Beta-lactams

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Disclosures

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

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

  - 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.
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, 1/2 had a vague reaction history

Penicillin Skin Test Reagents

Penicillin Skin Testing Without Penicilloate and/or Penicilloate

- ~10% of penicillin ST+ patients positive to only penicilloate and/or penicilloate
  - 15/171 (8.8%)
  - 7/84 (10.9%)
  - 11/101 (10.9%)
  - 9/136 (6.6%)
  - 6/84 (12.5%)
- NPV of skin testing with this MDM is comparable to NPV of skin testing with penicilin and without the other MDM

Penicillin Skin Testing - Negative Predictive Value

- United States
  - >95%
  - Reactions to challenge generally mild
- Europe
  - 70-90%
  - Reactions to challenge sometimes severe

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 - 20 mg/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

References:
Penicillin Skin Testing – Positive Predictive Value

- Based on limited # of patients
- PPV = ~50% (33-100%) \(^1-6\)
- Recent "outlier" study\(^6\): PPV = 10%
  - Only patients with mild reactions > 3 years prior
  - Skin test-positive rate = 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
  - Intestinal 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 there uncertain predictive value. They are not suitable substitutes for penicillin skin testing.”

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

Penicillins

Cephalosporins

Cephalosporin administration to patients with history of penicillin allergy

[Diagram of the process]

Cephalosporin administration to patients with history of allergy to another cephalosporin

Skin test to new cephalosporin at concentration of 3mg/ml or a 1:10 dilution. This testing is not standardized.

1. Give via graded challenge
2. Possibly desensitize

Use cephalosporin that does not share similar side chain with first cephalosporin via graded challenge

Classes of β-Lactam Antibiotics

- Penicillins
- Cephalosporins
- Carbapenems
- Monobactams
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

Penicillin testing in ER setting


<table>
<thead>
<tr>
<th>Med cost first choice</th>
<th>Medium cost of second choice</th>
<th>Difference</th>
</tr>
</thead>
<tbody>
<tr>
<td>History Pos skin test neg (21)</td>
<td>$30.30</td>
<td>$104.15</td>
</tr>
<tr>
<td>History Pos skin test pos (7)</td>
<td>$30.36</td>
<td>$108.76</td>
</tr>
</tbody>
</table>

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>
<thead>
<tr>
<th>Antibiotic used</th>
<th>Patients, No. (%)</th>
<th>Before</th>
<th>After</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vancomycin</td>
<td>79 (71)</td>
<td>9 (9)</td>
<td></td>
</tr>
<tr>
<td>Erythromycin</td>
<td>36 (32)</td>
<td>5 (5)</td>
<td></td>
</tr>
<tr>
<td>Penicillin</td>
<td>3 (3)</td>
<td>3 (3)</td>
<td></td>
</tr>
<tr>
<td>Second generation cephalosporin</td>
<td>3 (3)</td>
<td>0 (0)</td>
<td></td>
</tr>
<tr>
<td>Third generation cephalosporin</td>
<td>4 (4)</td>
<td>0 (0)</td>
<td></td>
</tr>
<tr>
<td>Imipenem</td>
<td>3 (3)</td>
<td>0 (0)</td>
<td></td>
</tr>
<tr>
<td>Aztreonam</td>
<td>22 (20)</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Aminoglycoside</td>
<td>20 (18)</td>
<td>11 (11)</td>
<td></td>
</tr>
<tr>
<td>Ceftriaxone</td>
<td>2 (2)</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Others</td>
<td>2 (2)</td>
<td>0</td>
<td></td>
</tr>
</tbody>
</table>

Some patients received more than 1 antibiotic. Drug, some antibiotics excluded by manufacturer were not reviewed.

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

Penicillin Skin Testing – Effect on Antibiotic Use

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


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
  - Most patients received clindamycin or vancomycin
  - GBS sensitivity testing frequently not performed
  - GBS resistance to clindamycin (28%) and erythromycin (37%) is increasing
  - GBS-positive women with history of penicillin allergy often receive inappropriate antibiotic prophylaxis


Penicillin Skin Testing of GBS-Positive Pregnant Women

<table>
<thead>
<tr>
<th>Study</th>
<th># of Patients</th>
<th># (% of Patients) Pcn Skin Test Negative</th>
<th># (% of ST-Neg Patients Treated with Penicillin)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Macy E (2006)</td>
<td>56</td>
<td>53/55 (95%)</td>
<td>47/53 (89%)</td>
</tr>
<tr>
<td>Phillipson EH (2007)</td>
<td>28</td>
<td>25/28 (93%)</td>
<td>20/28 (100%)</td>
</tr>
</tbody>
</table>

Macy E. Ann Allergy Asthma Immunol 2006;97:154

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