

Beta-lactam Allergy: Diagnosis and Management

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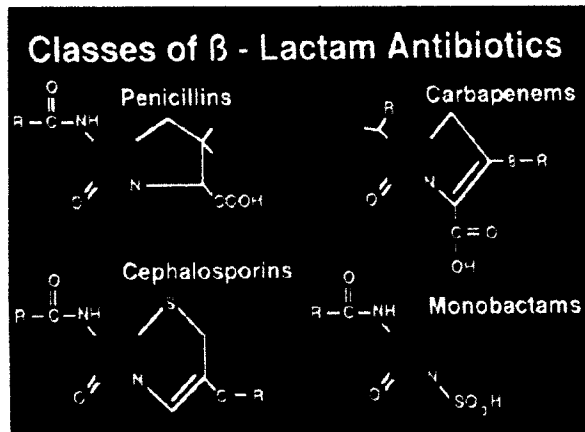
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Ann Allergy Asthma Immunol 2010;105:273e1-e78.

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 – European Network for Drug Allergy (ENDA)



Penicillin and Aminopenicillin Allergy

- Penicillin allergy is reported in approximately 10 - 20% of patients
 - Penicillin allergy label associated with:
 - Increase use of vancomycin & quinolones
 - Increased medical cost
- Up to 90% of these individuals labeled as penicillin allergic are able to tolerate penicillins.
- Penicillin skin test positive rate is declining.

Reasons Why Majority of People Labeled As Allergic to Penicillin Can Tolerate It.

- Lose sensitivity with time
- Virus that caused the reaction
- Virus plus the penicillin caused the reaction
 - Amp/Amox and mono or cytomegalic
- Amp/Amox maculopapular reaction
- Bacteria (strep.) Caused the reaction
- Pseudo reaction
- Don't know

Problems With Using An Alternative Antibiotic

- Less effective
- More toxic
- More expensive
- Increase risk of the development of bacteria resistance to more potent antibiotic
- Development of reaction to antibiotic for which we have no test
- Need alternative antibiotic for prophylaxis in the future after certain surgeries or medical conditions

Evaluation of patient with history of penicillin allergy

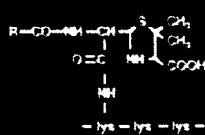
- *History:*
 - Patient's reaction history is often a poor predictor of skin test reactivity
 - Patients often cannot recall reaction details
 - Patients with convincing histories (i.e., anaphylaxis) lose penicillin-specific IgE over time
 - Incidence of severe anaphylaxis secondary to oral administration 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 an immediate life threatening reaction is by:

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

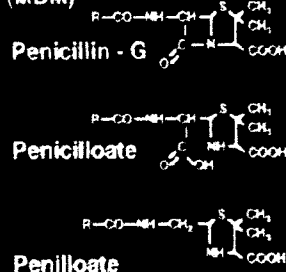
Penicillin Skin Testing Reagents

Major Determinant (PPL)

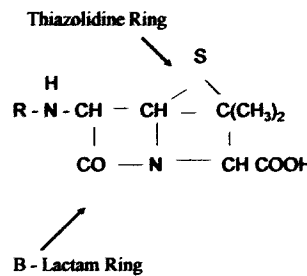


Penicilloyl - polylysine (PrePen®)

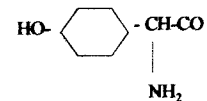
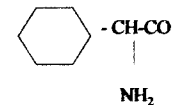
Minor Determinant Mixture (MDM)



Penicillin



Ampicillin



Amoxicillin

Penicillin Skin Test Reagents

Penicillin skin testing reagents

- Major Determinant
 - Benzyl penicilloyl polysine(Pre Pen®), PPL
 - If don't use miss 26- 90% of all positive reactors
 - Always prick before intradermal skin tests
 - Inject too much get non specific irritant reaction
 - Do in duplicate

Penicillin skin testing reagents

- Major Determinant
 - Benzyl penicilloyl-polysine (Pre Pen)
 - Use alone miss 6 -75% of all positive reactors
 - Inject to much get non specific irritant reaction
- Minor Determinants (MDM)
 - Pen G 10,000 units/ml
 - Make fresh- 100,000 U/ml concentration can be stored for one week
 - 10,000 units /ml frozen keep 6 months
 - Always prick skin test first followed by intradermal

Penicillin allergy testing using only Pre-Pen and Pen G

- Major determinant and Penicillin alone.
 - Reaction rate <3% (<24 hours 1%)
- Adding penicillin G to Major determinant identifies an additional 2.7%-4% of skin test positive patients. (3000 patients)

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 reagents (cont.)

- Minor Determinants (MDM)
 - Pen G 10,000 units/ml
 - Penicilloate and Penilloate not commercially available (all at 10^{-2} M) in USA. Available in Spain and some European Countries (Diater).

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 the other MDM⁶⁻⁸

- Jost B, et al. *Ann Allergy Asthma Immunol* 2006; 97:807-12.
- Park MA, et al. *Ann Allergy Asthma Immunol* 2007; 98:54-8.
- Macy E and Burchette RJ. *Allergy* 2002; 57:1151-8.
- Bouquet PJ, et al. *JACI* 2005; 115:1314-6.
- Mathieu V, et al. *J Investing Allergol Clin Immunol* 2007; 17:257-60.
- Green GR, et al. *JACI* 1977; 69:339-45.
- del Real GA, et al. *Ann Allergy Asthma Immunol* 2007; 98:355-9.
- Shepherd G. *JACI* 1997; 99:3134.

Amoxicillin/ampicillin-specific Reactors (Europe)

Reference (Year)	# of History-Positive Patients	# of ST-Positive Patients	# Positive to <u>Only</u> Amox/Amp	% Positive to <u>Only</u> Amox/Amp in: ST+ Patients + All Patients
Torres MJ (2001)	?	283	92	• 92/283 = 48% •
Bouquet PJ (2005)	824 ^a	88	44	• 44/88 = 50% • 44/824 = 5.3%
Mathieu (2007)	?	69	17	• 17/69 = 25% •
Romano A (2008)	?	308	113	• 113/308 = 37% •
Moreno E (2011)	1631	284	116	• 116/284 = 41.2%

Amoxicillin/ampicillin-specific Reactors (US)

Reference (Year)	# History-Positive Patients	# ST-Positive Patients	# Positive to <u>Only</u> Amox/Amp	% Positive to <u>Only</u> Amox/Amp in: ST+ Patients + All Patients
Macy E (1997, 2002)	1429	161	5	• 5/161 = 3.1% • 5/1429 = 0.35%
Park MA (2007)	1759	64	2	• 2/64 = 3.1% • 2/1759 = 0.11%
Lin E (2010)	1068	243	14	• 14/243 = 5.8% • 14/1068 = 1.3%

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

Penicillin Skin Testing – Negative Predictive Value

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

- Sogn DD, et al. *Arch Intern Med* 1982; 152:1025-32.
- Gadde J, et al. *JAMA* 1983; 270:2456-63.
- Mendelson LM. *JACI* 1984; 73:76-81.
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- Torres MJ, et al. *Allergy* 2001; 56:950-8.
- Bouquet PJ, et al. *Allergy* 2007; 62:872-8.
- Bouquet PJ, et al. *Allergy* 2008; 63:1495-90.
- Bouquet PJ, et al. *JACI* 2005; 115:1314-6.
- Desmoly P, et al. *Allergy* 2010; 65:327-32.
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Penicillin Skin Testing – Positive Predictive Value

- Based on limited # of patients
- PPV = ~50% (33-100%)¹⁻⁸
- Recent "outlier" study⁹: PPV = 10%
 - Only patients with mild reactions > 3 years prior
 - Skin test-positive rate = 43%

- Sogn DD, et al. *Arch Intern Med* 1982; 152:1025-32.
- Chandra RK, et al. *Arch Dis Child* 1980; 55:857-60.
- Green GR, et al. *JACI* 1977; 69:339-45.
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- Adkinson NF, et al. *N Engl J Med* 1971; 46:457-60.
- Levine BB, Zolov DM. *J Allergy* 1969; 43:231-44.
- Macy E and Burchette RJ. *Allergy* 2002; 57:1151-8.
- Caubet JC, et al. *JACI* 2011; 127:218-22.
- Goldberg A, et al. *Ann Allergy Asthma Immunol* 2008; 100:37-43.

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

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.

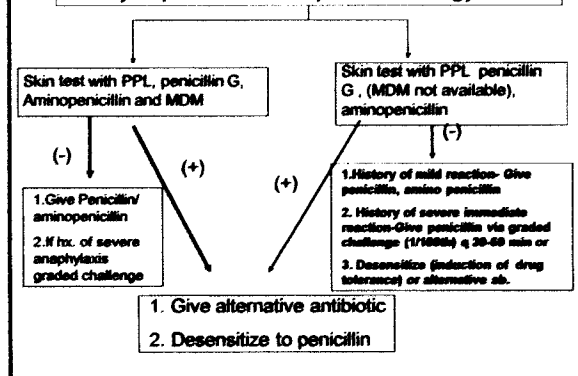
Serologic test for penicillin allergy

- “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: Which Patients to Skin Test?

- Any patient with a history of a reaction to a penicillin class antibiotic that may have been IgE-mediated

History of penicillin/aminopenicillin allergy



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

Resensitization After Oral Penicillins

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* Most reactions not allergic in nature
 ** One patient repeat ST-negative
 *** Five patients repeat ST/oral challenge-negative

Resensitization After Parenteral Penicillin

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*One patient underwent repeat penicillin skin testing and was negative

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 in reaction rate 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

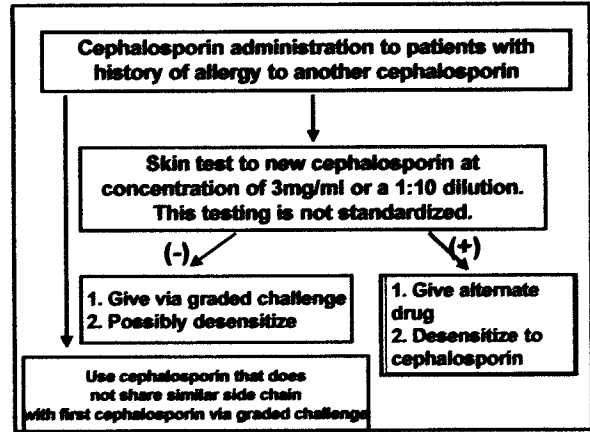
Summary Statement #81:

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 Non-irritating Intradermal Skin Test Concentrations

Antibiotic	Full strength conc. (mg/ml)	Non-irritating conc. (1:10 dilution from full strength)
Ceftriaxone	100	10 mg/ml
Cefuroxime	100	10 mg/ml
Cefazolin	500	50 mg/ml
Cefazidime	100	10 mg/ml
Ceftazidime	100	10 mg/ml

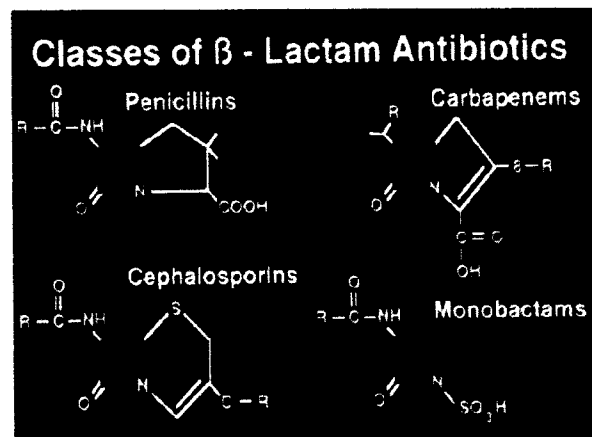
* If R1, R2, R3, IgE mediated allergy probably present
 * If R1, R2, R3, Cannot rule out IgE mediated allergy
 * If R1, R2, R3, Cannot rule out IgE mediated allergy



Use of Cephalosporin in patient with history of Cephalosporin Allergy

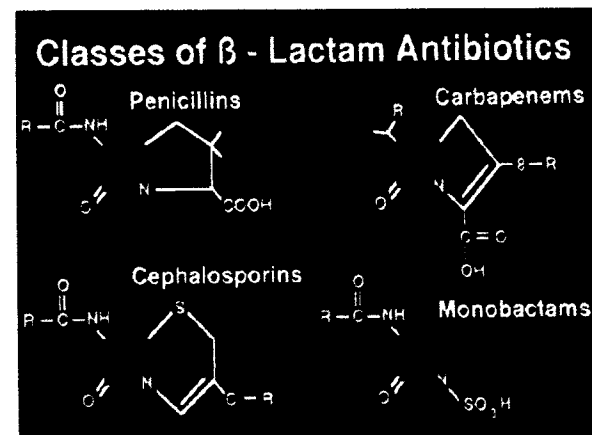
Summary Statement #95:

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"

Induction of Drug Tolerance & Graded Challenge

- Induction of drug tolerance (desensitization)
 - Allows patients with IgE-mediated allergy to a drug to take it safely
 - Should be performed
 - ONLY in patients with IgE-mediated allergy
 - ONLY if a non-cross-reactive drug cannot be substituted
 - ONLY with IV access and anaphylaxis meds
- Graded Challenge
 - Cautious administration of a drug to patient who is unlikely to be allergic to it
 - Used when negative predictive value of diagnostic testing is imperfect

Classes of β - Lactam Antibiotics

