Session 3: Infectious Disease
B: Pharmacist Managed Penicillin Skin Testing: An Antimicrobial Stewardship Initiative
3:00pm - 4:00pm

ACPE UAN 107-000-12-020-L01-P 0.1 CEU/1.0 Hr
Activity Type: Application-Based

Program Objectives for Pharmacists: Upon completion of this CPE activity participants should be able to:
1. Discuss the immunologic background of drug allergy
2. Describe the modified Gell and Coombs system for classifying drug allergy reactions
3. Discuss the clinical impact of penicillin allergy
4. Relate the history of penicillin skin testing
5. Describe the role of skin testing in antimicrobial stewardship
6. Convey the testing procedure and how pharmacists can implement such a service

Speaker: Geoffrey C. Wall, PharmD, FCCP, BCPS, CGP, is an Associate Professor, Department of Pharmacy Practice, College of Pharmacy at Drake University, and Clinical Assistant Professor, Department of Pharmacology and Physiology at Des Moines University, College of Osteopathic Medicine. His clinical practices include the Internal Medicine and Medical Intensive Care Teaching Services at Iowa Methodist Medical Center as well as the Inflammatory Bowel Disease Center in Des Moines, IA. Dr. Wall received his Bachelor of Science in Pharmacy from the University of Utah in 1992 and his Doctor of Pharmacy from Idaho State University in 1998. He completed an ASHP-accredited Internal Medicine Specialty Residency at Scott and White Memorial Hospitals and Clinics in 1999. He is Board-Certified in Pharmacotherapy and is a Certified Geriatric Pharmacist. He is a Fellow of the American College of Clinical Pharmacy. Dr. Wall has written a number of peer-reviewed papers and textbook chapters on a variety of topics, and has designed or participated in several clinical trials. His research interests include drug treatment of gastrointestinal disorders, including inflammatory bowel disease (IBD), drug allergy and rheumatologic disorders. He has been selected for several teaching awards and was the Drake University Madelyn Levitt Mentor of the Year in 2008. He was also named Hospital Pharmacist of the Year by the Iowa Pharmacy Association in 2004.

Speaker Disclosure: Geoff Wall reports consulting for ALK-Abello and is a speaker’s bureau member for ALK-Abello, Merck & Takada. Off-label use of medications will be discussed during this presentation.
Pharmacist Managed Penicillin Skin Testing: An Antimicrobial Stewardship Initiative

Geoffrey C. Wall, Pharm.D., FCCP, BCPS, CGP
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Iowa Methodist Medical Center
Professor of Pharmacy Practice
Drake University College of Pharmacy
Des Moines, IA

Objectives

- Discuss the immunologic background of drug allergy
- Describe the modified Gell and Coombs system for classifying drug allergy reactions and discuss drugs that fit each category
- Discuss the clinical impact of penicillin allergy
- Relate the history of penicillin skin testing
- Describe the role of skin testing in aiding antimicrobial stewardship goals in a health-system
- Convey the testing procedure and how pharmacists can implement such a service

Introduction

- Adverse drug reactions are a major problem in the U.S.
  - Estimated 2 MILLION serious ADRs yearly
  - Various figures on attributable mortality but may be as many as 100,000 deaths/year
  - Little data on ambulatory ADRs

Drug Allergy

- Hypersensitivity reactions
  - Account for up to 20% of all serious ADRs
  - Global incidence of 2.3% of hospitalized patients
  - Mortality ranges from 0.2-1.2% depending on study
  - Often predictable and avoidable

Disclosures

Dr. Wall is on the Speaker's bureau of Merck, Takeda, ALK-Abello, and Sanofi Pharmaceuticals

CEI has taken steps to resolve any potential conflicts through a peer review process involving 2 independent reviewers. If there are any questions regarding this process, please contact admin@TheCEInstitute.org.

Problems Studying Drug Allergy

- Definitions
  - Allergy (immune-mediated) vs ADR
- Multiple drugs may be responsible
- Lack of diagnostic procedures
- Relies on patient history
- Other factors can confound
- Training in this area
  - Despite being one of the more common DI questions posed to Pharmacists
Assessment Question #1
- As a hospital pharmacist, you perform an intake medication history on a new patient admitted for atrial fibrillation and an asthma exacerbation. When questioned about allergy history the patient claims an allergy to Metoprolol, claiming it caused his, “heart rate to drop too low”. Which of the following statements is MOST pertinent concerning this case?
  - a. He should not receive any other beta-blockers because of his allergy to Metoprolol
  - b. His reaction to Metoprolol is an expected pharmacologic effect of the drug and is not an allergy
  - c. Extended release Metoprolol would be more likely to be tolerated in this patient
  - d. Propranolol would be preferred to Metoprolol in this patient as it is less likely to cause bradycardia

Definition of Drug Allergy
- An adverse reaction to a medication that meets several criteria:
  - The reaction is NOT an expected pharmacologic effect
  - Clinical symptoms resemble an allergic reaction (e.g. skin reactions, anaphylaxis)
  - Reaction can occur at a dose below that needed for pharmacologic effect
  - Resolution occurs within days/weeks of D/C’ing agent
  - Chemical cross-reactivity can occur

Assessment Question #2
- Hemolytic anemia associated with penicillin would be classified as what kind of reaction according to the modified Gell and Coombs system?
  - a. I
  - b. II
  - c. IV-A
  - d. IV-C

Modified Gell and Coombs System

<table>
<thead>
<tr>
<th>Reaction Type</th>
<th>Clinical Symptoms</th>
<th>Immune Cause</th>
<th>Example Drug</th>
<th>Future Use?</th>
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<tbody>
<tr>
<td>I</td>
<td>Urticaria, Anaphylaxis</td>
<td>IgE</td>
<td>Penicillin</td>
<td>Desensitize</td>
</tr>
<tr>
<td>II</td>
<td>Hemolytic Anemia, Immune Thrombocytopenia</td>
<td>IgG</td>
<td>Penicillin</td>
<td>C/I</td>
</tr>
<tr>
<td>III</td>
<td>Delayed Fever, Arthralgias</td>
<td>IgG</td>
<td>Phenytoin</td>
<td>C/I</td>
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<tr>
<td>IV_A</td>
<td>Contact Dermatitis (CD)/PPD RXN</td>
<td>Th1</td>
<td>Latex</td>
<td>C/I</td>
</tr>
<tr>
<td>IV_B</td>
<td>Delayed MP Rash</td>
<td>Th2</td>
<td>Sulfonamides</td>
<td>May reuse</td>
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<tr>
<td>IV_C</td>
<td>SJ/S/TEN/CD</td>
<td>CTC</td>
<td>Sulfonamides</td>
<td>C/I</td>
</tr>
<tr>
<td>IV_D</td>
<td>Psoriasis</td>
<td>CD8</td>
<td>?</td>
<td>?</td>
</tr>
</tbody>
</table>

Assessment Question #3
- What manifestation of a Type IV_b allergic reaction would a pharmacist MOST likely encounter in clinical practice?
  - a. Urticaria from Ciprofloxacin?
  - b. Hypersensitivity syndrome from Allopurinol
  - c. Maculopapular rash from Bactrim®
  - d. Hives from an infusion of infliximab

Other Drug Allergy Reactions
- Anaphylactoid reactions
  - Caused by direct release of mediators to mast cells—Not by IgE
  - Example: IV contrast media
- Hypersensitivity syndrome
  - Extensive rash, fever, CNS changes, ARF
  - Examples: Anticonvulsants, Sulfonamides, Allopurinol
  - NOTE: MP (Molliform) rash is most common type of hypersensitivity reaction
Mobilliform (Maculopapular) rash

- The “classic” Drug rash
- Usually delayed reaction
- Starts on trunk/back and spreads
- Face/Palms/Soles spared
- May or may not be pruritic

Urticaria

- Classic for IgE reactions
- Usually occurs immediately
- Very pruritic
- Confluent welts on trunk/back
- May spread to face

Facial angioedema

- Also IgE mediated
- Usually immediate
- PCNs, ACEI, CCB, other agents can cause
- Can be life-threatening
- ARBs in this population?

Stevens-Johnson syndrome

- Sulfonamides, Anticonvulsants, CCBs implicated
- 10% mortality
- Skin blistering common
- Must treat as severe burn
- Offending agent absolutely C/I

Toxic epidermal necrolysis

- Most severe form of blistering type allergic reactions
- Greater skin detachment
- Same agents as SJS
- Usually treated in Burn units
- 30% mortality
- Steroids controversial
- Again, absolutely C/I

Classic poison ivy dermatitis

- Usually occurs with topical exposure
- Delayed reaction
- Intensely pruritic
- May take weeks to resolve even with systemic steroids
- Usually not life-threatening
Penicillin Allergy

- Approximately 10-15% of hospital patients claim this allergy
- Positive skin reactions in one study in children was 10%
- About 70% of patients who had a childhood reaction to PCN, become tolerant to the molecule by adulthood
- Only drug allergy with standardized testing (Type I reactions only)


Reported Reactions to Penicillin

Exanthem (20%)
Anaphylaxis (7%)
Urticaria (35%)
Other (28%)
Uncertain (9%)


Determinants of PCN Allergy

- The ONLY standardized drug allergy test
- 99% Negative predictive value (NPV)
- Safe even in extremely allergic patients IF scratch testing used first
- Can be used “preemptively” for future uses of ABX
- Relatively simple procedure

Annals of Allergy, Asthma & Immunology 1999:83:665-700

Assessment Question #4

- Which of the following statements is true concerning Penicillin allergy skin testing?

  a. If the test is negative the patient has no chance of developing a penicillin allergy
  b. It could be used to rule out the possibility of interstitial nephritis with penicillin
  c. Testing is safe if scratch testing is done first
  d. None of the above statements are true

PCN Allergy Skin Test

- The ONLY standardized drug allergy test
- 99% Negative predictive value (NPV)
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History of Penicillin Skin Testing in US

- 1965 – 2004: PRE-PEN Production
  - Kremers-Urban, Schwartz-Pharma, Hollister-Steir
- 2004: Last H-S lot recalled due to suspected instability
  - Production of Pre-Pen abandoned
- 2004-2009: Penicillin skin testing largely discontinued
  - Without Pre-Pen skin testing has low NPV
- 2009: AllerQuest, LLC & ALK bring PRE-PEN back to market
  - FDA Approval date: September 18
  - Distribution begins: December, 2009
Pre-Pen® is the Major Determinant of PCN IgE Mediated Allergy

Determinants of PCN Allergy
- Pre-Pen®
  - Responsible for 90% of all Type I allergies
- Minor Determinants (MDM)
  - Penicillin G
  - Penicilloate
  - Penilloate
  - Responsible for about 8-9% of all Type I reactions
  - Not available commercially in the U.S.

Value of Skin testing with Pre-Pen® + MDM
- Penicillin skin test results with Pre-Pen® + MDM are highly predictive of current tolerance of Beta-Lactam treatment
  - PPV - 50 – 70%
  - NPV - 2 – 5% [all mild, self-limited]
  - 75% of positive PCN skin tests detected by PRE-PEN (major determinant) alone in a study of 5063 patients at an STD clinic.


How Important are Minor Determinants?
- MDM picks up 3-4% sensitized patients
- How important is the 3-4% missed patients?
  - Missing data: provocation of such pts
  - Some would be false +, as is true of Pre-Pen +
- Conclusion: We need MDM for highest negative predictive value

AAAAI Guidelines on PCN Allergy
- “Skin testing with penicilloylpolyllysine (Pre-Pen) and penicillin G appears to have adequate negative predictive value in the evaluation of penicillin allergy”

Annals of Allergy, Asthma & Immunology 1999;83:665-700

Candidates for Testing
- Candidates for Testing
  - Any patient with a history of a reaction to a penicillin antibiotic that may have been IgE-mediated
  - Any patient who is currently denied access to beta-Lactam antibiotics out of concern for such reactions
- Contraindications to Testing
  - Patients with clear histories of severe skin reactions such as Stevens-Johnson syndrome or toxic epidermal necrolysis
  - Severely immunocompromised?
Value of Penicillin Allergy Testing

- Access to a safe and cost effective treatment
  - Alternative antibiotics are more costly than penicillin as they are often Tier 3 medications and not commonly generic
  - Alternatives antibiotics are often more toxic than beta-Lactams
- Combating Drug Resistance
  - Expanded use of penicillin and related antibiotics ensures that broad spectrum antibiotics are reserved for the most serious cases.
- Ease patient and PCP concerns about restricted choices
- Antimicrobial Stewardship goals

The Methodist Experience with PCN Allergy Skin Testing

Service History

- Developed by clinical pharmacy staff in conjunction with allergist
- Specific protocol followed for each case
- Didactic and practical review on PCN allergy
- Penicillin G mixture made prior to test
- Most hospital patients eligible
- Strict inclusion/exclusion criteria
- Consult service approved by P&T Committee

Screening Patients

- Extensive drug/allergy history taken
- Antibiotics specifically questioned about:
  - Augmentin, cephaalexin, erythromycin, amoxicillin, levaquin, ceftin

Skin Testing Procedure

- Detects Type 1 allergic reactions only
- Training
  - Required per protocol
  - Allergic reactions
  - Skin testing procedure

Skin Testing Procedure

- Supplies
  - 0.9% sodium chloride (negative control)
  - Histamine base 0.1 mg/ml (positive control)
  - Pre-Pen® (major determinant)
  - Reconstituted Penicillin G, diluted to a strength of 10,000 U/ml (minor determinant)
  - 0.5-1.0 cc syringe w/ 26-28g needle: puncture device (e.g. Microlance® blood lancet or Duotip device)
  - Alcohol swipes, fine ball point pen, mm rule

Skin Testing Procedure

- No histamine blockers within 24 hrs
- Scratch Test
  - Positive
  - Negative
  - Indeterminate
- Intradermal Test
- Record results
- Dose challenge

Procedure for Penicillin Skin Testing

I. Preliminary scratch testing

- Supplies
  - Histamine, diluent control, PRE-PEN®, Pen G
  - 2-3 cm apart
  - Place drops of supplies on skins and scratch with lancet device or use Duotip device
- Read: 15-20 min; mark perimeter, measure, record

- Criteria for PRE-PEN® & Pen G
  - Positive >3mm increase in wheal diameter
  - If one or both negative or equivocal, continue with intradermal testing

II. Intradermal Testing

- Intradermal testing with Pre-Pen® and Penicillin G and diluent control
  - Duplicate placement >3cm apart
  - Mark perimeter of wheal at placement
  - Read 20 min; mark wheal (+/- eryth) perimeters
- Criteria: wheal size > diluent site {>3mm increase}

Graded Dose Challenge

- Rationale:
  - Extra margin safety w/o MDM
  - Proof of claim for patient and referring physician
  - Probably enhanced effectiveness of testing
- Optional, but recommended especially when
  - Reaction was recent or severe
  - Patient frightened of re-treatment

Graded Dose Challenge

- Start with ¼ to 1/8 target dose and give over 15 minutes. Observe for 15 minutes for reaction, then double dose until target dose achieved
- Oral or IV
Results (n = 51)

All R/O, Negative, and Indeterminate patients received Beta-lactam ABX without incident

Conclusions

- Skin testing is safe and reliable
- A pharmacist-run PCN allergy skin testing service has been successfully established at a large community teaching hospital


Service Hold

- Service on forced hold from 2005-2010 while Pre-Pen unavailable
- Now available—retraining and re-initiation of service with CPA completed
- Restarted 4/2011

Cross-reactivity of Penicillin and other Beta-Lactams

Cross-Reactivity With Other Beta-Lactams

- Cephalosporins
  - See later slides
- Carbapenems
  - Imipenem originally thought to be about 50% cross-reactive
  - Recent data suggests that meropenem or imipenem has little or no cross reactivity in PCN allergic patents—skin testing may be helpful in this case
- Monopenems (aztreonam) safe in PCN allergy


Cephalosporin Allergy

- Implicated in all types of allergic reactions
- Less known about determinants of reaction
- Wide variety of metabolites
- Significant differences in structure between cephalosporin "generations"
- Anaphylaxis rarer than with PCNs

Cross-Reactivity With PCNs

- Italian study looked at cross-reactivity rates in patients with positive PCN skin test
- N = 128 patients with IgE reaction + skin reactivity
- Skin tested with various cephalosporins then oral challenges
- Results: 14/128 (11%) had positive skin tests for cephalosporins
- Conclusions: about 10% of patients with + PCN skin tests are at risk for IgE reactions to cephalosporins


Assessment Question #5

- A patient with an IgE (hives) reaction to amoxicillin several years ago has developed a bronchitis that his physician would like to treat with a cephalosporin. Which of these agents has the LEAST chance of causing a drug allergy in the patient?
  - a. Cefpodoxime
  - b. Cefuroxime
  - c. Cephalexin
  - d. Cefadroxil

Cross-Reactivity With PCNs

- Some reactions may be side-chain specific
  - Some data to suggest that allergy to one cephalosporin does NOT predict a reaction to one in another generation
  - Cephalexin has a side-chain similar to ampicillin
  - Later generation cephalosporins have different side-chains and would be expected to have a lower cross-reactivity in PCN allergic patients
- Skin test to PCN if possible and cephalosporins are needed
  - A negative skin test means cephalosporins can be given

PCN Desensitization

- IgE reactions ONLY (NOT SJS/TENS)
- Should only when considered when PCN/Beta Lactam ABX absolutely necessary
- Double dose every 15 minutes until full therapeutic dose reached
- If interrupted must restart procedure
- 1/3 of patients will have minor reactions

PCN Desensitization Protocol

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<th>Step</th>
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<th>Amount (mL)</th>
<th>Dose (mg)</th>
<th>Cumulative dose (mg)</th>
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<td>800.0</td>
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<td>800.0</td>
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</table>

Primary Cephalosporin Allergy

- Would avoid other cephalosporins in a patient with a history of a previous severe reaction
- If a PCN is needed skin test is possible
- May desensitize if a certain cephalosporin is needed
- Many published protocols

* Interval between doses is 15 minutes.

**Poston SA et al. Pharmacotherapy 2004;24:668-72.**
Conclusions

- Pharmacists in all practices aid with drug selection in patients with a history of medication allergy
- Therefore, understanding the latest information on this subject is critical
- Penicillin allergy skin testing CAN be performed by pharmacists and can aid in antibiotic stewardship goals
Post-Assessment Questions

1. As a hospital pharmacist you perform an intake medication history on a new patient admitted for atrial fibrillation and an asthma exacerbation. When questioned about allergy history the patient claims an allergy to Metoprolol, claiming it caused his, “heart rate to drop too low”. Which of the following statements is MOST pertinent concerning this case?
   A. He should not receive any other beta-blockers because of his allergy to Metoprolol
   B. His reaction to Metoprolol is an expected pharmacologic effect of the drug and is not an allergy
   C. Extended release Metoprolol would be more likely to be tolerated in this patient
   D. Propranolol would be preferred to Metoprolol in this patient as it is less likely to cause bradycardia

2. Hemolytic anemia associated with penicillin would be classified as what kind of reaction according to the modified Gell and Coombs system?
   A. I
   B. II
   C. IV-A
   D. IV-C

3. What manifestation of a Type IVa allergic reaction would a pharmacist MOST likely encounter in clinical practice?
   A. Urticaria from Ciprofloxacin?
   B. Hypersensitivity syndrome from Allopurinol
   C. Maculopapular rash from Bactrim®
   D. Hives from an infusion of infliximab

4. Which of the following statements is true concerning Penicillin allergy skin testing?
   A. If the test is negative the patient has no chance of developing a penicillin allergy
   B. It could be used to rule out the possibility of interstitial nephritis with pencillin
   C. Testing is safe if scratch testing is done first
   D. None of the above statements are true

5. A patient with an IgE (hives) reaction to amoxicillin several years ago has developed a bronchitis that his physician would like to treat with a cephalosporin. Which of these agents has the LEAST chance of causing a drug allergy in the patient?
   A. Cefpodoxime
   B. Cefuroxime
   C. Cephalexin
   D. Cefadroxil
A 74-year old female is admitted to the hospital with weakness, confusion and dysuria. Urinalysis and culture reveals the patient has a urinary tract infection. Unfortunately this is the patient’s 4th such infection and hospitalization for this problem in the last year. The patient’s current culture and sensitivity is as follows:

Result: > 100,000 cfu/ml E. Coli

<table>
<thead>
<tr>
<th>Antimicrobial</th>
<th>MIC mcg/ml</th>
<th>Int</th>
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<td>CEFUROXIME</td>
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</table>

Complicating matters is her drug allergy history which includes a history of Stevens-Johnston syndrome to Bactrim® (20 years ago), history of breathing problems with penicillin (as a child), and recent episode of rash and hives to cephalexin only 6 months ago. The patient is started on intravenous imipenem and improves significantly. To assess the patient’s penicillin allergy, the staff pharmacist performs penicillin allergy skin testing which is negative. The patient is given a graded dose challenge of amoxicillin which she tolerates well and she is sent home on that medication. Two months later the patient is again admitted with signs and of a urinary tract infection and the admitting physician empirically starts intravenous imipenem. The physician, who was not present during the patient’s previous admission, notes the patient’s drug allergies as: Bactrim®, penicillin, and cephalexin.