Penicillin Skin Testing
The Role of the Pharmacist and Pharmacy Technician

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Disclosures

• Nicholas Torney has no potential or actual conflicts of interest to disclosure in relation to this presentation.

My Background

• Pharm.D. from Ferris State University 2014
• PGY-1 at Munson Medical Center (MMC)
• PGY-2 Infectious Diseases at MMC

• Penicillin allergy research
  – Inpatient Pharmacy-run Penicillin Skin Testing Service
    • P&T approved August 2015
Objectives

<table>
<thead>
<tr>
<th>Pharmacists</th>
<th>Pharmacy Technicians</th>
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<tbody>
<tr>
<td>1. Define a Penicillin Skin Test</td>
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<tr>
<td>What is it?</td>
<td>What does it tell you?</td>
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<tr>
<td>What can you do?</td>
<td>How do you do it?</td>
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<tr>
<td>2. Describe the viability of an inpatient pharmacy-run penicillin skin testing program and the steps you can take to implement one in your institution.</td>
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<td>3. Given a patient case, recommend a penicillin skin test based on a patient's allergy history, current antibiotics, and infectious process.</td>
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Abbreviations

- PCN = Penicillin
- PST = Penicillin Skin Testing
- EHR = Electronic Health Record

Overview

- Background & classification of PCN allergies
- Conducting an allergy history
- Patient case / Clinical significance
- Penicillin skin testing (PST)
  - Who, what, where, when, why
  - Myths and misconceptions
- Cross-reactivity
- Steps to Implement
- Pharmacy Implications
Significance of this presentation

- Beta-lactams are generally the safest and most effective class of antibiotics.
- Reported penicillin allergies are common
- This usually leads to use of alternative antibiotics (i.e. vancomycin and fluoroquinolones) without questioning the specific reaction
- Many patients with documented allergies can still safely receive these antibiotics
- The avoidance of alternative antibiotics will cut down on more toxic and broader spectrum antibiotics and lead to less resistance

How Common are PCN allergies?

- ~10% of the general population reports a PCN allergy
- 15 – 25% of patients at MMC
  - 45 to 70 patients per day
Are PCN allergies benign?

- Retrospective cohort
  - Kaiser group, CA
  - 51,582 PCN allergy
  - 103,164 control patients (matched by age/sex/admission date)
- PCN “allergy” history:
  - ↑ Vancomycin/Ciprofloxacin/Clindamycin
  - ↑ C. Difficile, MRSA, VRE prevalence
  - ↑ Length of stay and Cost $$


Classification

- Natural PCNs
  - Penicillin
- Aminopenicillins
  - Ampicillin, Amoxicillin
- Anti-staphylococcal PCNs
  - Nafcillin, Dicloxacillin, Oxacillin, Methicillin
- Anti-pseudomonal PCNs
  - Piperacillin, Ticarcillin

Mandell, Douglas, and Bennett's Principles and Practice of Infectious Diseases 7th Ed Copyright 2010

Allergy Classification

<table>
<thead>
<tr>
<th>Type I</th>
<th>Type II</th>
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</thead>
<tbody>
<tr>
<td>Anaphylactic (immediate hypersensitivity)</td>
<td>Cytotoxic – IgG, IgM</td>
</tr>
<tr>
<td>Anaphylaxis, urticaria, bronchospasm</td>
<td>Hemolytic anemia, nephritis</td>
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<tr>
<td></td>
<td>Idiopathic</td>
</tr>
<tr>
<td>Immune complex</td>
<td>Maculopapular eruptions</td>
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<tr>
<td>Ag–Ab</td>
<td>Eosinophilia</td>
</tr>
<tr>
<td>Serum sickness, drug fever</td>
<td>Stevens-Johnson syndrome</td>
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<tr>
<td></td>
<td>Exfoliative dermatitis</td>
</tr>
<tr>
<td></td>
<td>Cell-mediated by T Cells</td>
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<tr>
<td></td>
<td>Contact dermatitis</td>
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</table>

Idiopathic
Allergy Classification

**Type 1**
- Fast onset (< 1 hour)
  - But can take up to 72 hours
- IgE mediated
- Examples
  - Hives (urticaria)
  - Lip/throat swelling
  - Anaphylaxis
  - Trouble breathing (bronchospasms)

**Non-Type 1**
- Slower onset (usually > 72 hr)
- Not IgE mediated
- Examples
  - Maculopapular rash
  - Stevens Johnson Syndrome
  - Interstitial nephritis
  - Hemolytic anemia

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Imunochemistry

![Imunochemistry Diagram]

- Major antigenic determinant (benzyl penicilloyl)

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Major / Minor Antigenic Determinants

- **Major** (95%):
  - Benzyl penicilloyl

- **Minor** (5%):
  - Penicilloate, penilloate, and others…

*Important for penicillin skin testing*

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Mandell, Douglas, and Bennett's Principles and Practice of Infectious Diseases
7th Edition Copyright 2010
Conducting an Allergy History

- **Questions to ask:**
  1. What happened? When did the allergy occur? Were you informed by a family member?
  2. What antibiotic did you take? What route?
  3. Why were you taking it?
  4. How long after starting the drug did the reaction occur?
  5. How long did the reaction last? Was it relieved by diphenhydramine (Benadryl®) or steroids?
  6. What happened when the drug was discontinued?
  7. Have you taken any of these drugs before/after this reaction (say **brand** and **generic**)? If yes, what were the results?

Patient Case – H.P.

- **H.P.** = 32 year old male  **Ht:** 5’11”  **Wt:** 200lbs
- Admitted for a 2 day history of fever / chills and worsening left forearm cellulitis
- **Past medical history:**
  - IV drug abuse x 10 years
  - Recent left forearm cellulitis (started TMP/SMX 2 days ago)
  - Asthma
  - Seasonal allergies

Patient Case – H.P.

- **Medications:**
  - Albuterol MDI 2 puffs q6hr PRN bronchospasm
  - Mometasone 220 mcg 1 puff BID
  - Ibuprofen 200 mg PRN pain
  - Claritin 10 mg PRN allergies
- **Allergies:**
  - Penicillin, cats
Patient Case – H.P.

• Vitals:
  - HR 110 bpm
  - BP 115/82 mmHg
  - RR 18 breaths/min
  - Tmax 39.3

• Labs:
  - WBC 19.6
  - SCr 1.1
  - All other labs within normal limits

Patient Case – H.P.

• Physical Exam:
  - Injection site abscess + diffuse erythematus rash on left forearm extending from the wrist to the elbow.
  - All other findings within normal limits.

Patient Case – H.P.

• ED Course:
  - Fluid bolus given
  - Blood cultures drawn x2
  - STAT antibiotics:
    • Vancomycin pharmacy to dose
    • Meropenem 500 mg q6hr

• Sent to OR for Incision/drainage of forearm abscess and culture/sensitivity of organism
Patient Case – H.P.

- **Vitals:**
  - HR 110 bpm
  - BP 115/82 mmHg
  - RR 18 breaths/min
  - Tmax 39.3

- **Labs:**
  - WBC 19.6
  - SCr 1.1
  - All other labs within normal limits

3/4 Systemic Inflammatory Response Syndrome (SIRS) criteria met

SIRS + Source of infection = Sepsis

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Patient Case – H.P.

- **Diagnosis / Plan:**
  - Sepsis secondary to left forearm abscess/cellulitis
  - Continue current antibiotics (vancomycin + meropenem)
  - Await blood/abscess cultures

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Patient Case – H.P.

- When you arrive to work the next day……

- Blood cultures (2/2) and abscess culture
  - Gram positive cocci
  - Later identified as: **Methicillin sensitive staphylococcus aureus (MSSA)**
Patient Case – H.P.

• Questions to ponder:
  1. What is/are the drug(s) of choice for MSSA bacteremia?
  2. What about his allergy to penicillin?

Comparative Effectiveness of Beta-Lactams Versus Vancomycin for Treatment of Methicillin-Susceptible Staphylococcus aureus Bloodstream Infections Among 122 Hospitals

Vanco vs. β-lactam for MSSA

• 122 Veterans Affairs (VA) hospitals
• Retrospective cohort >5000 patients
• Primary outcome: 30-day all-cause mortality
  – Defined as death occurring within 30 days after the first MSSA positive blood culture was collected.
Vanco vs. β-lactam for MSSA

- Definitive therapy
  - Cefazolin/Nafcillin vs. Vancomycin
    - 43% reduced hazard of mortality compared with vanco
    - Hazard Ratio = 0.57; [95% CI, 0.46–0.71]
    - After adjusting for severity of illness, aggregate comorbidities, osteomyelitis, age, beta-lactam allergy, and dialysis/ESRD

  - “Among the patients who received definitive therapy with vancomycin, 47% (440/935) had a beta-lactam allergy.”

Table adapted from: Clin Infect Dis. 2015;61(5):741–9

<table>
<thead>
<tr>
<th></th>
<th>Vancomycin</th>
<th>Cefazolin</th>
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<tbody>
<tr>
<td>MSSA cure</td>
<td>82%</td>
<td>85%</td>
</tr>
<tr>
<td>MSSA recurrence</td>
<td>19%</td>
<td>9%</td>
</tr>
<tr>
<td>MSSA mortality</td>
<td>19%</td>
<td>6%</td>
</tr>
</tbody>
</table>

Table adapted from:

Vanco vs. β-lactam for MSSA

- IDSA guideline consensus:
  - Vancomycin is a 2nd line for MSSA due to…
    - Slower bactericidal activity, higher failure rates, and higher associated morbidity and mortality.

Nafcillin
Cefazolin

Rev Infect Dis. 1987; 9:981–907
What is H.P.'s allergy to PCN

• Documented allergy = Anaphylaxis

• What should we do next?
  A. D/c meropenem, continue vancomycin
  B. Continue meropenem, D/c vancomycin
  C. Start Nafcillin 12 gm continuous infusion, D/c other antibiotics
  D. Conduct an allergy history and perform a skin test if necessary

Questions for H.P.

1. What happened? When did the allergy occur? Were you informed by a family member?
   • “My mom said I had a REALLY bad reaction when I was a baby.”
2. What antibiotic did you take? What route?
   • “It was penicillin. I think it was a liquid?”
3. Why were you taking it?
   • “Maybe strep throat? Not sure though”
4. How long after starting the drug did the reaction occur?
   • “Almost immediately – I’m pretty sure”
5. How long did the reaction last? Was it relieved by diphenhydramine (Benadryl®) or steroids?
   • “Sorry dude, No Idea.”
6. What happened when the drug was discontinued?
   • “I got better.”
7. Have you taken any of these drugs before/after this reaction (say brand and generic)? If yes, what were the results?
   • “I don’t know any of those drug names.”

H.P.'s Allergy History

• After looking into H.P.’s past administered medications, you find he hasn’t received any Beta-lactams at your institution in the past 10 years.

• Is it time for a penicillin skin test????
Penicillin Skin Testing

• What is a Penicillin Skin Test?
  – Objective way to help rule out a Type 1 (immediate) allergy to penicillin.

• History
  – PSTs began in the 1960s

• No commercially available product (major antigenic determinant) between:
  – 2004 – 2009
  • This led to a sparsity of data during this time

More PCN Allergy Stats

• Of the ~10 – 20% of people who report a PCN allergy...<10% will have a “True” allergy when skin tested

• Among PST positive patients:
  • ~50% will be skin test negative after 5 years
  • ~80% will be skin test negative after 10 years

Patients with recent reactions are more likely to be truly allergic than those with remote reactions

**Penicillin Skin Testing**

- **Negative Predictive Value**
  - 97 – 99%

- **Positive Predictive Value**
  - 40 – 100% (likely close to 50%)

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**Who should Get a PST?**

- **Inclusion Criteria at Munson Medical Center:**
  - Patient is ≥18 years old
  - History of a reaction to any penicillin antibiotic
  - Penicillin or a β-lactam antibiotic is the drug of choice for treatment in this patient
  - Patient verbally consents to this procedure.

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**Who should NOT get a PST?**

- **Exclusion Criteria at Munson Medical Center:**
  - Patient reports an immediate reaction (within 1 hour) to a penicillin antibiotic within the last 5 years.
  - Patient is pregnant or nursing.
  - Patient has taken a first generation H1 receptor antagonist (i.e. diphenhydramine) in the past 24 hours, OR a second generation H1 receptor antagonist (i.e. loratadine, fexofenadine, cetirizine) in the past 5 days. **If unsure, a positive histamine scratch test will clarify**
  - Patient reports a hypersensitivity reaction other than a Type I reaction (hemolytic anemia, interstitial nephritis, Stevens-Johnson syndrome, etc.).
  - Patient has an intolerance to the antibiotic (i.e. stomach upset), not a true allergy.
  - Patient has severe immunosuppression (i.e. Neutropenia, HIV+ with CD4 < 200, immunosuppressives for organ transplant), not including diabetes or corticosteroid use.
Penicillin Skin Testing – REVIEW

Patient is determined to be a candidate

1. Scratch test (4 reagents)
   - Positive
   - Negative

2. Intradermal Testing (3 reagents)
   - Positive
   - Negative

Conclude testing – consider desensitization if β-Lactam needed

3. Oral / IV Challenge (optional)
   - Positive
   - Negative

Initiate therapy

Conclude testing – consider desensitization if β-Lactam needed

Penicillin Skin Testing

- Reagents:
  1. Benzylpenicilloyl polylysine (PPL) - (major determinant)
  2. Dilute Pen G 10,000 u/mL – (minor determinant)
  3. Histamine – (positive control)
  4. Sodium chloride – (negative control)

PRE-PEN® = only FDA approved major determinant product in USA

Penicillin Skin Testing

PRE-PEN® Penicillin G 10,000 units/mL Normal Saline Histamine

PRE-PEN® = only FDA approved major determinant product in USA
Penicillin Skin Testing

• Preparation:
  – Draw up reagents in 1 mL TB syringe
  – Label each syringe (!! Very important)
  – Alcohol swab forearm
• Map out reagents for scratch test

Penicillin Skin Testing

• Procedures:
  1. Scratch test with all 4 reagents – Wait 15 – 20 minutes
     • If positive, conclude testing
     • If negative, move on to step 2

Penicillin Skin Testing

• Scratch test results
  – Positive: PRE-PEN® or Pen G scratch test induration \( \geq 3 \text{mm} \) than the saline control
  – Negative: Induration < 3mm than the saline control

Must have a positive histamine wheal
*Ideally \( \geq 5 \text{mm} \)
If not, conduct testing on another day
Penicillin Skin Testing

- Procedures:
  2. **Intradermal test** with:
     - Benzylpenicilloyl polylysine (PPL)
     - Dilute Pen G
     - Sodium chloride control
     - 5 total intradermal blebs
     - Test Sites:
       - Forearm opposite to the scratch test site
       - Back of upper arm (may be more comfortable for patients)

Penicillin Skin Testing

- Intradermal Test
  - Same preparation as with the scratch test
  - Insert 2-3 mm bleb – circle original size
  - Wait 15 – 20 minutes
Penicillin Skin Testing

- Intradermal Test Results
  - **Positive**:
    - Significant increase in bleb size
    - Wheal diameter 3mm or larger
    - Itching and flare are common
  - **Negative**:
    - NO increase in bleb size
    - NO reaction greater than the control site

Penicillin Allergy Skin Testing with PRE-PEN® for Hospitals

https://www.youtube.com/watch?v=eRkfXn97Af8

Penicillin Skin Testing

- Oral / Intravenous Challenge (*Optional*)
  - Usually challenge with the treatment of choice
  - Observe patient for up to 1 hour
  - More of a concern in the outpatient setting
  - Examples:
    - Amoxicillin 250 mg x1 or Pen VK 250mg x1

Penicillin Skin Testing

- Cost/Time:
  - ~$100 for supplies (if done once weekly)
  - ~1.5 hour to perform allergy history and PST
  - Total Cost = no greater than $200
Penicillin Skin Testing

- Billing and reimbursement...
  - **Inpatient**: Likely lumped into DRG
  - **Outpatient**: Better chance at directly billing for product and services

Back to our patient, H.P.

- PST was conducted
  - Result = NEGATIVE
- Nafcillin 12gm continuous infusion was started.
- No reaction noted within the 1st hour
- Nursing made aware to continue monitoring

Patient Case H.P.

- What did we do for our patient?
  - Potentially reduced mortality (according to literature)
  - Avoided vancomycin monitoring and nephrotoxicity
  - Avoided risk of selecting for resistant organisms
  - De-labeled PCN allergy (future antibiotic courses)
    - Added “Penicillin Allergy Skin Test Negative” to EHR
- At what cost?
  - 1.5 hours of pharmacist time
  - $100 product

Is that worth it?
PST in hospitalized patients

5. Frigas E, et al. Potential Cost Savings

Potential Cost Savings

Suggested Improved Outcomes

Author’s Conclusion

“A pharmacist-managed penicillin allergy skin-testing service at a tertiary care teaching hospital was well received by physicians and showed potential to avoid unnecessary use of alternative antibiotics.”

Cross-Reactivity
Monobactam

- **Monobactam** – No cross reactivity

- Aztreonam is the only available monobactam
  - Same side chain as **Ceftazidime**

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Carbapenems

Historically, cross-reactivity ~50% in one study*

Newer trials show < 1%

<table>
<thead>
<tr>
<th>Prospective Clinical Trial</th>
<th>Penicillin Sensitive (n)</th>
<th>Tolerated Carbapenem (n)</th>
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<tbody>
<tr>
<td>Ann Intern Med. 2007; 146(4):266-9</td>
<td>104</td>
<td>103</td>
</tr>
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Cephalosporins

- **Cephalosporins** and penicillin
  - Before 1980 \(\rightarrow 10\%\)
    - **Reason**?
      - Contamination
      - Study design
  - Since 1980 \(\rightarrow ~2\%\)
    - 1st gen >> 2nd 3rd 4th 5th
  - **Why**?
Cephalosporins – Side Chains

Patient with a history of penicillin allergy requires a cephalosporin (ie for CAP)

Low Risk
- Penicillin reaction occurred >10 years ago
- Penicillin reaction did not include features of IgE mediated reaction

Give cephalosporin directly

Moderate Risk
- Penicillin reaction occurred within the past 10 years
- Penicillin reaction included features of IgE mediated reaction

High Risk
- Patients with probable anaphylaxis to penicillin based on history
- Perform PST

Adapted from: Christopher Ludlum, MD, Infectious Disease Physician

Steps to Implementation

1. Determine a core group that will be doing the testing (i.e. pharmacist, nurse, allergist, other) and designate a PST champion(s)
2. Develop a protocol that works for your setting
3. Education (pharmacists, pharmacy technicians, nurses, physicians)
   - How to perform the test and read results
4. Determine how you'll document in the EHR
5. Develop annual competency

Challenges to Implementation

1. Who’s going to do it?
2. Time commitment
3. Support from the medical staff
   - Physicians
   - Nursing
   - Administration

Future Directions

- Where can this be implemented?
  - Pre-operative setting (PST shown to decrease use of Vanco)*
  - Outpatient setting (easier to bill for)
  - Inpatient setting
    - Emergency departments
    - Intensive care units

Antimicrobial Stewardship

Penicillin Skin Testing: Potential Implications for Antimicrobial Stewardship

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1Department of Pharmacy Practice, Nova Southeastern University College of Pharmacy, Pompano Beach, Florida; 2Department of Pharmacy Practice, Nova Southeastern University College of Pharmacy, Fort Lauderdale, Florida.

As the progression of multidrug-resistant organisms and lack of novel antibiotics move us closer toward a potential post-antibiotic era, it is paramount to preserve the longevity of current therapeutic agents. Moreover, novel interventions for antimicrobial stewardship programs are integral to combating antimicrobial resistance worldwide. One unique method that may decrease the use of second-line antibiotics (e.g., linezolid, vancomycin) while facilitating access to a preferred antibiotic regimen is penicillin skin testing. While not all patients who self-report a penicillin allergy will have an altered cutaneous reaction, approximately 3% of the general population and 10% of patients with a self-reported penicillin allergy will demonstrate a true penicillin allergy. Significant potential exists to utilize a penicillin skin test to safely identify those who may receive penicillin as a first-line antibiotic. In this article, we provide information on the background, associated costs, currently available literature, pharmacists’ role, antimicrobial stewardship implications, potential barriers, and misconceptions, as well as future directions associated with the penicillin skin test.

Key Words: antimicrobial stewardship, beta-lactam/penicillin, penicillin allergy, penicillin skin test.


Penicillin Skin Testing

The Role of the Pharmacist and Pharmacy Technician

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