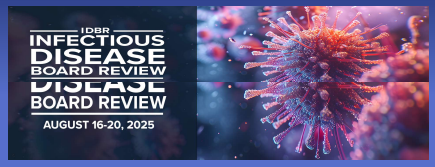

Penicillin Allergy

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8/5/2025

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Disclosures of Financial Relationships with Relevant Commercial Interests

- None

2

Question #1

A 73-year-old woman undergoing chemotherapy for cholangiocarcinoma is hospitalized for bacteremia and sepsis due to ampicillin-susceptible *Enterococcus faecalis*. She is currently receiving IV vancomycin but has had progressive renal injury. She has a history of allergy to amoxicillin that is listed in the records as rash; the family recalls that she went to the ED when the rash occurred several years earlier. She is delirious and not able to corroborate the history; no additional documentation of the reaction is available.

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3

Question #1

You are asked about optimal antibiotic treatment.

What do you advise?

A. Administer IV ampicillin without prior testing
B. Skin test for penicillin reaction; if negative then administer full dose ampicillin
C. Skin test for penicillin reaction; if negative then administer test dose ampicillin followed by full dose ampicillin
D. Desensitize to ampicillin
E. Continue vancomycin; there is no safe path for transition to ampicillin

4

4

53 Penicillin Allergies
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Penicillin (PCN) Allergy: Premise

- 10% of the US population have reported penicillin allergy
- Majority with history of PCN allergy can safely receive penicillins (with appropriate evaluation and testing)
  - Some reactions are not allergic
  - Allergic reactions do not always recur
  - Allergies often wane with time
- PCN allergy is associated with important morbidity
  - Higher risk of MRSA and VRE, *C difficile* colitis, surgical site infection
  - Greater associated antimicrobial costs and toxicities

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5

Likelihood of True Penicillin Allergy

- Positive skin test most likely with:
  - **F** ive or fewer years since the reaction
  - **A** naphylaxis or angioedema
  - **S** evere cutaneous adverse reaction
  - **T** reatment required for reaction

PEN-FAST Tool

Questions

1. **PEN - Penicillin allergy reported by patient**
2. F - Five years or less since reaction
3. A - Anaphylaxis or angioedema
4. S - Severe cutaneous adverse reaction
5. T - Treatment required for reaction

About

The PEN-FAST penicillin allergy clinical decision rule enables point-of-care risk assessment of patient-reported penicillin allergies. It requires three clinical criteria:

- Time (five years or less) from penicillin allergy episode (2 points)
- Phenotype (anaphylaxis/angioedema OR SCAR) (2 points)
- Treatment required for penicillin allergy episode (1 point)

The risk of a positive penicillin allergy test can be accurately predicted from these criteria:

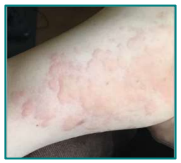
- 0 points – Very low risk of positive penicillin allergy test <1%
- 1-2 points – Low risk of positive penicillin allergy test 5%
- 3 points – Moderate risk of positive penicillin allergy test 20%
- 4 points – High risk of positive penicillin allergy test 50%

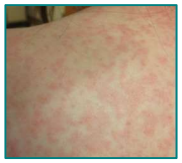
PEN-FAST Decision Tool: https://qxmd.com/calculate/calculator_752/pen-fast-penicillin-allergy-risk-tool 6

6

Deciphering Cutaneous Reactions

- IgE Mediated Reactions (hives)
  - Occur within minutes to hours, resolve within 24 hours
  - Often recurs with repeat exposure
- Benign T-cell mediated
  - Morbilliform or maculopapular
  - May have associated eosinophilia
  - Usual onset days to weeks
  - Persists longer than 24 hours and resolves over days to weeks
  - May not recur with subsequent exposure
  - Can ”treat through” with monitoring if drug essential





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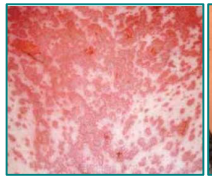
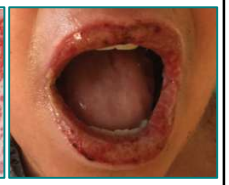
7

Deciphering Cutaneous Reactions

- Severe cutaneous reactions
  - DRESS, AGEP and SJS/TEN
  - Usual onset days to weeks
  - Blistering, mucosal involvement, severe skin desquamation, organ involvement
- Vague or unknown skin reaction
  - Evaluate risk of severe cutaneous reaction
  - Assume possibly IgE mediated





DRESS: Drug Reaction with Eosinophilia and Systemic Symptoms
AGEP: Acute Generalized Exanthematous Pustulosis
SJS: Stevens-Johnson Syndrome
TEN: Toxic Epidermal Necrolysis
Shenoy JAMA 2019;321:188
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8

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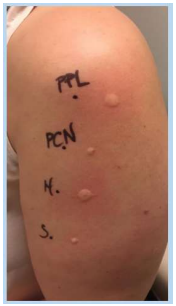
Options for Approaching PCN Allergy

1. Monitored oral challenge
   - Use with low-risk reactions (e.g., remote rash)
2. Penicillin skin testing
   - Procedure: percutaneous and intradermal administration of PPL (Pre-Pen®) and penicillin G (minor antigen)
   - Use with history of or suspected IgE mediated reaction
   - Consider for unknown history when other high-risk features
   - If negative, followed by test dose of amoxicillin or of implicated or desired drug



Positive Intradermal Test

PPL: penicilloyl polylysine Shenoy JAMA 2019;321:188 9

9

Options for Approaching PCN Allergy

3. Graded challenge (also called test dose procedure)
   - Procedure: 1/4th to 1/10th dose, followed by full dose 30-60 minutes later
   - Can be used as a first step if suspicion for immediate reaction is low
   - Also used after negative PCN skin testing
4. Desensitization
   - Administration of increasing doses every 15-30 minutes until therapeutic dose reached
   - Used for positive skin test and/or confirmed immediate reaction when a penicillin is the best therapy for an important infection
   - Desensitization wanes with missed doses (3 half-lives)
5. Use of alternate therapy

10

10

Putting it All Together: Penicillin Skin Reactions

IgE Mediated (Urticaria)	Penicillin Skin testing If positive: desensitization or alternative therapy If negative: test dose amoxicillin or desired drug
Benign Skin Rash	If a penicillin: amoxicillin oral challenge Any cephalosporin safe
Severe Cutaneous Adverse Reaction SJS/TEN, DRESS, AGEP	Avoid beta-lactams

11

11

What About Non-cutaneous Reactions?

IgE Mediated Angioedema and Anaphylaxis	Penicillin Skin testing If positive: desensitization or alternative therapy If negative: test dose amoxicillin or desired drug
Antibody mediated (*Hemolytic anemia, neutropenia, thrombocytopenia*) Immune-complex (*vasculitis, serum sickness*) Cell-mediated (*Interstitial nephritis, drug-induced liver injury*)	No available testing In general, when severe avoid beta-lactams

12

12

53 Penicillin Allergies

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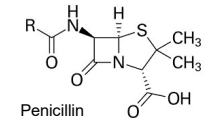
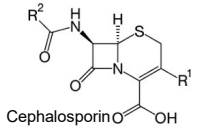
PCN Allergy and Use of Cephalosporins

- Significant cross reactivity rare
  - higher with earlier generation cephalosporins
- For IgE mediated PCN allergy:
  - use structurally dissimilar cephalosporin (e.g. all 3rd/4th generation; cefazolin) without prior testing
  - use structurally similar (most 1st/2nd gen) after PCN skin testing and amoxicillin challenge
- Mild delayed drug rash:
  - any cephalosporin OK
- Avoid if severe reaction to PCN





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13

Question #2

A 43-year-old man with diabetes is hospitalized with a closed tibial fracture. Three years ago, when he was being treated for a foot infection with cefepime he developed a very itchy rash after several weeks of treatment. The anesthesiologist calls to ask advice about surgical antibiotic prophylaxis prior to operative fixation.

14

14

Question #2

What do you do counsel?

A. Administer clindamycin
B. Administer cefazolin
C. Administer cefazolin after intraoperative test dose
D. Administer ceftriaxone
E. Administer vancomycin

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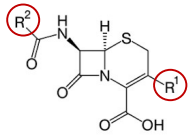
Cephalosporin Allergy



- Allergy often arises from side chains
  - More common than beta-lactam ring
- Probability of reaction higher when cephalosporins with similar side chains used (R1 > R2)
- Side chain tables are available to guide cross-reactivity

Similar Side Chain Groups (R1)
Amoxicillin, Cefadroxil, Cefprozil
Ampicillin, Cefaclor, Cephalexin
Cefepime, Ceftriaxone, Cefotaxime, Cefpodoxime
Ceftazidime, Cefiderocol, Aztreonam

https://adsp.nm.org/allergy-resources.html

16

16

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A Few More Testable Points

- Selective allergy to the aminopenicillins occurs
  - A patient that tolerates PCN may still be allergic to aminopenicillins
  - A patient that tolerates aminopenicillins is not allergic to PCN
- Cefazolin has different side chains from all other cephalosporins
  - Can be administered in patients with IgE mediated reaction to penicillins
- Ceftazidime does not share side chains with ceftriaxone or cefepime
- Aztreonam can be safely used in individuals with beta-lactam allergy except for those allergic to ceftazidime or cefiderocol

17

17

Thank you and good luck!

"The penicillin looks good."

18

18