Penicillin Allergy

Sandra B. Nelson, MD

Massachusetts General Hospital
Harvard Medical School

6/4/2026

1

Disclosures of Financial Relationships with Relevant Commercial Interests

- None

2

Penicillin (PCN) Allergy: Premise

- 10% of the US population have penicillin allergy label
- Majority with history of PCN allergy can safely receive penicillins (with appropriate evaluation and testing)
  - Some reactions are not allergic
  - Allergies often wane with time
  - Allergic reactions do not always recur
- 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

3

3

Approach to Penicillin Allergy

- Penicillin allergy history
  - Type of reaction
  - Timeline of reaction
  - Severity of reaction
- Assess need (and timeline) for beta-lactam drug

4

4

OL9 Penicillin Allergy
Speaker: Sandra Nelson, MD

Question #1

A 44-year-old previously healthy woman was diagnosed with septic arthritis of the knee due to *Streptococcus dysgalactiae*. After surgical debridement and several days of IV ceftriaxone, she was discharged on high-dose oral amoxicillin. Two weeks following discharge she developed fever and malaise, followed by a generalized maculopapular rash involving her torso and extremities.

On examination, the rash had become confluent in areas and involved >50% of her skin. There was no mucosal involvement. Other notable examination findings included facial edema and generalized lymphadenopathy. The surgical incision was healing well without effusion or erythema.

Laboratory studies:
WBC 12.6 (68% pmns;13.5% eosinophils) Hgb 11.4 PLT 488
BUN 24 Creat 1.7
AST 78 ALT 112 Alk Phos 144 Tbili 0.8

5

5

Question #1

What do you advise?

A. Continue amoxicillin with close monitoring
B. Stop amoxicillin, start cefadroxil
C. Admit to the hospital, stop amoxicillin, resume IV ceftriaxone
D. Admit to the hospital, stop amoxicillin, start vancomycin
E. Admit to the hospital, stop amoxicillin, start vancomycin and corticosteroids

6

6

Question #1

What do you advise?

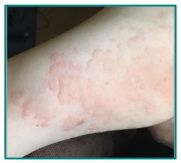
A. Continue amoxicillin with close monitoring
B. Stop amoxicillin, start cefadroxil
C. Admit to the hospital, stop amoxicillin, resume IV ceftriaxone
D. Admit to the hospital, stop amoxicillin, start vancomycin
E. Admit to the hospital, stop amoxicillin, start vancomycin and corticosteroids

7

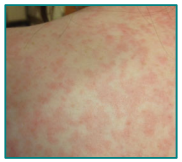
7

Deciphering Cutaneous Reactions

- IgE-mediated reactions (urticaria)
  - Occur within minutes to hours, resolve within 24 hours
  - Often recurs with repeat exposure
  - Wheal and flare appearance
  - Isolated urticaria may be considered non-severe



- Benign T-cell mediated
  - Morbilliform or maculopapular, usually pruritic
  - May have associated eosinophilia
  - Usual onset days to weeks
  - Persists longer than 24 hours; resolves over days to weeks
  - May not recur with subsequent exposure
  - Can "treat through" with monitoring if drug essential



Shenoy JAMA 2019;321:188

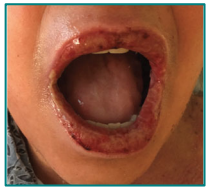
8

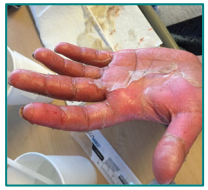
8

OL9 Penicillin Allergy
Speaker: Sandra Nelson, MD

Severe Cutaneous Adverse Reactions (SCARs)

- T-cell mediated
- Types
  - Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS)
  - Acute Generalized Exanthematous Pustulosis (AGEP)
  - Stevens-Johnson Syndrome / Toxic Epidermal Necrolysis (SJS/TEN)
- Common Features:
  - Delayed onset
  - Blistering
  - Mucosal involvement
  - Severe skin desquamation
  - Organ involvement



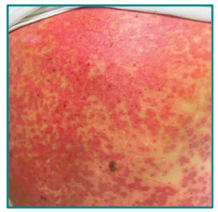


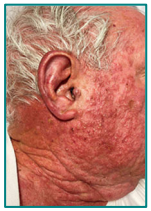
Shenoy JAMA 2019;321:188 9

9

DRESS Syndrome

- Onset 10-14 days after drug exposure but may be longer
- Clinical Features:
  - Rash (often morbilliform, but may be pleomorphic)
  - Facial edema
  - Generalized lymphadenopathy
  - Organ involvement (renal and hepatic most common)
  - Eosinophilia and atypical lymphocytosis
- Most common implicated antimicrobials:
  - Vancomycin, trimethoprim-sulfamethoxazole
  - Also β-lactams, anti-TB medications, dapsone, minocycline
- Treatment: drug discontinuation, prolonged steroids



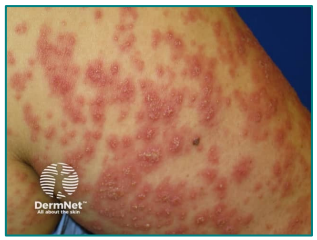


DRESS: Drug Reaction with Eosinophilia and Systemic Symptoms Kroshinsky et al. NEJM 2024; 391:2242 10

10

AGEP

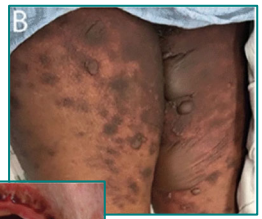
- Onset earlier, within 24-72 hours
- Clinical features:
  - Fever and rash (with small pustules)
  - Desquamation and mucosal involvement less common than DRESS
- Implicated antimicrobials
  - β-lactams, macrolides, clindamycin, fluoroquinolones
- Treatment
  - Drug discontinuation, topical steroids
- Less severe than DRESS

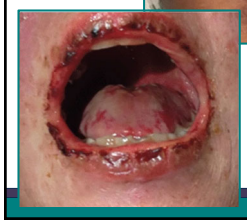


AGEP: Acute Generalized Exanthematous Pustulosis 11

11

Stevens-Johnson Syndrome





- Onset 5-28 days after drug exposure
- Clinical features:
  - Fever, URI symptoms, cough
  - Then erythematous, targetoid, annular, or purpuric macules that progress to flaccid bullae
  - Mucosal involvement common (oral, ocular, genital)
- Implicated antimicrobials:
  - Trimethoprim-sulfamethoxazole most common
  - Also: β-lactams, fluoroquinolones, macrolides, nitrofurantoin
- Treatment:
  - Drug discontinuation, wound care
  - Steroids and other immunomodulators

Shah et al. Am J Clin Dermatol 2024;25:891 12

12

OL9 Penicillin Allergy

Speaker: Sandra Nelson, MD

Question #2

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 three years ago. She is delirious and not able to corroborate the history; no additional documentation of the reaction is available.

13

Question #2

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

14

Question #2

You are asked about optimal antibiotic treatment

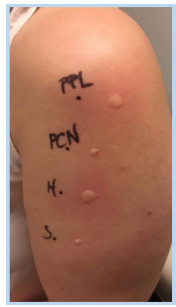
What do you advise?

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

15

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

16

OL9 Penicillin Allergy
Speaker: Sandra Nelson, MD

Options for Approaching PCN Allergy

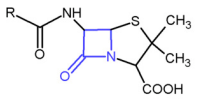
3. Graded challenge (also called test dose procedure)
   - Procedure: 1/4th to 1/10th dose, followed by full dose 30-60 minutes later
   - Can be used as a first step if suspicion for immediate reaction is low
   - Also used after negative PCN skin testing
4. Desensitization
   - Administration of increasing 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

17

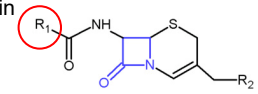
17

PCN Allergy and Use of Cephalosporins

- Significant cross reactivity rare
  - Based on R1 side chain structure
- For IgE mediated PCN allergy:
  - Use structurally dissimilar cephalosporin without prior testing
  - Use structurally similar cephalosporin after PCN skin testing and amoxicillin challenge
- Mild delayed drug rash:
  - Any cephalosporin OK
- Avoid if severe reaction (e.g. SCAR) to PCN



Penicillins



Cephalosporins

18

18

Putting it all together: penicillin reactions (IgE)

Isolated urticaria	If PCN or cross-reactive cephalosporin indicated: PCN Skin testing If positive: desensitization or alternative therapy If negative: test dose amoxicillin or desired drug Safe to administer non-cross-reactive cephalosporin
Extensive urticaria Urticaria with anaphylaxis or angioedema	PCN Skin testing If positive: desensitization or alternative therapy If negative: test dose amoxicillin or desired drug

19

19

Putting it all together: non-IgE penicillin reactions

Benign Skin Rash	If a penicillin indicated: amoxicillin oral challenge Any cephalosporin safe
Severe Cutaneous Adverse Reaction SJS/TEN, DRESS, AGEP	Avoid β-lactams
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 β-lactams

20

20

Question #3

A 35-year-old healthy woman presents to your primary care clinic with sore throat and fever. Two of her school-age children were recently diagnosed with strep throat.

On exam, she is afebrile. She has pharyngeal erythema, tonsillar exudate, and bilateral cervical lymphadenopathy.

Rapid Group A streptococcal testing is positive.

She has a history of penicillin allergy that occurred when she was a child. She has no direct recall of the reaction. She has not to her knowledge received penicillins or cephalosporins since.

21

21

Question #3

What do you do advise?

A. Prescribe amoxicillin with monitored first dose
B. Prescribe clindamycin
C. Prescribe cephalexin
D. Prescribe azithromycin
E. Urgent referral to allergy clinic

22

22

Question #3

What do you do advise?

A. Prescribe amoxicillin with monitored first dose
B. Prescribe clindamycin
C. Prescribe cephalexin
D. Prescribe azithromycin
E. Urgent referral to allergy clinic

23

23

Clinical Decision tools

Designed to identify low risk penicillin allergies

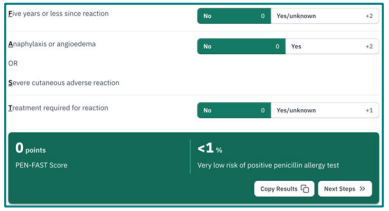
Clinical features:

- **F** ive or fewer years since the reaction (2 points)
- **A** naphylaxis or angioedema OR
  S evere cutaneous adverse reaction (2 points)
- **T** reatment required for reaction (1 point)

Risk of positive allergy test:

- 0-2 points: low risk → Oral challenge
- ≥ 3 points: additional triage

PEN-FAST Tool



https://www.mdcalc.com/calc/10422/penicillin-allergy-decision-rule-pen-fast

24

24

OL9 Penicillin Allergy
Speaker: Sandra Nelson, MD

Question #4

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.

25

25

Question #4

What do you do counsel?

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

26

26

Question #4

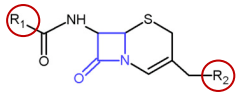
What do you do counsel?

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

27

27

Cephalosporin Allergy



- Allergy arises from side chains
- 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, Loracarbef
Cefepime, Ceftriaxone, Cefotaxime, Cefpodoxime, Cefuroxime
Ceftazidime, Cefiderocol, Aztreonam

- Avoid cephalosporins if SCAR to cephalosporin

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

28

28

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
- Cefaclor is associated with serum sickness reaction in children
  - Does not predict cross reactivity with penicillin or other cephalosporins

29

29

A Few More Testable Points

- 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

30

30

Thank you and good luck!

"The penicillin looks good."

31

31