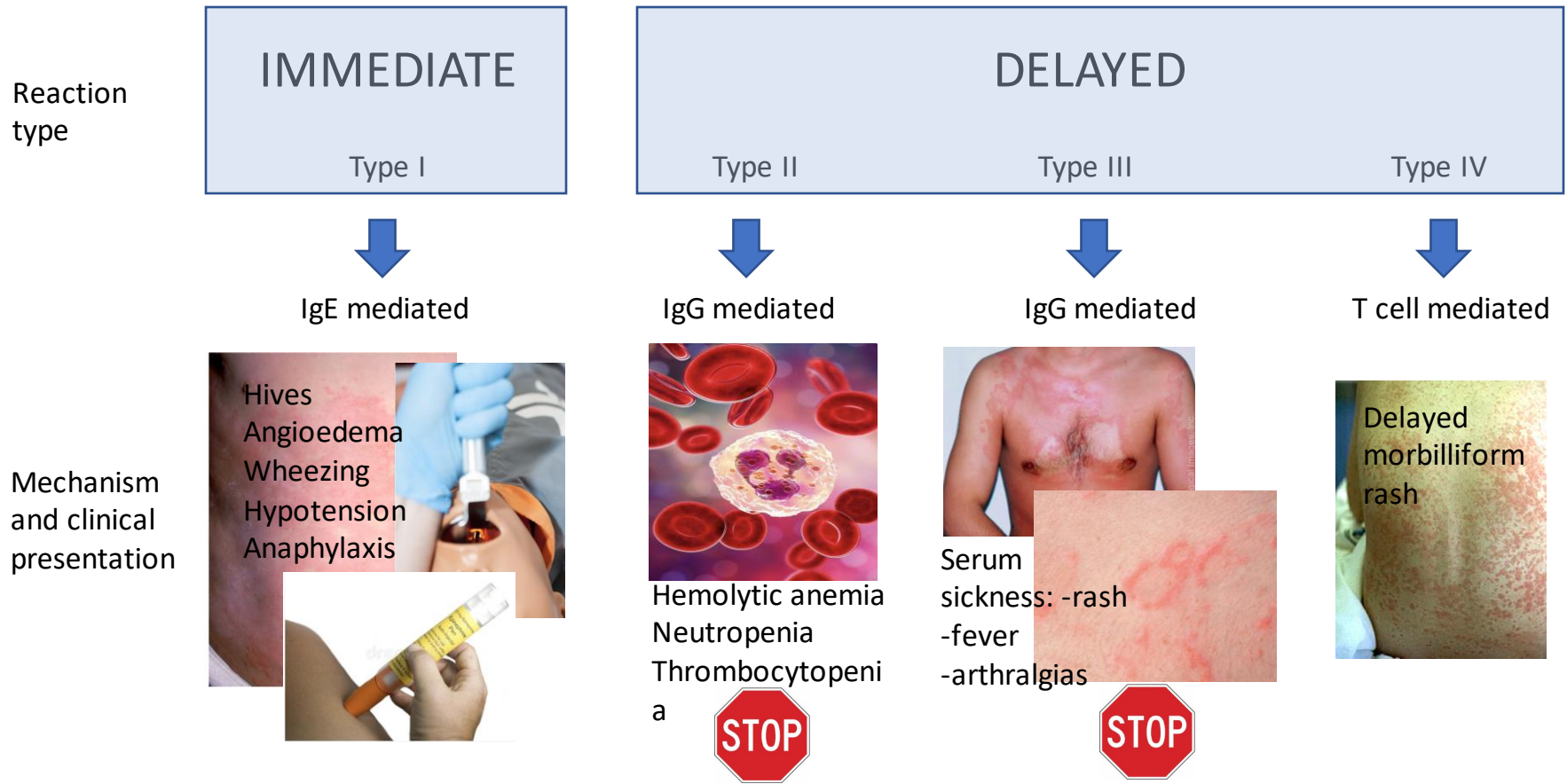
10% of the population reports a penicillin allergy but <1% of the whole population is truly allergic.



- Patients with penicillin allergy label are more likely to receive alternative therapy, associated with longer hospital stays, increased cost, risk of antibiotic resistance, more surgical site infections
- Approximately 80% of patients with IgE-mediated penicillin allergy lose their sensitivity after 10 years.

<https://www.cdc.gov/antibiotic-use/community/pdfs/penicillin-factsheet.pdf>

Types of hypersensitivity reactions



Other types of hypersensitivity reactions

Severe cutaneous drug reactions (SCARs)

- Drug Rash with Eosinophilia and Systemic Symptoms (**DRESS**) a.k.a drug induced hypersensitivity syndrome (**DiHS**)
- Steven Johnson's Syndrome/Toxic Epidermal Necrolysis (**SJS/TEN**)

AGEP (acute generalized exanthematous pustulosis)

- Fever, pustular eruption, leukocytosis hours to days after starting a drug, resolves rapidly with drug discontinuation

Fixed drug reaction

- Rash in the same location (anywhere on the body) with each use of specific drug, starting within hours (most often) to few weeks

History of the above is an indication for lifelong avoidance of the culprit drug



Organ specific hypersensitivity reactions

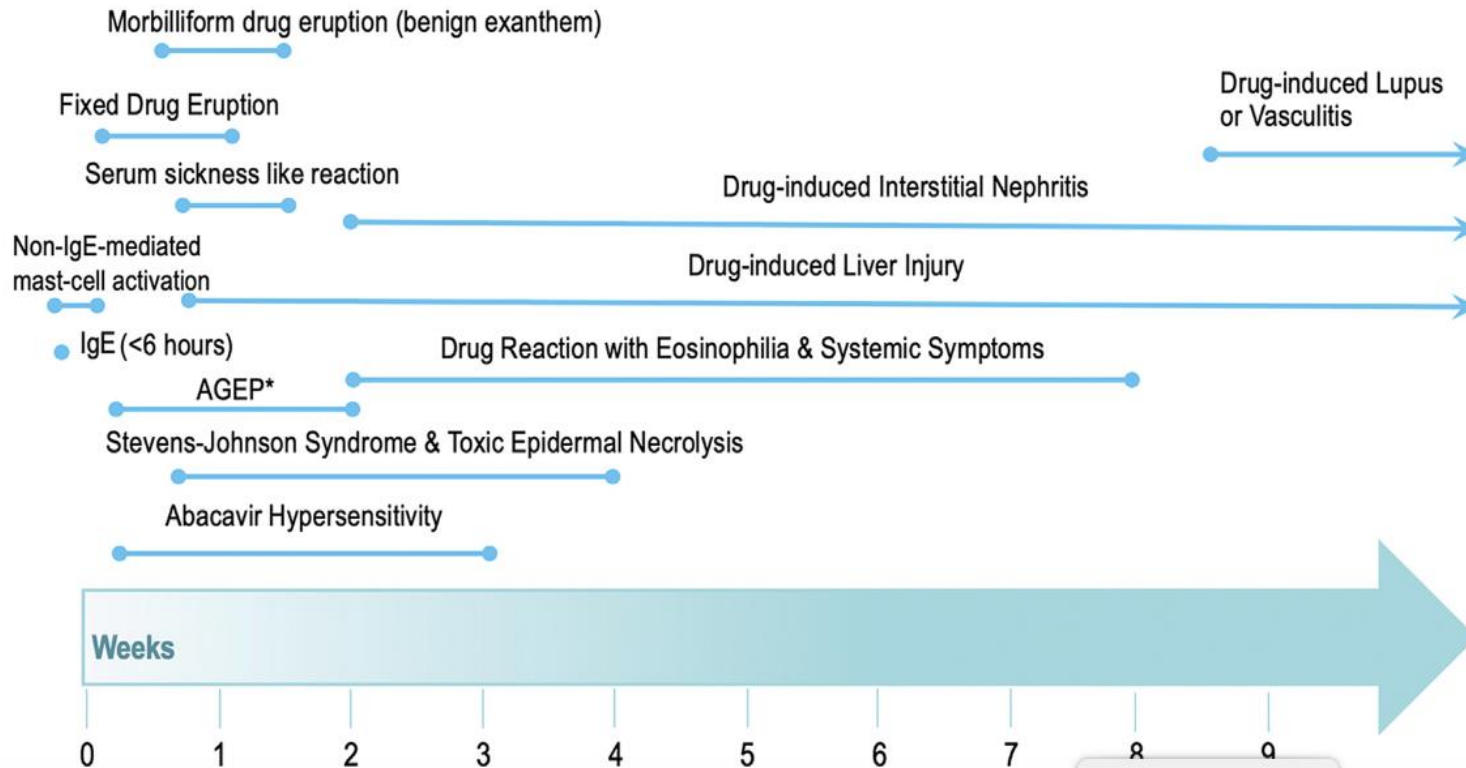
- Acute interstitial nephritis
- Autoimmune hepatitis



Characterizing the timeline

1338 KHAN ET AL

J ALLERGY CLIN IMMUNOL
DECEMBER 2022



* acute generalized exanthematous pustulosis

Screenshot



Types of hypersensitivity reactions

Reaction
type

IMMEDIATE

Type I

DELAYED

Type II

Type III

Type IV

Evaluation
and
management
options

Clinical history

Skin prick and intradermal testing*
Drug challenge
Desensitization

*Available for select drugs only,
this includes penicillin

Clinical history

Risk vs. benefit stratification
Limited options for skin based testing*
Drug challenge
Desensitization*

*None for delayed reactions to penicillin



Penicillin allergy: obtaining history

When was the reaction?

How soon after taking a dose?

How far into the course of the antibiotic?

Has the patient used the same antibiotic or antibiotic in the same class since the reaction?

What were the symptoms?

Did the patient require medical attention or treatment?

Is there anticipated need for use of this medication in the near future?



Toolkit A Penicillin Allergy History

Patient ID/ Sticker:

Date of reaction: _____

Route of last administration: ☐ Oral ☐ Intravenous

Reaction details (check all that apply):

Intolerance histories

- ☐ Isolated GI upset (diarrhea, nausea, vomiting, abdominal pain) ☐ Chills (rigors) ☐ Headache ☐ Fatigue

Low-risk allergy histories

- ☐ Family history ☐ Itching (pruritus)
☐ Unknown, remote (> 10 yr ago) reaction ☐ Patient denies allergy but is on record

Moderate-high risk allergy histories (potential IgE reactions)

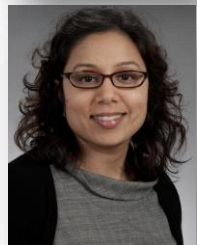
- ☐ Anaphylaxis ☐ Angioedema/swelling ☐ Bronchospasm (chest tightness)



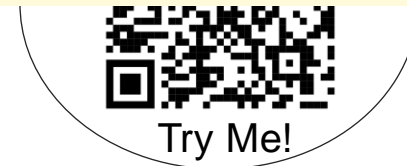
Vidya Atluri,
Senior ID Fellow
Infectious Disease



Paul Pottinger
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Clinical Associate Professor
Infectious Diseases



<https://redcap.iths.org/surveys/?s=7HJ8HMY87A7C7NRJ>

<https://jamanetwork.com/journals/jama/fullarticle/2735813>



Audience Response

You have a patient with a history of penicillin allergy (**reaction N/V/D**) and they require cefazolin for surgical prophylaxis.

As a clinician, you do the following:

- a. HARD STOP, change to vancomycin
- b. Give the patient a test dose of cefazolin
- c. Ok to give cefazolin without any additional monitoring



Assessment of Patient Reported Penicillin Allergy

Minor risk reactions

"never took b/c whole family is allergic"
"headache"
"upset stomach"

Non allergic minor reactions

(Appendix 1)

Low risk reactions

Any non-severe non-anaphylactic reaction

Ex.
Possible non-anaphylactic IgE mediated reaction >5 years ago

Maculopapular rash (type IV HSR*)

Medical record lists allergy but patient denies

Unknown reaction >10 years ago not requiring medical care (includes "mom told me that I had a reaction as a baby")

OK to use full dose:

Any penicillin

OK to administer after test dose:

Penicillin

OK to use full dose:

Cephalosporin
Aztreonam
Carbapenem
Non-beta-lactam antibiotics

*HSR: Hypersensitivity reaction. **See Appendix 4 for test dose procedure

** See beta lactam cross-reactivity table

Assessment of Patient Reported Penicillin Allergy

Higher risk (IgE mediated reactions that were severe or recent)

Anaphylaxis (any time in the past)

Any of the following within 6 hours of dosing and <5 years ago:

- Angioedema /laryngeal edema
- Hives/itching/rash/flushing
- Wheezing
- Hypotension
- Severe GI symptoms

Any urticarial rash within the past 5 years.

Positive penicillin skin test with no prior reaction

Any unknown reaction <10 years or >10 years if required medical care

OK to use full dose:

Cephalosporin with dissimilar side chain (ie. cefazolin, ceftriaxone, cefepime)
Carbapenem
Aztreonam
Non-beta-lactam antibiotics

If penicillin or cephalosporin with similar side chain indicated, call Allergy for Penicillin skin testing or desensitization

Can

porin?

	Cefazolin (1 st)	Cefaclor (2 nd)	Cefadroxil (1 st)	Cefamandole(2 nd)	Cefdinir (3 rd)	Cefepime (4 th)	Cefixime (3 rd)	Cefoperazone (3 rd)	Cefotaxime (3 rd)	Cefotetan (2 nd)	Cefoxitin(2 nd)	Cefpirome(4 th)	Cefpodoxime (3 rd)	Cefprozil (2 nd)	Ceftazidime (3 rd)	Ceftolozane (2nd)	Ceftibuten (3 rd)	Ceftizoxime (3 rd)	Ceftriaxone (3 rd)	Cefuroxime (2 nd)	Cephalexin (1 st)	Cephaloridine (1 st)	Cephadrine (1 st)	Cefditoren (3 rd)	Ceftaroline (5 th)	Amoxicillin	Ampicillin	Penicillin G	Aztreonam
Cefazolin (1 st)	-																												
Cefaclor (2 nd)		-	⚠	⚠									⚠								⚠				⚠	⚠	⚠		
Cefadroxil (1 st)		⚠	-	⚠									⚠								⚠				⚠	⚠	⚠		
Cefamandole (2 nd)		⚠	⚠	-				⚠	⚠				⚠								⚠			⚠	⚠	⚠	⚠		
Cefdinir (3 rd)					-		⚠																						
Cefepime (4 th)						-	⚠		⚠			⚠	⚠		⚠	⚠		⚠	⚠	⚠			⚠					⚠	
Cefixime (3 rd)					⚠	⚠	-		⚠			⚠	⚠		⚠	⚠		⚠	⚠	⚠			⚠					⚠	
Cefoperazone (3 rd)				⚠				-		⚠																			
Cefotaxime (3 rd)						⚠	⚠		-			⚠	⚠		⚠	⚠		⚠	⚠	⚠			⚠					⚠	
Cefotetan (2 nd)				⚠				⚠		-																			⚠
Cefoxitin (2 nd)											-									⚠		⚠						⚠	
Cefpirome (4 th)						⚠	⚠		⚠			-	⚠		⚠	⚠		⚠	⚠	⚠			⚠					⚠	
Cefpodoxime (3 rd)						⚠	⚠		⚠			⚠	-		⚠	⚠		⚠	⚠	⚠			⚠					⚠	
Cefprozil (2 nd)		⚠	⚠	⚠										-							⚠		⚠			⚠			
Ceftazidime (3 rd)						⚠	⚠		⚠			⚠	⚠		-	⚠		⚠	⚠	⚠				⚠				⚠	
Ceftolozane (2nd)						⚠	⚠		⚠			⚠	⚠		⚠	-		⚠	⚠	⚠				⚠				⚠	
Ceftibuten (3 rd)																	-	⚠											
Ceftizoxime (3 rd)						⚠	⚠		⚠			⚠	⚠		⚠	⚠		⚠	-	⚠			⚠					⚠	
Ceftriaxone (3 rd)						⚠	⚠		⚠			⚠	⚠		⚠	⚠		⚠	-	⚠			⚠					⚠	
Cefuroxime (2 nd)						⚠	⚠		⚠			⚠	⚠		⚠	⚠		⚠	⚠	-			⚠					⚠	
Cephalexin (1 st)		⚠	⚠	⚠										⚠							-		⚠			⚠	⚠		
Cephaloridine (1 st)										⚠												-						⚠	
Cephadrine (1 st)		⚠	⚠	⚠										⚠							⚠		-			⚠	⚠		
Cefditoren (3 rd)						⚠	⚠		⚠			⚠	⚠		⚠	⚠		⚠	⚠	⚠				-				⚠	
Ceftaroline (5 th)																									-				
Amoxicillin		⚠	⚠	⚠									⚠								⚠		⚠			-	⚠		
Ampicillin		⚠	⚠	⚠										⚠							⚠		⚠			⚠	-		
Penicillin G											⚠											⚠						-	
Aztreonam						⚠	⚠		⚠			⚠	⚠		⚠	⚠		⚠	⚠	⚠				⚠				-	

1. Drug challenge procedure
2. Induction of procedure

The Journal of Allergy and
Clinical Immunology: In Practice
2020 8s16-s116

citations

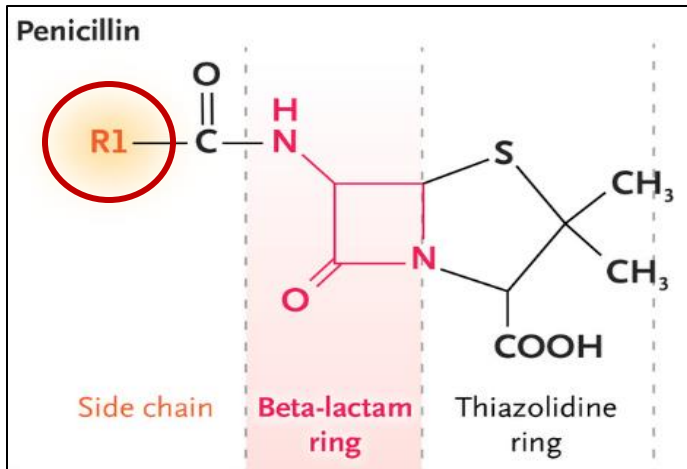


Audience Response

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- As a clinician, you do the following:
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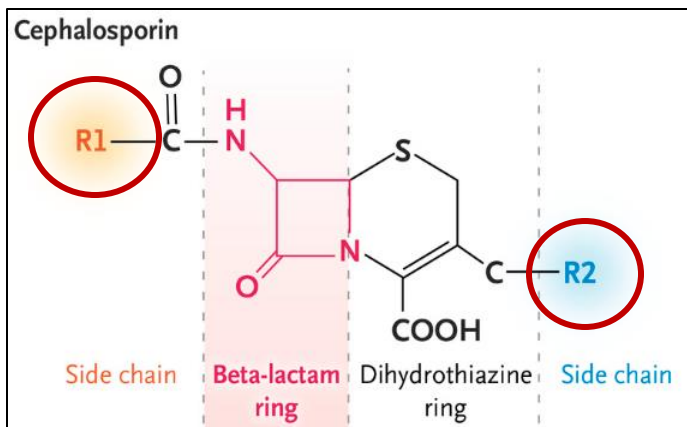


Why it's OK to give cefazolin



- Risk of cross-reactivity between penicillin and cephalosporins → similar **R-side chains**

- NOT because of shared beta-lactam ring



- Cefazolin → unique side chain that is distinct from other cephalosporins and beta-lactams



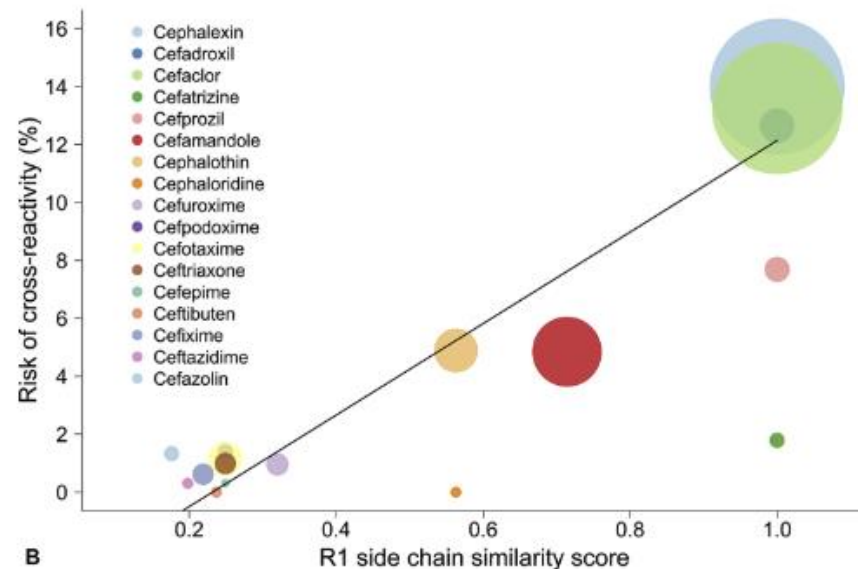
Cross-Reactivity to Cephalosporins and Carbapenems in Penicillin-Allergic Patients: Two Systematic Reviews and Meta-Analyses



Cephalosporins		Penicillins						
		Penicillin G	Penicillin V	Ampicillin	Amoxicillin	Cloxacillin	Piperacillin	Ticarcillin
1 st	Cefadroxil	0,371	0,220	0,618	1,000	0,179	0,060	0,333
	Cephalexin	0,592	0,333	1,000	0,618	0,208	0,043	0,371
	Cefazolin	0,176	0,110	0,099	0,088	0,078	0,032	0,088
	Cefradine	0,344	0,200	0,517	0,371	0,155	0,082	0,263
	Cephalothin	0,563	0,321	0,337	0,295	0,154	0,035	0,268
	Cefatrizine	0,371	0,220	0,618	1,000	0,179	0,060	0,333
	Cephaloridine	0,563	0,321	0,337	0,295	0,154	0,035	0,268
2 nd	Cefaclor	0,592	0,333	1,000	0,618	0,208	0,043	0,371
	Cefoxitin	0,330	0,245	0,211	0,180	0,148	0,043	0,180
	Cefprozil	0,371	0,220	0,618	1,000	0,179	0,060	0,333
	Cefuroxime	0,304	0,220	0,274	0,248	0,320	0,044	0,228
	Cefamandole	0,592	0,333	0,714	0,485	0,208	0,043	0,412
3 rd	Cefixime	0,110	0,110	0,098	0,157	0,219	0,084	0,138
	Cefotaxime	0,141	0,090	0,138	0,142	0,249	0,049	0,182
	Ceftazidime	0,092	0,087	0,092	0,142	0,198	0,064	0,127
	Ceftriaxone	0,141	0,090	0,138	0,142	0,249	0,049	0,182
	Cefpodoxime	0,141	0,090	0,138	0,142	0,249	0,049	0,182
	Cefdinir	0,147	0,083	0,143	0,156	0,207	0,047	0,238
	Ceftibuten	0,167	0,127	0,148	0,165	0,237	0,079	0,165
	Cefepime	0,141	0,090	0,138	0,142	0,249	0,049	0,182

A

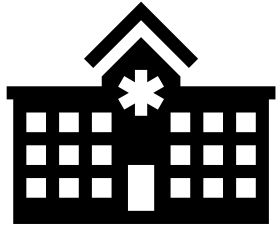
the risk of cross-reactivity to any carbapenem was 0.87%



B

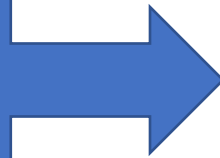
FIGURE 2. Similarity between R1 side chains of penicillins and cephalosporins and its association with the risk of cross-reactivity. **A**, Heatmap of similarities between R1 side chains. Score of "0" corresponds to no similarity and "1" to identical side chains. **B**, Association between the AR of cross-reactivity and R1 side chain similarity. Weights are inversely proportional to the estimated standard error of the AR of cross-reactivity obtained for each meta-analysis.

To remove or not remove



17.9%
cephalosporins used
in pen allergic

Turned off
cephalosporin
alert for patients
with penicillin
allergy

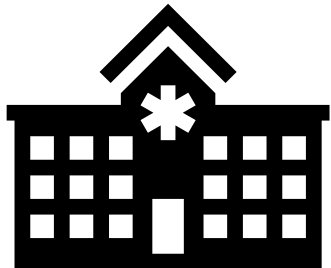


27.0%
cephalosporins
used in pen allergic

Ceph use increased by 47%
compared to other
hospital

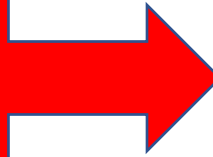
No significant differences
in anaphylaxis, new
allergies, or treatment
failures

NO difference in MRSA,
VRE or Cdiff



15.3% cephalosporins
used in pen allergic pts

Kept
cephalosporin
alert for patients
with penicillin
allergy



16.2%
cephalosporins used in
pen allergic

4 206 480 patients met all
inclusion criteria

10 652 014 antibiotic
courses

Assessment of Patient Reported Penicillin Allergy

Severe risk reactions (delayed severe cutaneous)

Steven Johnson syndrome/

Toxic epidermal necrolysis

Any severe/generalized rash with skin sloughing/skin peeling

Drug rash eosinophilia systemic symptoms (DRESS) syndrome

Serum Sickness - fever, rash, arthritis

Generalized bullous reactions

Acute interstitial nephritis

Drug induced hemolytic anemia/thrombocytopenia

Hepatitis

OK to use full dose:

Aztreonam

Non-beta lactam antibiotics

Avoid

Penicillin, Cephalosporins,
Carbapenem

If clinical indication for beta-lactam-
consult Allergy/Immunology and
Infectious Disease

Summary points

- Get a good allergy history from your patients
 - History of other beta-lactams administration
 - Onset of symptoms and how long ago
 - Characterization of symptoms
- Patients can get cephalosporins even if they have a penicillin allergy
- Educate our patients about the consequences of penicillin allergies



If you do skin testing at your site....

Recommend proactive approach to penicillin allergy de-labeling



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 delabeled

Consideration for direct amoxicillin challenge in adults with low-risk penicillin allergy histories

Recommendation to define a positive skin test as a wheal that is ≥ 3 mm than the negative control for prick/puncture or intradermal tests accompanied by a ≥ 5 mm flare

* AAAAI = American Academy of Allergy, Asthma, and Immunology

[https://www.jacionline.org/article/S0091-6749\(22\)01186-1/fulltext](https://www.jacionline.org/article/S0091-6749(22)01186-1/fulltext)

References and Reading

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[Evaluation and Management of Penicillin Allergy: A Review.](#)

Shenoy ES, Macy E, Rowe T, Blumenthal KG. JAMA. 2019 Jan 15;321(2):188-199. doi: 10.1001/jama.2018.19283. PMID: 30644987

Jones, B. M. & Bland, C. M. Penicillin skin testing as an antimicrobial stewardship initiative. *Am. J. Health. Syst. Pharm.* **74**, 232–237 (2017).











