

## Beta-lactams

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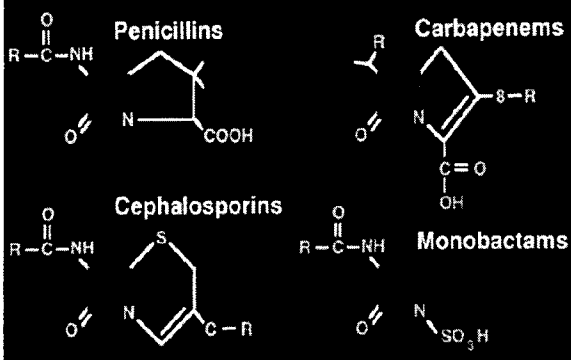
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Ann Allergy Asthma Immunol 2010;105:273e1-e78.

## References

- 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 $\beta$ - Lactam Antibiotics



## 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.

### 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

## 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%)<sup>1</sup>
  - 7/64 (10.9%)<sup>2</sup>
  - 11/101 (10.9%)<sup>3</sup>
  - 9/136 (6.6%)<sup>4</sup>
  - 8/64 (12.5%)<sup>5</sup>
- NPV of skin testing with this MDM is comparable to NPV of skin testing with penicillin and without the other MDM<sup>6-8</sup>

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. Mathieu V, et al. *J Investig Allergol Clin Immunol* 2007; 17:257-60.
6. Green GR, et al. *JACI* 1977; 60:339-45.
7. del Real GA, et al. *Ann Allergy Asthma Immunol* 2007; 98:355-9.
8. Shepherd G. *JACI* 1997; 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

### Penicillin Skin Testing – Negative Predictive Value

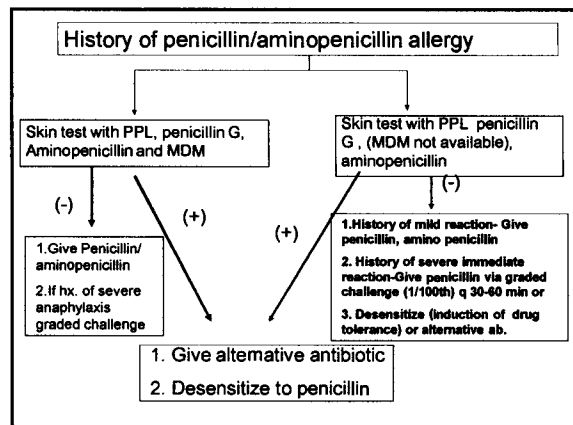
- United States<sup>1-5</sup>
  - >95%
  - Reactions to challenge generally mild
- Europe<sup>8-12</sup>
  - 70-99%
  - Reactions to challenge sometimes severe

1. Sogn DD, et al. *Arch Intern Med* 1992; 152:1025-32.
2. Geddes J, et al. *JAMA* 1993; 270:2546-63.
3. Mendell LM, et al. *AMA* 1984; 251:736-81.
4. Gray E, et al. *JACI* 2003; 111:1111-5.
5. de laet GA, et al. *Ann Allergy Asthma Immunol* 2007; 98:35-40.
6. Torres MJ, et al. *Allergy* 2001; 56:850-6.
7. Bousquet P.J, et al. *Allergy* 2007; 62:872-6.
8. Bousquet P.J, et al. *Allergy* 2008; 38:185-90.
9. Bousquet P.J, et al. *JACI* 2005; 115:1314-6.
10. Demoly P, et al. *Allergy* 2010; 65:327-32.
11. Mathieu V, et al. *JACI* 2005; 116:1167-8.
12. Mathieu V, et al. *J Invest Allergol Clin Immunol* 2007; 17:57-60.

### Penicillin Skin Testing – Positive Predictive Value

- Based on limited # of patients
- PPV = ~50% (33-100%)<sup>1-8</sup>
- Recent "outlier" study<sup>9</sup>: PPV = 10%
  - Only patients with mild reactions > 3 years prior
  - Skin test-positive rate = 43%

1. Sogn DD, et al. *Arch Intern Med* 1992; 152:1025-32.
2. Chandra RK, et al. *Arch Dis Child* 1980; 55:857-60.
3. Green GR, et al. *JACI* 1977; 60:339-45.
4. Solley GO, et al. *JACI* 1982; 69:238-44.
5. Adkinson NF, et al. *N Engl J Med* 1971; 48:457-60.
6. Levine BB, Zolov DM. *J Allergy* 1969; 43:231-44.
7. Macy E and Burchette RJ. *Allergy* 2002; 57:1151-6.
8. Caubet JC, et al. *JACI* 2011; 127:218-22.
9. Goldberg A, et al. *Ann Allergy Asthma Immunol* 2008; 100:37-43.



### 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

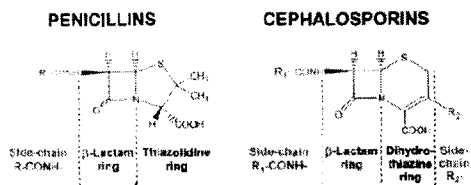
## Elective testing for penicillin allergy

- History
- Skin test for penicillin allergy
- Oral challenge

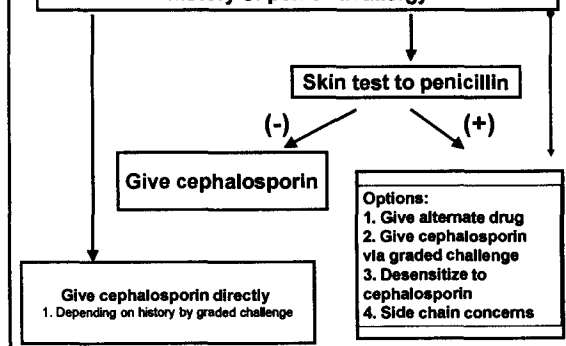
## Why do oral challenge ?

- 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

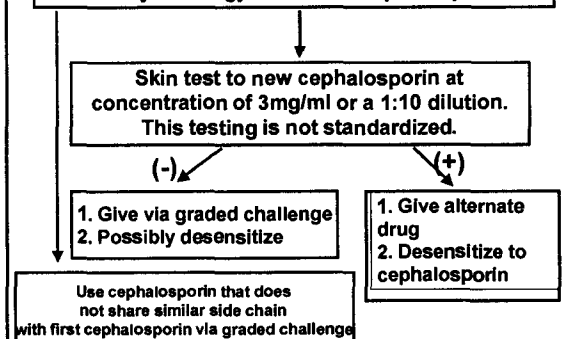
## Structure of penicillins and cephalosporins



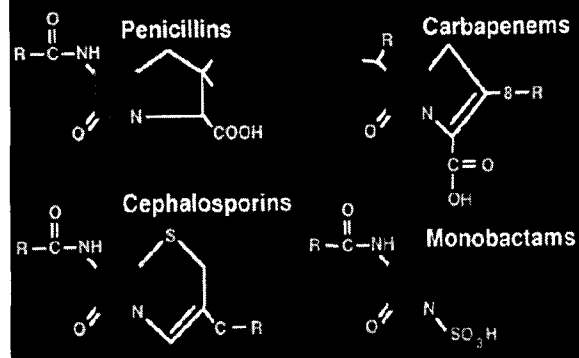
## Cephalosporin administration to patients with history of penicillin allergy



## Cephalosporin administration to patients with history of allergy to another cephalosporin



## Classes of $\beta$ - Lactam Antibiotics



### Testing patients with history of penicillin allergy

- Good for the cost of medical care

### Elective Penicillin Skin Testing – Cost Savings

- 236 outpatients
- 83% penicillin skin test-negative
- Average antibiotic cost per penicillin skin test-negative patient
  - \$71.17 during year before penicillin skin test
  - \$49.63 during year after penicillin skin test
  - P value = 0.0001

Macy E. JACI 1998; 102:281-5.

### Penicillin testing in ER setting

Raja et al. Ann of Emergency Medicine. 2009;54:72

	Med cost first choice	Medium cost of second choice	Difference
History Pos. skin test neg. (21)	\$30.36	\$104.16	\$73.80
History Pos skin test pos. (7)	\$30.36	\$109.76	\$79.40

137/150 patients with positive history for penicillin allergy had negative skin test

### Testing patients with history of penicillin allergy

- Good for the cost of medical care
- Good for the patient

### Utility of Penicillin Skin Testing

Table 2. Antibiotics Used Before and After Penicillin Skin Testing (PST) in 101 Patients Studied\*

Antibiotic used	Patients, No. (%)	
	Before PST	After PST
Vancomycin	78 (77)	8 (8)
Fluoroquinolones	26 (26)	3 (3)
Penicillin	0	7 (7)
Semisynthetic penicillin	0	27 (27)
First-generation cephalosporins	0	32 (32)
Second-generation cephalosporins	0	0
Third-generation cephalosporins	4 (4)	13 (13)
Imipenem	0	12 (12)
Aztreonam	20 (20)	0
Aminoglycoside	20 (20)	11 (11)
Clindamycin	9 (9)	2 (2)
Others	3 (3)	1 (1)

\* Some patients received more than 1 antibiotic drug. Some antibiotic drugs used (eg, methicillin) were not reviewed.

- 101 consecutive pen skin test consults at community teaching hospital
- 92% skin test-negative

Nadarajah K, et al. Ann Allergy Asthma Immunol 2009; 95:541-5

### Penicillin Skin Testing – Effect on Antibiotic Use

Study	% Pcn ST Negative	Effect on Broad Spectrum Antibiotic Use (% of Patients)
Harris AD (1999)	86%	Vancomycin 25% → 0% Quinolones 27% → 14%
Arroliga ME (2003)	89%	Vanco/Quinolones 100% → 58%
Nadarajah K (2005)	92%	Vancomycin 77% → 8% Quinolones 26% → 3%
Park M (2006)	96%	Vancomycin 30% → 16%
del Real GA (2007)	88%	Vancomycin 37% → 16% Quinolones 36% → 13%
Frigas E (2008)	?	Vancomycin 28% → 10%

## Penicillin Allergy in Pregnant Women

- CDC Recommendations for GBS prophylaxis in women with history of penicillin allergy:
  - Patients not at high risk for anaphylaxis
    - Cefazolin
  - Patients at high risk for anaphylaxis
    - Clindamycin or erythromycin – if GBS susceptible
    - Vancomycin – if resistant to clindamycin/erythromycin or if susceptibility unknown

Schrag S, et al *MMWR* 2002; 51:1-22.

## Antibiotic Choices for GBS Prophylaxis in Women with History of Penicillin Allergy

- Adherence to 2002 CDC Guidelines for GBS prophylaxis in penicillin allergic patients is poor
  - 84-96% treatments deviated from CDC Guidelines<sup>1,2</sup>
  - Most patients received clindamycin or vancomycin
  - GBS sensitivity testing frequently not performed
  - GBS resistance to clindamycin (26%) and erythromycin (37%) is increasing<sup>1</sup>
- GBS-positive women with history of penicillin allergy often receive inappropriate antibiotic prophylaxis

1. Matteson KA, et al. *Obstet Gynecol* 2008; 111:356-64.
2. Pelaez LM, et al. *J Perinat Med* 2009; 37:487-9.

## Penicillin Skin Testing of GBS-Positive Pregnant Women

Study	# of Patients	# (%) of Patients Pcn Skin Test Negative	# (%) of ST-Neg Patients Treated with Penicillin
Macy E (2006)	56	53/56 (95%)	47/53 (89%)
Phillipson EH (2007)	28	25/28 (89%)	25/25 (100%)

Macy E. *Ann Allergy Asthma Immunol* 2006;97:164  
Phillipson EH. *J Reprod Med* 2007 Jun;52 (6) 480-484

## Penicillin testing good for patients

- Question :
  - Should all female children and women of child bearing age with a history of penicillin allergy be tested before they get pregnant?

## Testing patients with history of penicillin allergy

- Good for the cost of medical care
- Good for the patient
  - Decrease chance of antibiotic resistance and more potential toxicity
  - Decrease chance of reactions to antibiotics for which we have no test
  - Prophylaxis for dental or other procedures
    - Very appreciative patients
  - Not growing up with history my mother or physician told me I am allergic and never to take penicillin

## Testing patients with history of penicillin allergy

- Good for the cost of medical care
- Good for the patient
- Good for the specialty of allergy
  - Reinforces the image of the allergist in the community and hospital as the expert in antibiotic allergy management.
  - Increases image of allergist in community and hospital
  - Providing a new service for existing patients
  - Attracting new patient referrals
  - Expanding your referral network

