25 – Penicillin Allergy

Speaker: Sandra Nelson, MD

Penicillin Allergies

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Disclosures of Financial Relationships with Relevant Commercial Interests

- **None**

Penicillin (PCN) Allergy: Premise

- 10% of the US population have documentation of penicillin allergy
  - Rash most common adverse drug reaction (ADR)
  - Others include "unknown", angioedema, GI symptoms, itching
  - More common in older adults and hospitalized patients
- Vast majority of patients with penicillin allergy can be made to tolerate penicillin
  - Reactions are mild drug rashes that do not always recur
  - Reactions wane with time
  - Some reactions are not allergic

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PCN Allergy: Consequences

- Alternative antimicrobial use
  - Less effective, more toxic, more broad spectrum
- Associated with:
  - increased risk of MRSA infections
  - increased risk of C difficile colitis
  - increased risk of surgical site infection
  - increased mortality
- An important target of stewardship efforts

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Case #1

67 year old woman is hospitalized with nosocomial meningitis due to MSSA. She has a history of allergy to penicillin that is listed in the records as rash; the family recalls that she went to the ED when the rash occurred. She is not able to corroborate history. She has not received penicillin or cephalosporin antibiotics since the rash occurred a few years ago. Two of her daughters have allergies to penicillin.

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Case #1: Vote

You are asked about optimal antibiotic treatment. What do you advise?

A. Administer nafcillin without prior testing
B. Administer nafcillin after test dose
C. Skin test for penicillin reaction; if negative then administer nafcillin after test dose
D. Administer vancomycin
E. Desensitize to nafcillin

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Classification of Drug Allergy (Gell and Coombs)

Type	Immune mechanism	Clinical example
I: Immediate (usually within one hour)	IgE-mediated	Anaphylaxis, Urticaria, Angioedema, Bronchospasm
II: Often <72 hours, but up to 2 weeks	Antibody-dependent (IgG)	Hemolytic Anemia Thrombocytopenia Neutropenia
III: Days to weeks	Immune Complex	Serum Sickness Vasculitis
IV: Days to weeks	Cell mediated	Cutaneous drug reactions - Mild maculopapular - Severe (DRESS, SJS, TEN) Interstitial nephritis Hepatitis

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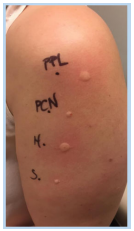
Options for Approaching PCN Allergy

- Monitored oral challenge
  - Useful for outpatients with low-risk reactions (remote rash, pruritus) without imminent need of beta-lactam therapy
- Penicillin skin testing
  - Epicutaneous and intradermal administration of PLL (penicilloyl polylysine, Pre-Pen) and penicillin G
  - Useful for inpatients and outpatients with a history of IgE mediated reaction
  - Useful for sick patient with unknown reaction
  - Avoid in unstable patients



Shenoy JAMA 2019;321:188

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Options for Approaching PCN Allergy

- Graded Challenge (1/10th test dose)
  - As a first step if suspicion for immediate reaction is low
  - After negative PCN skin testing when a related drug is desired (e.g. nafcillin) or in high risk of IgE mediated reaction
- Desensitization
  - 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)
- Use of alternate therapy

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Classification of Drug Allergy (Gell and Coombs)

Type	Immune mechanism	Clinical example	Management
I: Immediate (usually within one hour)	IgE-mediated	Anaphylaxis, Urticaria, Angioedema, Bronchospasm	Penicillin skin testing followed by drug challenge
II: Often <72 hours, but up to 2 weeks	Antibody-dependent (IgG)	Hemolytic Anemia Thrombocytopenia Neutropenia	No testing; generally avoid re-use
III: Days to weeks	Immune Complex	Serum Sickness Vasculitis	No testing; generally avoid re-use
IV: Days to weeks	Cell mediated	Cutaneous drug reactions Interstitial nephritis Hepatitis	Varies; for severe reactions and organ involvement avoid re-use

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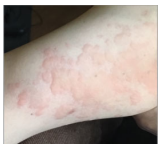
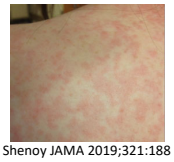
Deciphering Cutaneous Reactions

- IgE Mediated Reactions (hives)
  - Occur within minutes to hours
    - ➡ skin testing appropriate
  - if positive – desensitize or use alternate therapy
  - If negative – graded challenge



- Benign T-cell mediated
  - morbilliform or maculopapular
  - Usual onset days to weeks; persists >24 hours and resolves over days to weeks
    - ➡ cephalosporins safe; PCNs by test dose



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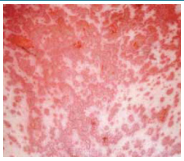
Deciphering Cutaneous Reactions

- Severe cutaneous reactions
  - DRESS and SJS/TEN
  - Usual onset days to weeks
  - Blistering, mucosal involvement, severe skin desquamation, organ involvement
    - ➡ avoid any beta-lactam
- Unknown reaction
  - If hospitalized and/or critical illness:
  - Assume possibly IgE mediated
    - ➡ skin test then test dose



Stern NEJM 2012;366:2492
Shenoy JAMA 2019;321:188

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Case #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 piperacillin-tazobactam 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.

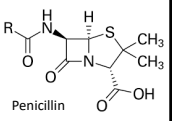
Case #2: Vote

What do you do counsel?

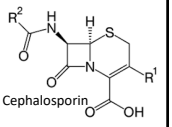
A. Administer clindamycin
B. Administer cefazolin
C. Administer cefazolin after intraoperative test dose
D. Administer ceftriaxone
E. Administer vancomycin

PCN Allergy and other beta-lactams

- Cephalosporins:
  - Significant cross reactivity 2%
  - Higher risk with earlier generation cephs
  - If suggestive type I PCN allergy:
    - use 3rd/4th gen (graded challenge preferred)
    - use 1st/2nd after PCN skin testing
  - If mild type IV reaction:
    - any cephalosporin OK
  - Avoid if severe reaction to PCN
- Carbapenems <1%
- Aztreonam: no cross reactivity

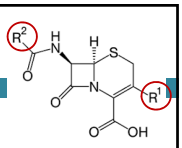


Penicillin



Cephalosporin

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)
- Testable point:
  - Cefazolin has different side chains from all other cephalosporins

Thank you and good luck!


"The penicillin looks good."