The Role of Beta Lactam Allergy in Antibiotic Stewardship

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Disclosures

- I have no disclosures.
Outline

- Discuss how beta lactam allergies lead to worse health outcomes
- Review beta-lactam allergy epidemiology and cross-reactivity
- Introduce a pathway for non-allergists to approach beta-lactam allergy
Would you feel comfortable giving...

- Amoxicillin to a 74 yo F with a history of childhood rash to penicillin?
  - How about cefepime?

- Ceftriaxone to a 56 yo M with a history of penicillin anaphylaxis?

- Cefpodoxime to a 62 yo F with a history of angioedema to cephalexin?
Beta Lactam Antibiotics

- Include **penicillins** (top) and **cephalosporins** (bottom), carbapenems, and monobactams
- Have a beta lactam ring structure in common, highlighted in red
- Our focus today is on penicillin and cephalosporin allergy
- Up to 10% of the general population and 15% of hospitalized patients list penicillin as an allergy\(^1\), \(^2\)
Beta Lactam Allergy: Not a Benign Diagnosis
Penicillin “Allergic” Patients are More Likely to...

- Receive fluoroquinolones, vancomycin, clindamycin$^3, 4$
- Harbor drug resistant organisms such as MRSA (14-55%)$^3, 5$ and VRE (30%)$^3$
- Develop *C. difficile* colitis (23%-35% increase)$^3, 5$
  - Estimated mortality rate is 7%-35%$^6, 7$
Penicillin “Allergic” Patients are More Likely to...

- Experience treatment failure (33% vs. 16%), infection recurrence (15% vs. 9%), and death (18% vs. 7%) from MSSA bacteremia
- Experience treatment failure in gram negative bacteremia (38.7% vs 27.4%)
- Experience a delay in empiric antibiotic treatment (Ave: 50 min)
- Experience a surgical site infection (50% increased odds)
Penicillin “Allergic” Patients are More Likely to…

- Develop new antibiotic “allergies” with alternative therapies\(^3, 8\)
- Have an allergic reaction to vancomycin than cefazolin (3% vs. 2.4\%)\(^8\)
- Have side effects or toxicities from second-line therapies\(^8\)
Economic Costs

- Penicillin-allergic patients have higher drug costs
  - $14-193 higher outpatient antibiotic cost per patient\(^9\)
  - $300 more per patient per day of inpatient antibiotic therapy\(^4\)
  - $1253 more in length of stay costs per patient per admission\(^3\)

- Penicillin-allergic patients have longer hospital stays
  - 10% longer hospital stays, estimated cost of $21.5 million per year\(^3\)
Penicillin Allergy: Not an Accurate Diagnosis

Most patients who list a penicillin allergy are not truly allergic

- Less than 10% of these allergies are confirmed when tested\(^1\)
- Two studies showed only 3% were truly allergic, and one of them was a very large study of 1300 patients\(^3,10\)
AAAAAI Consensus Statement

“A misdiagnosis of allergy to beta lactams results in dramatically poorer clinical outcomes for patients and is not acceptable any longer.”11
Penicillin Allergy: How Did We Get Here?
Why is Penicillin Allergy so Over Diagnosed?

- **Childhood viral rashes are often misdiagnosed as drug rashes**
  - Only 7-16% of kids with “drug allergy” during an infection later test positive to the drug\(^1\)

- **Even if a patient is truly allergic, most people “outgrow” penicillin allergy**
  - Over 50% of people with confirmed allergy to penicillin lose their allergy after 5 years\(^1\)
  - Over 80% will lose it in 10 years\(^1\)
Cephalosporin Trivia

- In a patient reporting a penicillin allergy, what is the overall likelihood of reacting to any cephalosporin?
  - A) <1%
  - B) 2%
  - C) 10%
  - D) 15%
Cephalosporin Trivia

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- In a patient with *confirmed* penicillin allergy, what is the overall likelihood of reacting to *any* cephalosporin?
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In a patient with confirmed penicillin allergy, what is the overall likelihood of reacting to any cephalosporin?

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- D) 15%
Cephalosporin Cross-Reactivity with Penicillin

- Overall cross-reactivity based on multiple studies is actually very low:
  - In a reported (but unconfirmed) penicillin allergy: 0.1%¹
  - In a confirmed penicillin allergy: 2%¹
  - New cases of cephalosporin allergy (with no prior penicillin allergy) occur at a rate 0.5-1% in the US³
  - These numbers exclude patients with penicillin anaphylaxis
Where Did 10% Come From?

- Drug preparations have changed. Early on these drugs were created from mold cultures; now they are synthetic.

- The available cephalosporins have changed.
Throwing the Beta Lactams out with the Bath Water

- Despite more reassuring statistics, the 10% myth is still quoted by clinicians, and there is still reluctance to use cephalosporins in patients with penicillin allergy

- Result: more broad spectrum antibiotic use
Penicillin Skin Testing

- Limited resource: scarcity of allergists
- Time consuming (takes about 1 hour)
- Reagents expensive (~$100)
- If negative: <2% risk of allergy
- If positive: 50% risk of allergy
- Must be followed by a drug challenge to confirm

http://www.chp.edu/our-services/allergy-immunology/skin-allergy-testing
Predicting Cross-Reactivity:
Beta Lactam Allergy is not a Class Effect
Cephalosporin Cross-Reactivity with Penicillin

- Research indicates cross-reactivity is due almost entirely to the R1 side chain, not the beta lactam ring.
Cephalosporin Cross-Reactivity with Penicillin

- Research indicates cross-reactivity is due almost entirely to the R1 side chain, not the beta lactam ring.
### Example of Cross-Reactivity Chart

**Beta Lactam Side Chain Cross-Reactivity Chart**

*X* = shared side chain (avoid)

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<tr>
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<th><strong>Penicillins</strong></th>
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<th><strong>2nd Gen. CEPH</strong></th>
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Cephalosporin Cross-Reactivity with Penicillin

- A meta-analysis found an average rate of cross-reactivity between **1-10% for first generation cephalosporins** and **NO significant cross-reactivity for 2nd generation and higher cephalosporins**
  - Most cross-reactive side chains are in **1st and 2nd generation cephalosporins**
- AAP has advocated giving **2nd gen and up cephalosporins** to patients with non-anaphylactic reactions to penicillin for over 10 years now
Cephalosporin Cross-Reactivity with Penicillin

- Highest cross-reactivity for confirmed penicillin allergy observed in cefadroxil (27%)\textsuperscript{10}

- Risk for cephalexin reaction in confirmed penicillin allergy is 7-10\% vs. 1\% for penicillin non-allergic\textsuperscript{12,13}

- Cefazolin is low risk. There were NO reactions in a retrospective cohort of 299 penicillin allergic patients who got cefazolin for orthopedic surgery\textsuperscript{17}
Cephalosporin Anaphylaxis in Penicillin “Allergy”

• Study of 820,000 patients found that, out of nearly 70,000 patients with a PCN allergy label who got cephalosporins, only 3 had anaphylaxis over a period of 2 years (0.00005%)³

• Even if your patient was truly allergic to penicillin, they are still more likely than not to tolerate a first generation cephalosporin.
Cephalosporin/Cephalosporin Cross-Reactivity

NOT a class effect

- Based on the side chains (R1 and R2)
- Retrospective study of 820,000 patients: 3,313 patients with cephalosporin allergy label who received 6,404 courses of cephalosporins – no cases of anaphylaxis\(^3\)
Cephalosporin/Cephalosporin Cross-Reactivity

- Patients with one cephalosporin allergy may safely receive other cephalosporins via test dose
- Choose a cephalosporin that doesn’t share a side chain
Penicillin and Cephalosporin Allergies: Applying the Data
Blumententhal 2015

- 2014 MGH study looked at the safety and efficacy of using a beta lactam use pathway in penicillin and cephalosporin allergic patients \(^{30}\)
- Algorithm reduced broad-spectrum antibiotic use by 5-30%
- No increase in adverse drug reactions.
- Patients received beta lactams 2 days faster than before the pathway was introduced
- We have customized these MGH guidelines for use at DHMC
Dartmouth-Hitchcock Medical Center
Penicillin Allergy Treatment Guideline

**MILD REACTION**

Minor or Maculopapular rash, including a rash with childhood penicillin exposure (i.e., nonspecific rashes and mild Type IV HSRs)

EMR lists allergy, but patient denies

**TYPE I (IgE-mediated) HSR**

- Anaphylaxis
- Angioedema
- Wheezing
- Laryngeal edema
- Hypotension
- Hives/urticaria*

OR

Unknown reaction WITHOUT mucosal involvement, skin desquamation or organ involvement

**TYPE II-IV (Severe) HSR**

- Serum sickness
- Stevens-Johnson Syndrome
- Toxic Epidermal Necrolysis
- Acute Interstitial Nephritis
- Drug-Induced Hepatitis
- Drug Rash Eosinophilia and Systemic Symptoms (DRESS) Syndrome
- Hemolytic Anemia

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**CAN GIVE:**

| Full Dose | 3rd/4th generation cephalosporins and ceftaroline |
| Test Dose | 1st/2nd generation cephalosporin |
| Penicillins |

**CAN GIVE:**

| Test Dose |
| 3rd/4th generation cephalosporins and ceftaroline |
| [*Exception: If reaction was hives alone, can give full dose.] |

**Desensitization**

| 1st/2nd generation cephalosporins |
| [*Exception: If reaction was hives alone, can give test dose.] |

Penicillins

Avoid all penicillins and cephalosporins and use an alternative.

---

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Risk Stratification by Allergic Response

- Treatment options are based upon the allergy history and the type of allergic reaction

- Broken into 3 categories:
  - Mild, Delayed (Type IV)
  - Immediate (Type I)
  - Severe (Type II-IV)
Mild Type IV

- Slow onset – usually days into treatment course
- Itchy, mostly flat, red, blanching rash (when confluent can look like a sunburn)
- Uncomfortable but not life-threatening
- T-cell mediated
Immediate, Type I

- RAPID onset, usually within minutes of exposure
Time to Cardiovascular Collapse in Patients with Fatal Anaphylaxis

Foods: 30 min

Insect Sting: 15 min

Drugs: 5 min
Immediate, Type I

- RAPID onset, usually within minutes of exposure
- Activation of pre-formed IgE antibodies – prior exposure required
Immediate, Type I

- Hives most common (raised welts like mosquito bites or coalesced into larger plaques)
- May also get angioedema (dramatic swelling), wheezing, dizziness, hypotension…
- Treatable with epinephrine and antihistamines, resolution usually within 24h
Immediate, Type I

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Severe Reactions: Type II-IV

- Mechanisms include antibody complex deposits and T-cell responses

- Examples: Stevens-Johnson syndrome, hemolytic anemia, serum sickness, drug rash eosinophilia and systemic symptoms (DRESS), acute interstitial nephritis (AIN)

- Look for: cytopenias, easy bruising, jaundice, joint pains, fevers, abnormal liver/kidney function, blistering rashes, mucous membrane involvement
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Dartmouth-Hitchcock Medical Center
Penicillin Allergy Treatment Guideline

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TYPE I (IgE-mediated) HSR
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- Laryngeal edema
- Hypotension
- Hives/urticaria*
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  Unknown reaction WITHOUT mucosal involvement, skin desquamation or organ involvement

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CAN GIVE:

Full Dose
- 3rd/4th generation cephalosporins and ceftaroline
- 1st/2nd generation cephalosporin
- Penicillins

Test Dose
- 3rd/4th generation cephalosporins and ceftaroline
- [Exception: If reaction was hives alone, can give full dose.]

Desensitization
- 1st/2nd generation cephalosporins
- [Exception: If reaction was hives alone, can give test dose.]
- Penicillins

Avoid all penicillins and cephalosporins and use an alternative.

§ Search eDH SmartSets for “Test Dose” or “Desensitization” to find order sets. Protocols are available for the following beta lactam drugs: amoxicillin, ampicillin, cefazolin, cefepime, cefpodoxime, ceftazidime, ceftriaxone, cephalxin, meropenem, nafcillin, penicillin G, penicillin V, piperacillin-tazobactam.
IDENTIFICATION OF HYPERSENSITIVITY REACTIONS (HSRs)

Mild Reactions
- Mild and delayed rashes (Mild Type IV HSR): pruritic, morbilliform, without hives.
- Mild non-allergic adverse events: nausea, vomiting, diarrhea, mild lab abnormalities, local injection site reactions.

Type I (IgE-mediated) HSRs
- Hives/urticaria: raised, erythematous, pruritic rash. Lesions typically last less than 24 hours and resemble mosquito bites.
- Angioedema: swelling of the tongue, mouth, lips, or eyes that can be disfiguring in severity.
- Anaphylaxis: rapid onset systemic allergic reaction, often with respiratory or hemodynamic compromise.

Type II-IV (Severe) HSRs
- Hemolytic anemia, thrombocytopenia (Type II HSR): cytophenias, jaundice, easy bruising/bleeding, petechiae.
- Serum-sickness-like reactions, vasculitides (Type III HSRs): joint pains, fever, palpable purpura.
- Drug Rash, Eosinophilia, and Systemic Symptoms (DRESS), Acute Interstitial Nephritis (AIN) (Severe Type IV HSRs): Organ involvement such as liver, kidney, heart. Often with peripheral eosinophilia and fever.
- Stevens-Johnson Syndrome (SJS), Toxic Epidermal Necrolysis (TEN) (Severe Type IV HSRs): skin desquamation, lesions or ulcers over mouth, lips, eyes, or genitals.

TEST DOSE AND DESENSITIZATION

ORDERING AND ADMINISTRATION

1. To find orders, search eDH SmartSets. There will be IV and PO options for each:
   - For test dose: “IP Adult Test Dose”
   - For desensitization: “IP Adult Desensitization”
2. Select the order set that best matches the desired treatment dose of the antibiotic.
3. The order set will also include emergency medications for the bedside (epinephrine 1:1000 0.3mg IM and diphenhydramine 50mg IV, both prn allergic reaction)
4. Assess the patient prior to administering the medication: obtain vital signs, ask about baseline symptoms such as itching, and examine the patient for pre-existing rashes.
5. Monitor for new symptoms and check vital signs every 30 minutes until one hour after last dose.
   a. If a reaction occurs, treat with epinephrine and/or diphenhydramine as appropriate and stop the medication.
6. If patient tolerates medication, order it to be continued at recommended treatment dosing.
7. Additional recommendations:
   a. For test dose: If the patient does not react to the test dose, they are not allergic and can receive it in the future without precautions. Remove the drug from the allergy list or document on the allergy list for future reference that patient has tolerated the medication.
   b. For desensitization: this induces temporary tolerance, but the patient is still allergic to the drug. The medication must be continued uninterrupted for tolerance to be maintained. If more than 48h pass between doses, patient must be desensitized again.
Dartmouth-Hitchcock Medical Center
Cephalosporin Allergy Treatment Guideline

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Toxic Epidermal Necrolysis
Acute Interstitial Nephritis
Drug-Induced Hepatitis
Drug Rash Eosinophilia and Systemic Symptoms (DRESS) Syndrome
Hemolytic Anemia

CANNOT GIVE:

CAN GIVE:
Full Dose
Cephalosporin from different generation with dissimilar side chain

Test Dose
Penicillins
Cephalosporin from same generation or with similar side chain

Reaction to 1st/2nd Gen.

CAN GIVE:
Test Dose
3rd/4th gen. cephalosporin with dissimilar side chain or ceftaroline

Desensitization
1st/2nd gen. cephalosporin or similar side chain

Reaction to 3rd/4th Gen.

CAN GIVE:
Test Dose
Any cephalosporin with dissimilar side chain

Desensitization
Penicillins

Avoid all cephalosporins and use an alternative.

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<th>Cephalosporin Side Chain Cross-reactivity Chart</th>
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<th>2&lt;sup&gt;nd&lt;/sup&gt; Generation</th>
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Side chain cross-reacts with Aztreonam but not with other cephalosporins

The following drugs do not share a side chain with other cephalosporins: ceftazolin, ceftarolane.
Test Doses
Test Dose

- Small percentage of the total dose (usually 10%)
- Monitor for symptoms
- If none occur, full dose can be given
- Once tolerated, patient does not need test dose in the future for that drug
Test Dose

- Recommended when we **do not** believe the patient will have a reaction! Done out of caution.
- Only rule out *Immediate (Type I)* reactions
- Delayed-type reactions can still occur after a test dose, but these are not life-threatening
Communication: Patients

• WHAT NOT TO SAY: “We don’t really think you are allergic and we are going to give you this drug anyway.”

• WHAT TO SAY: “A lot of studies show people outgrow allergies. Your chances of reacting to this drug are less than 2%. If you react, it will mostly likely be a mild rash which we can treat. A different drug may not be as effective and may cause life-threatening side effects like C. diff and MRSA. Would you like to receive the drug while we monitor you closely?”
Communication: Team

• Nursing staff should be involved early on to arrange the necessary care at the bedside
  • We incorporate a life safety nurse consult who can arrange back-up nursing or facilitate transfer to ICU

• Order set in EMR and pharmacy preparation of test dose helps avoid errors and move process along more efficiently
FAQs
# Dartmouth-Hitchcock Medical Center Penicillin Allergy Treatment Guideline

## MILD REACTION
Minor or Maculopapular rash, including a rash with childhood penicillin exposure (i.e., nonspecific rashes and mild Type IV HSRs)

EMR lists allergy, but patient denies

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## TYPE I (IgE-mediated) HSR
- Anaphylaxis
- Angioedema
- Wheezing
- Laryngeal edema
- Hypotension
- Hives/urticaria *

OR

Unknown reaction WITHOUT mucosal involvement, skin desquamation or organ involvement

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## TYPE II-IV (Severe) HSR
- Serum sickness
- Stevens-Johnson Syndrome
- Toxic Epidermal Necrolysis
- Acute Interstitial Nephritis
- Drug-Induced Hepatitis
- Drug Rash Eosinophilia and Systemic Symptoms (DRESS) Syndrome
- Hemolytic Anemia

---

## CAN GIVE:

|                                   | Test Dose § | 3rd/4th generation cephalosporins and ceftaroline
|-----------------------------------|-------------|--------------------------------------------------
| **Full Dose**                     | Test Dose § | 1st/2nd generation cephalosporin
| Penicillins                       |             | 1st/2nd generation cephalosporin

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## CAN GIVE:

| Test Dose § | 3rd/4th generation cephalosporins and ceftaroline
|-------------|--------------------------------------------------
| Penicillins | 1st/2nd generation cephalosporins

---

## CAN GIVE:

- Avoid all penicillins and cephalosporins and use an alternative.
Drug Challenges without Testing

“You want me to give penicillin… to someone with a penicillin allergy… without testing?”

Yes!
Drug Challenges without Testing

AAAAI Consensus Statements\textsuperscript{11}:

• “Direct oral drug provocation tests are safe and effective in confirming or excluding drug hypersensitivity reactions to beta lactams in low risk patients with delayed-onset benign rashes.”

• “Regarding T-cell mediated non immediate reactions, skin prick testing is not mandatory.”

AAAAI Practice Parameters 2010 (most recent update)\textsuperscript{1}:

• “Patients with a vague and/or distant history of penicillin allergy may be candidates to receive penicillins via graded challenge.”
Caubet 2011

88 children: delayed onset rash to penicillins

- skin or blood test

11 (12.5%) (+) intradermal
2 (2.3%) (+) blood
75 (85%) (-)

• No challenge reactions were more severe than the index event

Challenge everyone regardless of result!

4 pos 7 neg 0 pos 2 neg 2 pos 73 neg

Allergy testing led to 9 false positives (10%) and 2 false negatives (2.3%)
818 children h/o amoxicillin allergy

Challenge! (no skin testing)

17 (2.1%) Immediate Reaction

Skin tested

1 (6%) pos
16 (94%) neg

31 (3.8%) Delayed Rash

770 (94%) No reaction

• All reactions were limited to skin and resolved with antihistamines
• No severe reactions occurred
• Skin testing would have missed 94% of the immediate reactions\(^{19}\)
Drug Challenges without Testing

• Tucker 2017: military recruits (ages 18-25) in San Diego with beta lactam allergy label (penicillin and cephalosporin). Initially, recruits had skin testing if they had a penicillin allergy, but...

  “Because of time constraints and 74 consecutive negative skin test results (followed by negative amoxicillin challenge), subsequent recruits bypassed skin testing and proceeded directly to amoxicillin challenge.”
Drug Challenges without Testing

- Out of 328 recruits:
  - 5 had a reaction to the challenge (1.5%)
- Combined with the first 74, the rate was only 1.2%.
- No cases of anaphylaxis
- All had cutaneous symptoms and 1 had a globus sensation which resolved without transfer to higher level of care
Confino-Cohen 2017

710 patients Beta-lactam allergy

642 delayed reactions

- 5.3% Skin test pos
- 32.4% equivocal
- 62.3% Skin test neg

Challenge all!

- 9 (1.5%) immed. rxn
- 24 (4%) delayed rxn

- Only one patient who reacted had a positive skin test
- All reactions were mild rashes
Drug Challenges without Testing

• Macy 2018: leader in drug allergy research at Kaiser San Diego. Standard protocol is to perform amoxicillin 250mg challenge without skin testing for benign rashes >12 mos. prior or unknown symptoms

• 398 challenges over the course of 1 year:
  • 1 (0.3%) acute reaction
  • 5 (1.3%) delayed reactions
  • None of the reactions were serious and all were managed in clinic
156 patients
Non-life-threatening Penicillin reaction

Placebo

80mg amoxicillin

500mg amoxicillin

16 “reactions”

4 (2.6%) Allergic reaction

15 (10%) Non-allergic reaction

120 (77%) No reaction

- All allergic reactions were limited to the skin
- No life-threatening reactions
- Most reactions were delayed
- Skipping skin testing in low risk patients did not lead to more positive challenges (2.6% vs. 1.8%, p=0.59)
FAQs
“Isn’t it possible my patient will have a worse reaction than the first one?”

Anything’s possible… but it is very, very unlikely.
Reaction Type

- 182 patients with positive beta lactam challenges

- Only risk factor for anaphylaxis was an initial reaction of anaphylaxis (>10 fold risk)$^{25}$.
  - This has been seen in numerous other studies as well

- Patients who report anaphylaxis are 2-4x more likely to have a true allergy and have increased risk of cross-reactivity with other beta lactams$^{25}$.

- Patients with no recall of their index reaction who have a positive challenge most often have only a benign rash$^{25}$.
Dartmouth-Hitchcock Medical Center
Penicillin Allergy Treatment Guideline

MILD REACTION
Minor or Maculopapular rash, including a rash with childhood penicillin exposure (i.e., nonspecific rashes and mild Type IV HSRs)
EMR lists allergy, but patient denies

TYPE I (IgE-mediated) HSR
- Anaphylaxis
- Angioedema
- Wheezing
- Laryngeal edema
- Hypotension
- Hives/urticaria*

*OR
Unknown reaction WITHOUT mucosal involvement, skin desquamation or organ involvement

CAN GIVE:
- Full Dose: 3rd/4th generation cephalosporins and ceftaroline
- Test Dose: 1st/2nd generation cephalosporin
- Penicillins

TYPE II-IV (Severe) HSR
- Serum sickness
- Stevens-Johnson Syndrome
- Toxic Epidermal Necrolysis
- Acute Interstitial Nephritis
- Drug-Induced Hepatitis
- Drug Rash Eosinophilia and Systemic Symptoms (DRESS) Syndrome
- Hemolytic Anemia

CAN GIVE:
- Test Dose: 3rd/4th generation cephalosporins and ceftaroline
  [*Exception: If reaction was hives alone, can give full dose.]
- 1st/2nd generation cephalosporins
  [*Exception: If reaction was hives alone, can give test dose.]
- Avoid all penicillins and cephalosporins and use an alternative.

Desensitization

§ Search eDH SmartSets for “Test Dose” or “Desensitization” to find order sets. Protocols are available for the following beta lactam drugs: amoxicillin, ampicillin, cefazolin, cefepime, cefpodoxime, ceftazidime, ceftriaxone, cephalexin, meropenem, nafcillin, penicillin G, penicillin V, piperacillin-tazobactam.
FAQs
Legal Concerns

“It’s all fun and games until someone loses a lawsuit. Can you guarantee I won’t get sued?”

No, but it would be very unlikely!

2018 review: “Malpractice lawsuits based on prescribing or administering penicillin to a patient with a known penicillin allergy is uncommon and rarely successful.”

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23
Legal Concerns

• For cephalosporins, judge ruled in favor clinicians for all cases that went to trial\textsuperscript{23}
  • Cited “lack of scientific evidence demonstrating that a cephalosporin or carbapenem was contraindicated”\textsuperscript{23}

• For penicillin, 3 cases of liability\textsuperscript{23}:
  • One in 1956 – very, very old…
  • One in 1998 – drug not contributory but awarded money for ”pain and suffering” anyway
  • One in 2007 – patient with a history of SJS
Dartmouth-Hitchcock Medical Center
Penicillin Allergy Treatment Guideline

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Toxic Epidermal Necrolysis
Acute Interstitial Nephritis
Drug-Induced Hepatitis
Drug Rash Eosinophilia and Systemic Symptoms (DRESS) Syndrome
Hemolytic Anemia

CAN GIVE:

<table>
<thead>
<tr>
<th>CAN GIVE:</th>
<th>CAN GIVE:</th>
</tr>
</thead>
<tbody>
<tr>
<td>Full Dose</td>
<td>Test Dose 5</td>
</tr>
<tr>
<td>1st/2nd generation cephalosporin</td>
<td>1st/2nd generation cephalosporins and ceftaroline</td>
</tr>
<tr>
<td>Penicillins</td>
<td>Penicillins</td>
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Avoid all penicillins and cephalosporins and use an alternative.

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Legal Concerns

The New York Times

TheUpshot

THE NEW HEALTH CARE

To Be Sued Less, Doctors Should Consider Talking to Patients More

Tamara Shopsin
Legal Concerns

• “Patients seeing doctors who were sued in the past were significantly more likely to report that their doctor rushed them, did not explain reasons for tests or ignored them… communication was the most common complaint.”

• “Primary care physicians sued less often are those more likely to spend time educating patients about their care, more likely to use humor and laugh with their patients and more likely to try to get their patients to talk and express their opinions.”
Would you feel comfortable giving…

• Amoxicillin to a 74 yo F with a history of childhood rash to penicillin?
  • How about cefepime?

• Ceftriaxone to a 56 yo M with a history of penicillin anaphylaxis?

• Cefpodoxime to a 62 yo F with a history of angioedema to cephalaxin?
**Dartmouth-Hitchcock Medical Center**
**Penicillin Allergy Treatment Guideline**

**MILD REACTION**
Minor or Maculopapular rash, including a rash with childhood penicillin exposure (i.e., nonspecific rashes and mild Type IV HSRs)

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Anaphylaxis
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Unknown reaction WITHOUT mucosal involvement, skin desquamation or organ involvement

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**TYPE II-IV (Severe) HSR**
Serum sickness
Stevens-Johnson Syndrome
Toxic Epidermal Necrolysis
Acute Interstitial Nephritis
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Drug Rash Eosinophilia and Systemic Symptoms (DRESS) Syndrome
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---

**CAN GIVE:**

<table>
<thead>
<tr>
<th>Full Dose</th>
<th>Test Dose</th>
<th>Desensitization</th>
</tr>
</thead>
<tbody>
<tr>
<td>3rd/4th generation cephalosporins and ceftaroline</td>
<td>3rd/4th generation cephalosporins and ceftaroline</td>
<td>1st/2nd generation cephalosporins</td>
</tr>
<tr>
<td>1st/2nd generation cephalosporin</td>
<td>[<em>Exception: If reaction was hives alone, can give full dose.</em>]</td>
<td>[<em>Exception: If reaction was hives alone, can give test dose.</em>]</td>
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<td>Penicillins</td>
<td></td>
<td>Penicillins</td>
</tr>
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Would you feel comfortable giving...

- Amoxicillin to a 74 yo F with a history of childhood rash to penicillin? **OK with a test dose**
  - How about cefepime? **OK with a full dose**

- Ceftriaxone to a 56 yo M with a history of penicillin anaphylaxis? **OK with a test dose**

- Cefpodoxime to a 62 yo F with a history of angioedema to cephalaxin?
# Dartmouth-Hitchcock Medical Center
## Cephalosporin Allergy Treatment Guideline

### MILD REACTION

Minor or Maculopapular rash, including a rash with childhood cephalosporin exposure (i.e., nonspecific rashes and mild Type IV HSR)

EMR lists allergy, but patient denies

![Image of a person sunbathing]

### TYPE I (IgE-mediated) HSR

- Anaphylaxis
- Angioedema
- Wheezing
- Laryngeal edema
- Hypotension
- Hives/urticaria

OR

Unknown reaction WITHOUT mucosal involvement, skin desquamation or organ involvement

![Image of a man sitting at a desk]

### TYPE II-IV (Severe) HSR

- Serum sickness
- Stevens-Johnson Syndrome
- Toxic Epidermal Necrolysis
- Acute Interstitial Nephritis
- Drug-Induced Hepatitis
- Drug Rash Eosinophilia and Systemic Symptoms (DRESS) Syndrome
- Hemolytic Anemia

![Image of bacteria and a cartoon character]

### CAN GIVE:

<table>
<thead>
<tr>
<th>CAN GIVE:</th>
<th>Reaction to 1st/2nd Gen. CAN GIVE:</th>
<th>Reaction to 3rd/4th Gen. CAN GIVE:</th>
<th>Avoid all cephalosporins and use an alternative.</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Full Dose</strong></td>
<td>Cephalosporin from different generation with dissimilar side chain</td>
<td>3rd/4th gen. cephalosporin with dissimilar side chain or ceftaroline</td>
<td>Any cephalosporin with dissimilar side chain</td>
</tr>
<tr>
<td><strong>Test Dose</strong></td>
<td>Penicillins</td>
<td>1st/2nd gen. cephalosporin or similar side chain</td>
<td>Penicillins</td>
</tr>
<tr>
<td><strong>Desensitization</strong></td>
<td>Cephalosporin from same generation or with similar side chain</td>
<td>Penicillins</td>
<td>Penicillins</td>
</tr>
</tbody>
</table>

§ Search eDH SmartSets for “Test Dose” or “Desensitization” to find order sets. Protocols are available for the following beta lactam drugs: amoxicillin, ampicillin, cefazolin, cefepime, cefpodoxime, ceftazidime, ceftriaxone, cephalaxin, meropenem, nafcillin, penicillin G, penicillin V, piperacillin-tazobactam.
Would you feel comfortable giving...

- Amoxicillin to a 74 yo F with a history of childhood rash to penicillin? **OK with a test dose**
  - How about cefepime? **OK with a full dose**

- Ceftriaxone to a 56 yo M with a history of penicillin anaphylaxis? **OK with a test dose**

- Cefpodoxime to a 62 yo F with a history of angioedema to cephalexin? **OK with a test dose**
Balancing Risk
We Need To Think About Risk Differently

- Risk of life-threatening reaction to beta lactams in those with reported allergies is exceedingly low if patients are screened for mild reactions and the drug is chosen carefully.

- Conversely, the risk of a life-threatening infection is much, much higher when alternative agents are used, and use of these agents is a growing public health issue.
  - *C. difficile* colitis kills 29,000 people a year (CDC.gov)
  - Anaphylaxis from all causes kills <225 people a year$^{24}$
Resources are Finite

- Allergy specialists cannot meet the population demands of penicillin allergy. Pathways created by allergists that empower non-allergists to address penicillin allergy are necessary\(^\text{25}\)

- Up to one third of patients continue to erroneously report a penicillin allergy after delabeling, further burdening the system\(^\text{25}\)
Other Creative Solutions

- Telemedicine allergy consults have been used to aid in skin testing programs\textsuperscript{26}

- Pharmacists, nurses, ID fellows, and other healthcare professionals have been trained to perform skin testing on selected inpatients with penicillin allergy labels and reduced length of stay and broad spectrum antibiotic use\textsuperscript{27, 28, 29}

- Pre-operative skin testing programs allow the use of beta-lactams in the OR
Summary

• Penicillin allergy is not a benign diagnosis and leads to poor health outcomes

• Most patients with a penicillin allergy label are not truly allergic

• Beta lactam cross-reactivity is not as extensive as once thought

• Clinical guidelines at an institutional level can help clinicians feel more comfortable reintroducing beta lactam antibiotics
Contact

Erin.L.Reigh@hitchcock.org


Additional References

PENICILLIN ALLERGY EVALUATION AT DARTMOUTH HITCHCOCK MEDICAL CENTER

M DesBiens, M.D.
Infectious Disease and Preventive Medicine Fellow, DHMC

March 20, 2019
DHMC COHORT

All adult patients aged 18 years or older, with admission date between 1/01/2017 and 12/31/2018, who received at least one antibiotic during their hospitalization

20,519 encounters
16,507 unique patients
<table>
<thead>
<tr>
<th>Reporting PCN allergy</th>
<th>Not reporting PCN allergy</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Receipt of any antibiotic, n patients (%)</td>
<td>2,654 (16%)</td>
<td>13,853 (84%)</td>
</tr>
<tr>
<td>Age in years, mean (range)</td>
<td>61 (18-101)</td>
<td>61 (18-100)</td>
</tr>
<tr>
<td>Female, n (%)</td>
<td>1,885 (71%)</td>
<td>6,799 (49%)</td>
</tr>
<tr>
<td>Presence of any other allergy, n (%)</td>
<td>2,053 (77%)</td>
<td>8,234 (59%)</td>
</tr>
<tr>
<td>Presence of any other antibiotic allergy, n (%)</td>
<td>1,007 (38%)</td>
<td>2,307 (17%)</td>
</tr>
<tr>
<td>Clostridioides difficile, OR (95% CI)</td>
<td>1.2 (0.9,1.6)</td>
<td></td>
</tr>
<tr>
<td>MRSA Blood Stream Infection, OR (95% CI)</td>
<td>1.5 (0.9, 2.6)</td>
<td></td>
</tr>
<tr>
<td>VRE infection, OR (95% CI)</td>
<td>1.9 (1.2, 2.9)</td>
<td></td>
</tr>
</tbody>
</table>
## Table 1b: Patients reporting penicillin allergy compared to patients not reporting penicillin allergy, encounters level data

<table>
<thead>
<tr>
<th></th>
<th>Reporting PCN allergy</th>
<th>Not reporting PCN allergy</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Receipt of any antibiotic, n encounters (%)</td>
<td>3,338 (16%)</td>
<td>17,181 (84%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Length of stay in days, average (95% CI)</td>
<td>7.2 (6.9, 7.6)</td>
<td>6.8 (6.6, 7.0)</td>
<td>0.039</td>
</tr>
<tr>
<td>Total antibiotic days, average (95% CI)</td>
<td>5.5 (5.26, 5.70)</td>
<td>5.0 (4.84, 5.12)</td>
<td>0.003</td>
</tr>
<tr>
<td>Encounters receiving a formulary restricted antibiotic, n (% within subgroup)</td>
<td>1,012 (30%)</td>
<td>2,304 (13%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Encounters receiving vancomycin, meropenem, and/or a fluoroquinolone, n (% within subgroup)</td>
<td>1,779 (53%)</td>
<td>5,250 (31%)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>
DHMC PENICILLIN EVALUATION PROJECT

Test Dose Protocol Implementation
- Order characteristics
- Outcomes
- Pertinent antibiotic use over time
61 test dose protocols completed
Feb 1, 2018-March 1, 2019
Medical/surgical services utilizing the test dose protocol

- HOSPITAL MEDICINE
- MICU
- ORTHOPEDICS
- CARDIOLOGY
- VASCULAR SURGERY
- ACS
- NEUROLOGY
- PLASTIC SURGERY
- SICU
- GENERAL SURGERY
- NEUROSURGERY
- OB/GYN
- PULMONARY
- THORACIC SURGERY
- UROLOGY

Legend:
- Blue bar: Number of TDP completed
- Orange bar: Number of associated ID consults
Antibiotics used in test dose protocols

- Ceftriaxone
- Piperacillin-Tazobactam
- Cefazolin
- Penicillin
- Amoxicillin
- Cefepime
- Ampicillin
- Ceftazidime
- Augmentin
- Cephalexin
- Naftillin

The bar chart shows the frequency of each antibiotic used in test dose protocols.
**CLINICAL/ANTIMICROBIAL OUTCOMES OF COMPLETED TEST DOSE PROTOCOLS**

- **TDP Completed**: 61
- **TDP Fully Tolerated**: 59
- **Transition to more appropriate antibiotics (Beta-Lactams)**: 56
- **Transition to more narrow-spectrum antibiotics**: 52

- **97%**
- **95%**
- **88%**
Number of encounters per month receiving meropenem, a fluorquinolone, and/or vancomycin in patients reporting PCN allergy

p = 0.001
PREDICTIVE MODELING

Antibiotic stewardship
C diff, MRSA, VRE
Antibiotic-related AKI
Drug Costs
Anticipated annual number of DHMC patients with improved clinical care following widespread PCN allergy evaluation

- Patients seen annually reporting PCN allergy: 1327
- Patients without IgE-mediated reaction: 1194
- Patients successfully completing TPD: 1159
Widespread PCN allergy evaluation can save, annually:

- 5 cases of *Clostridoides difficile* infection
- 3 cases of MRSA BSI
- 7 cases of VRE infection
- 4 AKIs (at least)
- Improved stewardship in 1,159 patients (priceless)
Modeled from 2017 data:
- 242 encounters with pts reporting PCN allergy
- 2,149 days of meropenem
  - 9 days per encounter

ASSUMPTIONS:
- 90% without IgE (218 encounters)
- 97% tolerate TDP (212)
- 1,908 days

pip-tazo: $52,088.4
meropenem: $151,113.60

DIFFERENCE: $99,025.20 per year
In a large sample of adults admitted to a northern New England tertiary care referral center, 16% reported allergy to penicillin.

Adults reporting penicillin allergy have longer lengths of stay, more antibiotic-days, more formulary restricted antibiotics, and are more likely to develop C diff infection, MRSA bacteremia, and VRE infections than those patients not reporting penicillin allergy.

Penicillin allergy may be safely and effectively evaluated with review of allergy history, and monitored dose challenge in patients without concern for severe reaction.

*Clinical guidelines at an institutional level can help all providers become better antibiotic stewards!*

“A misdiagnosis of allergy to beta lactams results in dramatically poorer clinical outcomes for patients and is not acceptable any longer.” (Torres 2019)
The more complex the world becomes, the more difficult it is to complete something without the cooperation with others

~ Alexander Fleming ~

Special thanks to my team:
Erin Reigh, MD
Michael Calderwood, MD, MPH
Craig Worby, PharmD
John Trummel, MD, MPH
Diane Beaulieu, BSN, RN
Priya Katari, MD
Steve Houston, MS, BS
REFERENCES


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