Assessment of β-lactam allergy

9 out of 10 patients who report a penicillin allergy are not truly allergic.

Evaluating your patients for true penicillin allergy means less use of broad-spectrum antibiotics and giving your patients the best care.
Disclosures

The following speaker of this CE activity have no relevant financial relationships with commercial interests to disclose:

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The accreditation compliance reviewer, Courtney Bryant, has no financial relationships with commercial interests to disclose.
Learning Objectives

1) Recognize structural side chain similarities consistent with beta-lactam allergies
2) Perform an appropriate allergy assessment
3) Explain graded challenge procedures and when they are appropriate
4) Summarize pharmacy’s role in beta-lactam skin testing
September 28th—the date Alexander Fleming discovered penicillin in 1928—has been designated National Penicillin Allergy Day, an annual celebration to raise awareness around the impact of carrying a penicillin allergy label and how it affects a patient's healthcare treatment.

To learn more about National Penicillin Allergy and how you can get involved, visit nationalpenicillinallergyday.com
63 yo M

- **PMH:** laparotomy, gastrojejunostomy, and serosal repair performed for gastric outlet obstruction (2016)
- **Last outpt clinic visit (4 mo previous):** “with long standing hx of gastroparesis and weight loss who in 2016 had gastrojejunostomy and J tube placement for c/o abd pain from prev gastric stimulator”
- Last hospital admission: 19 months previous
- Prev abx Hx: clindamycin po x 7d (7 months ago)
- Complicated post-op course
Day 8

<table>
<thead>
<tr>
<th></th>
<th>SUSC</th>
<th>INTP</th>
</tr>
</thead>
<tbody>
<tr>
<td>AMIKACIN</td>
<td>&lt;=2</td>
<td>S</td>
</tr>
<tr>
<td>AMPICILLIN</td>
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<td>R</td>
</tr>
<tr>
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<td>S</td>
</tr>
<tr>
<td>TRIMETHOPRIM/SULFA</td>
<td>&lt;=20</td>
<td>S</td>
</tr>
<tr>
<td>IMIPENEM</td>
<td>&lt;=0.25</td>
<td>S</td>
</tr>
<tr>
<td>CIPROFLOXACIN</td>
<td>&lt;=0.25</td>
<td>S</td>
</tr>
<tr>
<td>AMPICILLIN/SULBACTAM</td>
<td>4</td>
<td>S</td>
</tr>
<tr>
<td>LEVOFLOXACIN</td>
<td>&lt;=0.12</td>
<td>S</td>
</tr>
<tr>
<td>CEFEPIME</td>
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<td>CEFTAZIDIME</td>
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<td>S</td>
</tr>
<tr>
<td>CEFTRIAXONE1</td>
<td>&lt;=1</td>
<td>S</td>
</tr>
<tr>
<td>ESBL</td>
<td>Neg</td>
<td>-</td>
</tr>
</tbody>
</table>

Collection sample: **TRACHEAL ASPIRATE**  Collection date: xxxx
Site/Specimen: TRACHEAL CYTOLOGIC MATERIAL
Test(s) ordered: CULTURE (TRACHEAL ASPIRATE)... completed: xxxx

Reported: Jul 26, 2018  1+ GRAM NEGATIVE BACILLI
CULTURE RESULTS: **KLEBSIELLA PNEUMONIAE** SSP PNEUMONIAE -
Quantity: 3+

KLEBSIELLA PNEUMONIAE SSP PNEUMONIAE -
**Collection sample:** BLOOD CULTURE  
**Site/Specimen:** (growth identified in PICC line and L.A.-line)  
* BACTERIOLOGY FINAL REPORT => KLEBSIELLA PNEUMONIAE, CARBAPENEM RESISTANT (CRE)  
**Comment:** ESBL Confirmed  
**KPC CARBAPENAMASE** GENE DETECTED  
CONFRIMED BY XPERT CARBA-R PCR ASSAY

<table>
<thead>
<tr>
<th>Antibiotic</th>
<th>Susceptibility</th>
<th>Interpretation</th>
</tr>
</thead>
<tbody>
<tr>
<td>AMIKACIN</td>
<td>&lt;=2</td>
<td>S</td>
</tr>
<tr>
<td>AMPICILLIN</td>
<td>&gt;=32</td>
<td>R</td>
</tr>
<tr>
<td>CEFAZOLIN</td>
<td>&gt;=64</td>
<td>R</td>
</tr>
<tr>
<td>TRIMETHOPRIM/SULFA</td>
<td>&lt;=20</td>
<td>S</td>
</tr>
<tr>
<td>GENTAMICIN</td>
<td>&lt;=1</td>
<td>S</td>
</tr>
<tr>
<td>IMIPENEM</td>
<td>R</td>
<td>R</td>
</tr>
<tr>
<td>CIPROFLOXACIN</td>
<td>&lt;=0.25</td>
<td>S</td>
</tr>
<tr>
<td>AMPICILLIN/SULBACTAM (UNASYN)</td>
<td>&gt;=32</td>
<td>R</td>
</tr>
<tr>
<td>LEVOFLOXACIN</td>
<td>&lt;=0.12</td>
<td>S</td>
</tr>
<tr>
<td>CEFEPIME</td>
<td>&lt;=1</td>
<td>R</td>
</tr>
<tr>
<td>PIPERACILLIN/TAZOBACTAM</td>
<td>&gt;=128</td>
<td>R</td>
</tr>
<tr>
<td>CEFTAZIDIME</td>
<td>4</td>
<td>R</td>
</tr>
<tr>
<td>CEFTRIAXONE1</td>
<td>8</td>
<td>R</td>
</tr>
<tr>
<td>ESBL</td>
<td>Pos+</td>
<td></td>
</tr>
</tbody>
</table>
Background:

- 10% of population has PCN allergy listed in medical records, yet it is estimated that <1% have a true IgE mediated (type 1) allergy.
- Of those that have had a true allergy, approximately 80% will have lost this sensitization within 10 years.
- Charted PCN allergy has been associated with increased morbidity, including increased length of hospital stay, increase costs, and increased exposure to broad spectrum abx, placing patient at risk for developing resistance.
- No proven alternatives to penicillin are available for treating neurosyphilis, congenital syphilis, or syphilis in pregnant women.

<table>
<thead>
<tr>
<th>Category</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>True allergy</td>
<td>Patient reported symptoms consistent with immunological drug allergy, including but not limited to anaphylaxis, hives, itching, shortness of breath, swelling, rash/other serious skin reactions, or any other serious reaction where the drug or drug class would not be used again as determined by the investigator.</td>
</tr>
<tr>
<td>Adverse effect</td>
<td>Patient reported symptoms that are not consistent with immunological drug allergy, including but not limited to nausea, vomiting, diarrhea, dizziness, headache, drowsiness, weakness, chest pain, agitation, or any other reaction where the drug or drug class could be used again if needed as determined by the investigator.</td>
</tr>
<tr>
<td>Unclear/vague</td>
<td>Patient could not recall the reaction or the symptoms were not sufficiently descriptive to allow for classification, so a true allergy cannot be ruled out.</td>
</tr>
</tbody>
</table>
## Gell and Coombs classification of immunologic drug reactions

<table>
<thead>
<tr>
<th>Type</th>
<th>Description</th>
<th>Mechanism</th>
<th>Clinical features</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>IgE-mediated; immediate type</td>
<td>IgE-mediated activation of mast cells &amp; basophils → release of vasoactive substance (histamines, prostaglandins, leukotrienes)</td>
<td>Anaphylaxis, Angioedema, Bronchospasm, Urticaria (hives)</td>
</tr>
<tr>
<td>II</td>
<td>Antibody-dependent cytotoxicity</td>
<td>An antigen/hapten intimately a/w a cell binds to antibody → cell or tissue injury</td>
<td>Hemolytic anemia, Thrombocytopenia, Neutropenia</td>
</tr>
<tr>
<td>III</td>
<td>Immune complex disease</td>
<td>Deposition of antigen-antibody complexes in vessels or tissue → complement activation +/- recruitment of neutrophils by interaction of immune complexes with Fc IgG receptors.</td>
<td>Serum sickness, Arthus reaction</td>
</tr>
<tr>
<td>IV</td>
<td>Cell-mediated or delayed hypersensitivity</td>
<td>Antigen exposure activates T cells, which then mediate tissue injury. Depending upon the type of T cell activation and the other effector cells recruited, different subtypes can be differentiated (IVa to IVd).</td>
<td>Contact dermatitis, Morbilliform reactions, Exfoliative dermatoses (SJS/TEN), AGEP, DRESS/DiHS</td>
</tr>
</tbody>
</table>
Type I reactions

- Require prior exposure (exceptions follow) and the presence of drug specific IgE
- Itch, urticaria, angioedema, wheeze, vomiting, hypotension
- Timing is rapid; influenced by route of administration
- IV – sec to min
- Oral – 3-30 min (empty stomach); 10-60 min (with food)
- IgE-mediated anaphylactic reactions should NOT begin several days into a course of therapy, if the patient's exposure to the drug has been continuous
- If several doses are skipped, symptoms can appear when the drug is resumed.
Step 1

 Appropriately screen reported allergies
Concerns regarding the reaction include the following:

- Timing of the reaction in relation to drug administration
- Symptoms and evolution of the reaction
- Description of cutaneous symptoms (e.g., maculopapular, urticarial, bullous)
- Involvement of mucosal surfaces or internal organs
- Treatment administered, response, and duration of reaction
- History of prior exposure to the implicated agent
- Other medications ingested at the time of the reaction
- Was the medication or similar medications taken (and tolerated) thereafter?
- Are there potential confounders (e.g., underlying viral or bacterial infections)?
- History of other drug reactions and allergies (many patients with multiple drug intolerance syndrome do not have true drug allergies)
- Has the patient experienced recurrent, similar reactions without known exposures (e.g., chronic urticaria)?
1. Have you ever taken any medication that caused a reaction?
   □ Yes  □ No

2. Describe the reaction that occurred (check any/all the patient reports):
   Allergy related:
   □ hives (pink/red raised areas of the skin)
   □ rash/other serious skin reactions
   □ itching
   □ Angioedema (swelling around of face, mouth, throat, abdomen, extremities, genitalia)
   □ Shortness of breath/ wheezing/ throat tightness
   □ palpitations/ heart racing
   □ chest pain/tightness
   Non-allergy related:
   □ dizziness
   □ drowsiness
   □ headache
   □ stomach upset/pain
   □ nausea/vomiting
   □ diarrhea
   □ other _______________________________

3. How soon after taking the medication did the reaction occur?
   □ within minutes    □ within hours    □ within days    □ don’t recall

4. Did you seek medical attention for the reaction?
   □ No
   □ No, but treated with home remedies
   □ Yes – Doctor’s office
   □ Yes – Emergency Room visit
   □ Yes – resulted in hospitalization

   If yes, what did they do?
   □ advised Benadryl or other non-prescription remedies
   □ prescribed prednisone or other steroid
   □ administered injectable medications (steroids, Benadryl)
   □ administered epinephrine (adrenaline)

5. Was the medication stopped by the provider?
   □ Yes  □ No

6. Have you ever taken this medication or a similar one since that time?
   □ No
   □ Yes:
      □ amoxicillin (Amoxil or Augmentin)
      □ cephalexin (Keflex)
      □ cefaclor (Ceclor)
      □ ceftriaxone (Rocephin)
      □ Other (list:) __________________________________________________________________

   □ If yes, did you experience the same/similar reaction?
      □ Yes  □ No
Figure 4  Relative Risk for Clinically Relevant Change

- Female: 1.30 (1.01–1.69)
- Age > 65 years: 1.08 (0.86–1.35)
- > 5 home medications: 1.02 (0.79–1.31)
- > 1 hospital admission in past year: 0.97 (0.75–1.25)
- > 3 reported drug allergies: 1.31 (1.05–1.62)
Step 2

Evaluate for likelihood of Cross-Reactivity
“Although the shared β-lactam ring of penicillins and cephalosporins is not predictive of cross-reactivity, a considerable body of evidence has established that cross reactivity between different cephalosporins and between cephalosporins and penicillins is dependent on the side chain structure of these agents.”

Cross-reactivity based on side chain similarity

- A considerable body of evidence has established that cross-reactivity is dependent on the side chain structure of these agents rather than the core ring structure.
  - Between cephalosporins and penicillins: $R_1$
  - Between different cephalosporins: $R_1 \& R_2$

**Penicillin**

- 6-position

**Cephalosporin**

- 7-position
  - 3-position

FIG 2. General chemical structures of penicillin and cephalosporin molecules and chemical structures of the different beta-lactams used in this study.

Penicillin

Amoxicillin

Cephalexin

Cefazolin

Cefuroxime

Cefdinir

Ceftriaxone
# TABLE 23-1 β-Lactams with Common Side Chains

<table>
<thead>
<tr>
<th>Common Aminobenzyl Group</th>
<th>Common Aminobenzyl Group</th>
<th>Common Methylene Group</th>
</tr>
</thead>
<tbody>
<tr>
<td>Amoxicillin</td>
<td>Ampicillin</td>
<td>Benzyl penicillin</td>
</tr>
<tr>
<td>Cefadroxil</td>
<td>Cefaclor</td>
<td>Cephalothin</td>
</tr>
<tr>
<td>Cefazidime</td>
<td>Cephalexin</td>
<td></td>
</tr>
<tr>
<td>Cefprozil</td>
<td>Cefradine</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Cephaloglycin</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Loracarbef</td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th>Common Methoxyimino Group</th>
<th>Common Aminothiazole Group</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ceftriaxone</td>
<td>Ceftazidime</td>
</tr>
<tr>
<td>Cefuroxime</td>
<td>Aztreonam</td>
</tr>
<tr>
<td>Cefotaxime</td>
<td></td>
</tr>
<tr>
<td>Cefepime</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Six Groups of β-Lactams with Common R2 Side Chains</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cephalaxin</td>
</tr>
<tr>
<td>Cefadroxil</td>
</tr>
<tr>
<td>Cephalexin</td>
</tr>
<tr>
<td>Cefradine</td>
</tr>
<tr>
<td>Cefotetan</td>
</tr>
<tr>
<td>Cefamandole</td>
</tr>
<tr>
<td>Cefmetazole</td>
</tr>
<tr>
<td>Cefpiramide</td>
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</table>
Cross-reactivity between penicillins and cephalosporins based on side chain similarity

### 7-Position side chain

<table>
<thead>
<tr>
<th>Similar side chain/cross-reactivity possible within group&lt;sup&gt;a,b&lt;/sup&gt;</th>
<th>Similar side chain/cross-reactivity possible within group</th>
<th>Completely dissimilar side chains/unlikely cross-reactivity with each other&lt;sup&gt;b,c&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Cephaloridine (1st)</strong></td>
<td>Cefaclor (2nd)</td>
<td>Cefoperazone (3rd)</td>
</tr>
<tr>
<td><strong>Cephalothin (1st)</strong></td>
<td>Cephradine (1st)</td>
<td>Cefotaxime (3rd)</td>
</tr>
<tr>
<td><strong>Penicillin G</strong></td>
<td><strong>Cephalexin (1st)</strong></td>
<td>Cefpirome (4th)</td>
</tr>
<tr>
<td></td>
<td>Cefadroxil (1st)</td>
<td>Cefazolin (1st)</td>
</tr>
<tr>
<td></td>
<td>Amoxicillin</td>
<td>Cefpodoxime (3rd)</td>
</tr>
<tr>
<td></td>
<td>Ampicillin</td>
<td>Cefdinir (3rd)</td>
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### 3-Position side chain

<table>
<thead>
<tr>
<th>Similar side chain/cross-reactivity possible within group&lt;sup&gt;b,d&lt;/sup&gt;</th>
<th>Similar side chain/cross-reactivity possible within group</th>
<th>Similar side chain/cross-reactivity possible within group</th>
<th>Similar side chain/cross-reactivity possible within group</th>
<th>Similar side chain/cross-reactivity possible within group</th>
<th>Dissimilar side chain/unlikely cross-reactivity with each other&lt;sup&gt;b,e&lt;/sup&gt;</th>
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</thead>
<tbody>
<tr>
<td><strong>Cefadroxil (1st)</strong></td>
<td><strong>Cephalexin (1st)</strong></td>
<td>Cefotaxime (3rd)</td>
<td>Cefotetan (2nd)</td>
<td>Cefpirome (4th)</td>
<td>Cefpodoxime (3rd)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Cefbiprole (2nd)</td>
<td></td>
<td></td>
<td>Cefpodoxime (3rd)</td>
</tr>
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<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Cefpodoxime (3rd)</td>
</tr>
</tbody>
</table>

Step 3

Graded Challenge
Graded Challenge ("Allergy Provocation Test")

- Generally accepted as the gold standard to establish tolerance to a drug
- Recommended when the probability is determined to be low for a true drug allergy based on the history and available diagnostic tests
- Allows drug hypersensitivity to be excluded in a large % of patients
- Persons with a history of severe non-IgE-mediated reactions (e.g., Stevens-Johnson syndrome, toxic epidermal necrolysis, interstitial nephritis, and hemolytic anemia) are not candidates for skin testing or challenge and should avoid penicillins indefinitely
- Begin with 1/100th of therapeutic dose. Escalate every 30-60min to 1/10th dose, then the final therapeutic dose

Mandell, Douglas and Bennett “Principles and Practice of Infectious Disease” – 8th ed 2014
Step 4

Beta-lactam skin testing
Persons at high risk for anaphylaxis...

“In these situations, testing should be performed in a monitored setting in which treatment for an anaphylactic reaction is available. If possible, antihistamines... should not have been taken within 5 days of skin testing.”

Dilute the antigens in saline either 100-fold for preliminary testing (if the patient has had a IgE- mediated reaction to penicillin) or 10-fold (if the patient has had another type of immediate, generalized reaction to penicillin within the preceding year).
Preparing the Required Supplies

SKIN TESTING DEVICES

- 4 Scratch testing devices, DUOTIP-TEST II
- 4 26-28g syringes with labels
- Alcohol Swabs & Skin Marking Pen
- Reaction Guide, Timer, Recording Form

https://www.youtube.com/watch?v=le3oiT39s48
High pretest probability of Type I allergy

- Skin testing
  - Negative
    - Intradermal testing
      - Negative
        - Challenge
          - Negative
            - NOT ALLERGIC
          - Positive
            - Positive
              - ALLERGIC
386 patients
- 232 (60%) received preferred B-lactam after ASP/ID assessment
- 154 (40%) eligible for BLAST
  - 64 (42%) excluded
    - 5 (8%) hx of severe non-IgE-mediated rcns
    - documented IgE rcn w/in past 3mo
    - 22 (34%) discharged w/in 24 hrs of assessment
    - 13 (20%) refused consent
    - 10 (16%) nonpreferred agent became preferred agent
  - 90 (58%) underwent BLAST
    - 85 (94%) negative result
    - 1 (1%) positive result
    - 4 (4%) non-diagnostic (histamine prick test negative)

All 85 with negative BLAST tolerated B-lactam challenge
- 84 (99%) switched to preferred B-lactam therapy w/o incident
- 1 (1%) developed non-severe rash day 1
METHODS: Prospective, multicenter, open-label investigation of penicillin (pcn) skin testing using Penicillin Skin Test Kit. Skin test-negative subjects were challenged with 250 mg amoxicillin; skin test-positive patients were not challenged. Primary end point: NPV of the Penicillin Skin Test Kit, defined as % of subjects with negative skin test results who did not experience an IgE-dependent reaction within 72 hours of amoxicillin challenge.

RESULTS: 455 patients with hx of pcn allergy underwent skin testing. 63 (13.8%) had 1 or more positive test results; 65% of positive test results were to minor determinant mixture and/or amoxicillin alone. In the per protocol group of 373 skin test-negative subjects, 8 developed potential IgE-dependent rcns following oral amoxicillin challenge, translating to an NPV of 97.9% (95% CI, 95.8-99.1; P < .0001). All but 1 of the reactions was mild or moderate, and most subjects who required treatment received only antihistamines.
History of penicillin allergy

Penicillin skin test available?

No

Reaction benign and remote?

Yes

Consider full therapeutic dose of cephalosporin or carbapenem

Starting dose: 1/100–>1/10→ Full dose

No

Consider graded challenge to cephalosporin or carbapenem*

Positive

Full therapeutic dose of cephalosporin or carbapenem

Negative

Perform penicillin skin test

Yes

FIGURE 23-1 Approach to the use of β-lactams in patients with a history of penicillin allergy.

*All patients with prior drug reaction histories are at increased risk for future drug reactions. Drug challenges should therefore be performed with equipment and personnel available to treat anaphylaxis.
1. All the following are symptoms consistent with immunologic drug allergy except:
   rash
   swelling
   shortness of breath
   nausea/vomiting
Which of the following cephalosporins share similar molecular structure to ampicillin and may result in cross-reactivity allergy symptoms:

- cefuroxime
- cefdinir
- cephalaxin
- cefpodoxime