

Diagnosis of Betalactam Sensitivity

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Disclosures

- A principle owner and President of AllerQuest LLC, which manufactures penicilloyl-polysine (Pre-Pen®).

Drug Allergy: An Updated Practice Parameter

These parameters were developed by the Joint Task Force on Practice Parameters, representing the American Academy of Allergy, Asthma and Immunology, the American College of Allergy, Asthma and Immunology, and the Joint Council of Allergy, Asthma and Immunology.

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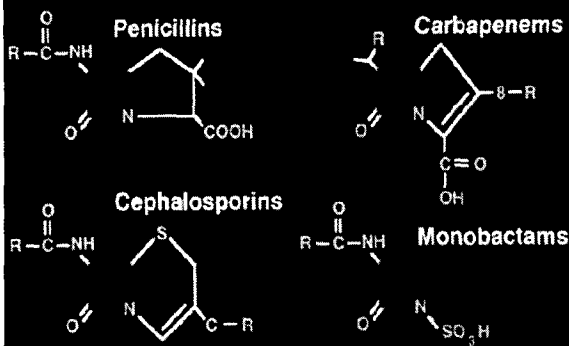
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Ann Allergy Asthma Immunol 2010;105:273e1-e78.

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- Fox S, Park MA. Penicillin skin testing in the evaluation and management of penicillin allergy. *Annals of Allergy, Asthma & Immunology*. 2011;106:1-7
- Blanca M, Romano A, Torres MJ, et al. Update on the evaluation of hypersensitivity reactions to betalactams. *Allergy*, 2009;64:183
– European Network for Drug Allergy (ENDA)

Classes of β - Lactam Antibiotics



Diagnosis

- History
- Skin test
- Challenge
- When to evaluate patient

Before Testing – Take a History

- Name of drug
- When during course did reaction occur
- Characteristics of reaction, systems involved
- Previous exposure to same or similar drug
- Reason for administration
- Concurrent medication at time of reaction
- Management required for reaction
- Time elapsed since reaction
- Subsequent exposure to the same or similar drug
- Similar symptoms in absence of drug treatment

Khan DA, Solensky R. J Allergy Clin Immunol 2010;115:S126-137

Evaluation of patient with history of penicillin allergy

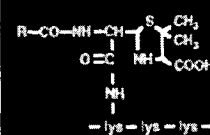
- *History:*
 - Patient's reaction history is often a poor predictor of skin test reactivity
 - Patients often cannot recall reaction details
 - Patients with convincing histories (i.e., anaphylaxis) lose penicillin-specific IgE over time
 - Incidence of severe anaphylaxis secondary to oral administration differs in USA and Europe
 - Patients with vague histories could be allergic
 - Review of published studies revealed that among history-positive/skin test-positive patients, 1/3 had a vague reaction history

The best way to determine whether a person with a history of penicillin allergy can tolerate this antibiotic without fear of a life threatening reaction is by:

- *Skin testing with the appropriate beta-lactam reagents*
 - Puncture followed by intradermal when skin testing.

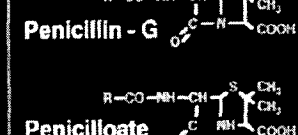
Pencillin Skin Testing Reagents

Major Determinant (PPL)

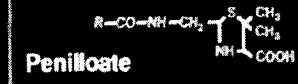


Penicilloyl - polylysine (PrePen®)

Minor Determinant Mixture (MDM)

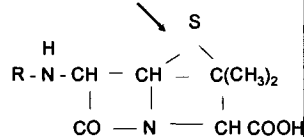


Penicilloate



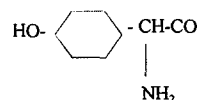
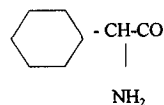
Penicillin

Thiazolidine Ring



B - Lactam Ring

Ampicillin



Amoxicillin

Penicillin Skin Test Reagents

Penicillin allergy testing using only Pre-Pen and Pen G

- "based on available literature, skin testing with penicilloyl-polysine and penicillin G appears to have adequate negative predictive value in the evaluation of penicillin allergy".

Drug Allergy: An updated practice parameter; Ann. Allergy Asthma Imm 2010;105:273 e44

Penicillin Skin Testing Without Penicilloate and/or Penilloate

- ~10% of penicillin ST+ patients positive to only penicilloate and/or penilloate
 - 15/171 (8.8%)¹
 - 7/64 (10.9%)²
 - 11/101 (10.9%)³
 - 9/136 (6.6%)⁴
 - 8/64 (12.5%)⁵
- NPV of skin testing with this MDM is comparable to NPV of skin testing with penicillin and without this in MDM⁶⁻⁸

1. Jost B, et al. *Ann Allergy Asthma Immunol* 2006; 97:807-12.
2. Park MA, et al. *Ann Allergy Asthma Immunol* 2007; 99:54-8.
3. Macy E and Burchette RJ. *Allergy* 2002; 57:1151-8.
4. Bousquet PJ, et al. *JACI* 2005; 115:1314-6.
5. Matheu V, et al. *J Invest Allergol Clin Immunol* 2007; 17:257-60.
6. Green GR, et al. *JACI* 1977; 80:339-45.
7. del Real GA, et al. *Ann Allergy Asthma Immunol* 2007; 98:355-9.
8. Shepherd G. *JACI* 1987; 99:S134.

Penicillin Allergy: Value of Including Amoxicillin as a determinant in Penicillin Skin Testing

- Addition of amoxicillin/ ampicillin skin test may detect additional penicillin allergic patients
- Concentration of amoxicillin (3.65 mg/ml - 20mg/ml) needs further study (European experience versus North American Experience)
 - Parenteral amoxicillin for human use not available in USA. Available in Europe
 - Ampicillin (12.5 to 20 mg/ml)
- Differences in positive skin test results to aminopenicillins between Spanish data and USA needs study
- Delayed skin test to aminopenicillin

Safety of Penicillin Skin Testing

- Should be performed by skilled personnel using proper technique
 - Puncture followed by intradermal
- American:
 - Systemic reaction rate:
 - 0.1-2% of all tested and 0.7- 9.4% of positive skin test reactors
 - none serious
- European:
 - Systemic reaction rate:
 - 1.3% of all tested and 8.8% of positive skin test reactors
 - 5 to prick test (4 anaphylaxis)
 - Patients with history of anaphylaxis or anaphylactic shock a risk factor

Penicillin Skin Testing – Negative Predictive Value

- United States¹⁻⁶
 - >95%
 - Reactions to challenge generally mild
- Europe⁶⁻¹²
 - 70-99%
 - Reactions to challenge sometimes severe

1. Sogn DD, et al. *Arch Intern Med* 1992; 152:1025-32.
2. Giedde J, et al. *JAMA* 1993; 270:2456-63.
3. Mendelson LM. *JACI* 1984; 73:76-81.
4. Macy E, et al. *JACI* 2003; 111:1111-5.
5. del Real GA, et al. *Ann Allergy Asthma Immunol* 2007; 98:355-9.
6. Torres MJ, et al. *Allergy* 2001; 56:850-6.
7. Bousquet PJ, et al. *Allergy* 2007; 62:872-6.
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10. Demoly P, et al. *Allergy* 2010; 65:327-32.
11. Matheu V, et al. *JACI* 2005; 118:1167-6.
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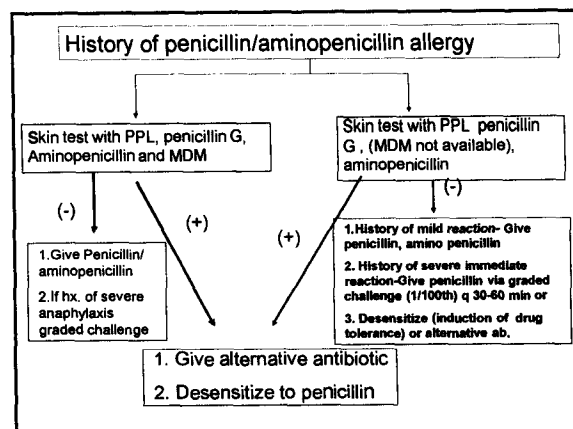
Skin testing useful for only IgE penicillin reactions

- Exclude from testing anyone with history of non IgE reactions such as:
 - Hemolytic anemia
 - Drug fever
 - Interstitial nephritis
 - Exfoliative dermatitis
 - Steven-Johnson syndrome
 - Contact dermatitis
- Commonly occur 72 hours after penicillin administration.

Serologic test for penicillin allergy

- "The usefulness of in vitro tests for penicillin specific IgE is limited by their uncertain predictive value. They are not suitable substitutes for penicillin skin testing."

• Drug allergy: an updated practice parameter 2010.



Penicillin Allergy: When to Skin Test?

- Electively – when patients are well and not in acute need of antibiotic treatment
 - Outpatient testing in acute situations is impractical or impossible to schedule
 - Patients inevitably receive alternate antibiotics and in children grow up with history my mother told me I was allergic.
- Resensitization = re-development of penicillin allergy in patients who have lost their sensitivity
 - Theoretical argument against elective penicillin skin testing

Drug Allergy: An Updated Practice Parameter

Summary Statement #84:

- Resensitization after treatment with oral penicillin is rare and therefore penicillin skin testing does not routinely need to be repeated in patients with a history of penicillin allergy who have tolerated one or more courses of oral penicillin
- Consideration given to retesting those with recent or particular severe reaction

Elective testing for penicillin allergy

- History
- Skin test for penicillin allergy
- Oral challenge

Why do oral challenge ?

- Confirm that patient can tolerate antibiotic in view of negative skin test.
 - Immediate reaction
 - Big difference between American and European data
 - Delayed reaction
 - Length of challenge
- Reluctance to take penicillin based upon negative skin test
 - Patient
 - Parent of patient
 - Referring physician
 - Future prescribing physician

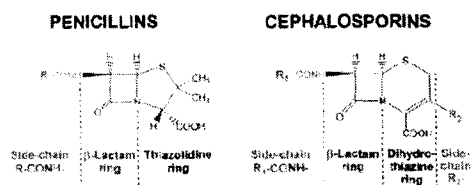
Penicillin Allergy – When to Skin Test

Summary Statement #81:

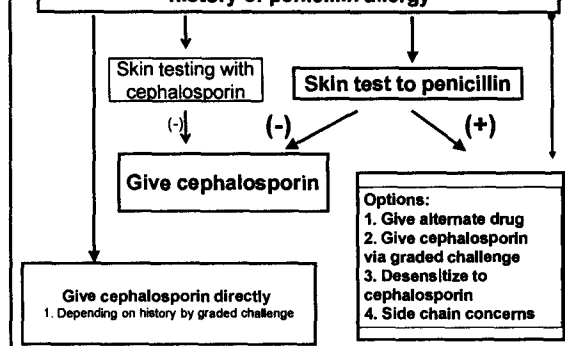
Penicillin skin testing may be performed electively – when patients are well and not in immediate need of antibiotic therapy. Alternatively, penicillin skin testing may be performed when treatment with a penicillin compound is contemplated.

Cephalosporin Administration to Patients With a History of Penicillin Allergy

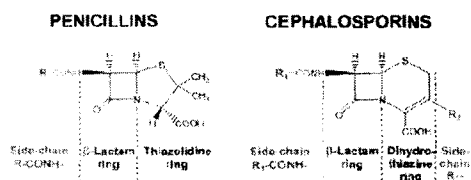
Structure of penicillins and cephalosporins



Cephalosporin administration to patients with history of penicillin allergy



Use of cephalosporins in patient with a history of cephalosporin allergy

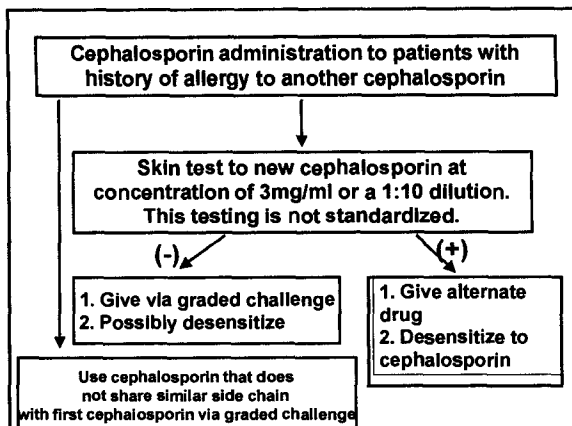


Cephalosporin Non-irritating Intradermal Skin Test Concentrations

Antibiotic	Full-strength conc. (mg/ml)	Non-irritating conc. (dilution from full strength)
Cefotaxime	100	10-fold
Cefuroxime	100	10-fold
Cefazolin	330	10-fold
Ceftazidime	100	10-fold
Ceftriaxone	100	10-fold

- If POSITIVE → IgE-mediated allergy probably present
- If NEGATIVE → Cannot rule out IgE-mediated allergy

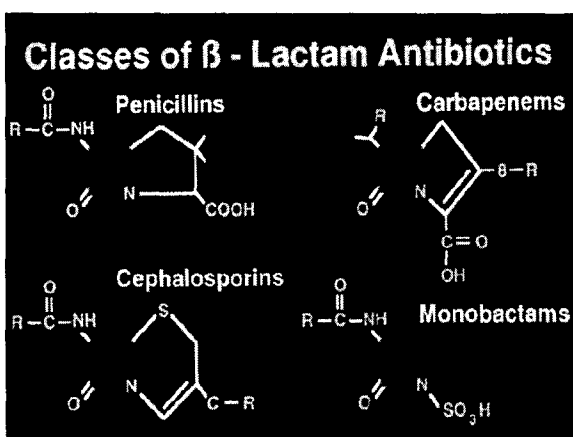
[Updated R. et al. JACI 2013; 112:429-30]



Use of Cephalosporin in patient with history of Cephalosporin Allergy

Summary Statement #95:

Patients with a past history of an immediate-type reaction to one cephalosporin should avoid cephalosporins with similar R-group side chains. Treatment with cephalosporins with dissimilar side chains may be considered, but the first dose should be given via graded challenge or induction of drug tolerance depending on the severity of the previous reaction.



Monobactams

- Monobactams (aztreonam)
 - "Aztreonam does not cross react with other β -lactam's except for ceftazidime, with which it shares an identical R-1-group side chain"

Carbapenems use in penicillin allergic patients

Carbapenems (imipenem, meropenem)

"limited data indicate lack of significant allergic cross reactivity between penicillin and carbapenems. Penicillin skin test negative patients may receive carbapenems. Penicillin skin tests positive patients and people with a history of penicillin allergy who do not undergo skin testing should receive carbapenems by graded challenge"

