Disclosures

- I have no actual or potential conflict of interest in relation to this program/presentation
Objectives

- Examine the epidemiology and cost of penicillin allergy
- Briefly review the immune system
- Appreciate the pathophysiology of beta lactam allergy
- Understand the testing procedure
- Discuss predictive value
- Evaluate efficacy and safety of testing in sub-populations
- Review cephalosporin cross reactivity
Penicillin Allergy
Penicillin Allergy

- Most commonly reported drug allergy

- Penicillin allergy is self-reported in 10% of American population
  - 20-25 million Americans
  - Type I immediate hypersensitivity

- Systematic review/meta-analysis of 2010 – 2015 databases; Prevalence of β-lactam hypersensitivity:
  - 1.98% pediatric group
  - 7.78% adult group
  - 2.84% combined group
Reasons for Discordance

- Decreasing rate of positive skin test results over last 20 years
  - Rates of positive penicillin testing declined from >10% to <5% from 1995-2007 (Macy et al. The Permanente Journal 2009)

- Waning reactivity

- Index reaction was not attributable to penicillin
  - Alternative antibiotic
  - Underlying illness
  - Interaction between infection and antibiotic
Penicillin specific IgE antibodies decrease over time
- 50% of patients lose sensitivity 5 years after last reaction
- 80% of patients lose sensitivity 10 years after last reaction

Prevalence of positive skin test was related to time elapsed from index reaction (Sullivan et al. JACI 1981)
- 93% positive 7-12 months after reaction
- 22% positive 10 years after reaction
Morbidity of β-Lactam Allergy

- Increased use of broad spectrum antibiotics
  - Vancomycin: 20-40% versus 12-17%
  - Fluoroquinolones: 25% versus 14%
  - Clindamycin: 24% versus 6%
  - 3rd generation cephalosporins

Macy et al. JACI 2014 & Picard et al. JACI In Practice, 2013
Morbidity of β-Lactam Allergy

- Antibiotic resistance
  - Vancomycin resistant enterococci
    - 30% more VRE
    - Risk factors: Vancomycin, cephalosporins & quinolones
  - MRSA: 14% more often
  - Clostridium difficile
    - 23% more often
    - Quinolones and cephalosporin

Macy et al. JACI 2014 & Picard et al. JACI In Practice, 2013
Surgical Morbidity

- 2016 study examining preoperative prophylactic antibiotic choice and surgical site infection rates after hysterectomy
- Patients received β-lactam or alternative to β-lactam antibiotics
- 21,000 + hysterectomies
- Overall rate of surgical site infection: 2.06%
  - β-lactam: 1.8%
  - Non-β-lactam: 3.1%; adjusted OR 1.7

Uppal, Obstet Gynecol Feb 2016
Retrospective, matched cohort study of 52,000 patients with charted allergy to penicillin on admission

- Kaiser Foundation hospitals 2010-2012
- 11.2% of hospitalized patients

Primary and secondary goals

Cases with penicillin allergy

- Averaged 0.59 more hospital days
- Significantly more fluoroquinilones, clindamycine and vancomycin (p<.0001)
- Increased prevalence of C. difficile, MRSA and VRE infections
Antibiotics associated with increased risk of C. difficile

N: Courses of antibiotics
n: Unique subjects exposed

**TABLE IV. The top 10 antibiotics used by cases and control subjects during hospitalizations**

<table>
<thead>
<tr>
<th></th>
<th>Cases (51,582)</th>
<th>Control subjects (103,164)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Vancomycin:</td>
<td>Cefazolin:</td>
</tr>
<tr>
<td></td>
<td>N = 16,685</td>
<td>N = 38,117</td>
</tr>
<tr>
<td></td>
<td>n = 10,872</td>
<td>n = 32,614</td>
</tr>
<tr>
<td></td>
<td>(21.2%)</td>
<td>(31.6%)</td>
</tr>
<tr>
<td>2</td>
<td>Ciprofloxacin*:</td>
<td>Ceftriaxone*:</td>
</tr>
<tr>
<td></td>
<td>N = 15,154</td>
<td>N = 30,220</td>
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<tr>
<td></td>
<td>n = 10,888</td>
<td>n = 21,726</td>
</tr>
<tr>
<td></td>
<td>(21.1%)</td>
<td>(21.1%)</td>
</tr>
<tr>
<td>3</td>
<td>Clindamycin*:</td>
<td>Vancomycin:</td>
</tr>
<tr>
<td></td>
<td>N = 14,447</td>
<td>N = 20,099</td>
</tr>
<tr>
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<td>n = 12,579</td>
<td>n = 12,772</td>
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<tr>
<td></td>
<td>(24.4%)</td>
<td>(12.4%)</td>
</tr>
<tr>
<td>4</td>
<td>Ceftriaxone*:</td>
<td>Metronidazole:</td>
</tr>
<tr>
<td></td>
<td>N = 11,683</td>
<td>N = 18,392</td>
</tr>
<tr>
<td></td>
<td>n = 8,570</td>
<td>n = 14,341</td>
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<tr>
<td></td>
<td>(16.6%)</td>
<td>(13.9%)</td>
</tr>
<tr>
<td>5</td>
<td>Metronidazole:</td>
<td>Ciprofloxacin*:</td>
</tr>
<tr>
<td></td>
<td>N = 11,427</td>
<td>N = 17,461</td>
</tr>
<tr>
<td></td>
<td>n = 8,542</td>
<td>n = 13,416</td>
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<tr>
<td></td>
<td>(16.6%)</td>
<td>(13.0%)</td>
</tr>
<tr>
<td>6</td>
<td>Cefazolin:</td>
<td>Piperacillin:</td>
</tr>
<tr>
<td></td>
<td>N = 8,489</td>
<td>N = 14,561</td>
</tr>
<tr>
<td></td>
<td>n = 7,490</td>
<td>n = 11,157</td>
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<tr>
<td></td>
<td>(14.5%)</td>
<td>(10.8%)</td>
</tr>
<tr>
<td>7</td>
<td>Gentamicin:</td>
<td>Azithromycin:</td>
</tr>
<tr>
<td></td>
<td>N = 6,025</td>
<td>N = 12,837</td>
</tr>
<tr>
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<td>n = 5,329</td>
<td>n = 10,045</td>
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<tr>
<td></td>
<td>(10.3%)</td>
<td>(9.7%)</td>
</tr>
<tr>
<td>8</td>
<td>Azithromycin:</td>
<td>Ampicillin:</td>
</tr>
<tr>
<td></td>
<td>N = 5,812</td>
<td>N = 7,153</td>
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<tr>
<td></td>
<td>n = 4,610</td>
<td>n = 6,536</td>
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<tr>
<td></td>
<td>(8.9%)</td>
<td>(6.3%)</td>
</tr>
<tr>
<td>9</td>
<td>Moxifloxacin*:</td>
<td>Gentamicin:</td>
</tr>
<tr>
<td></td>
<td>N = 3,908</td>
<td>N = 6,480</td>
</tr>
<tr>
<td></td>
<td>n = 3,194</td>
<td>n = 5,809</td>
</tr>
<tr>
<td></td>
<td>(6.2%)</td>
<td>(5.6%)</td>
</tr>
<tr>
<td>10</td>
<td>Ceftazidime*:</td>
<td>Ceftazidime*:</td>
</tr>
<tr>
<td></td>
<td>N = 3,641</td>
<td>N = 5,916</td>
</tr>
<tr>
<td></td>
<td>n = 2,741</td>
<td>n = 4,641</td>
</tr>
<tr>
<td></td>
<td>(5.3%)</td>
<td>(4.5%)</td>
</tr>
</tbody>
</table>

Macy JACI March 2014
Economic Cost of β-lactam Allergy

- Outpatient antibiotic cost
  - $26.81 versus $16.28

- Inpatient antibiotic cost
  - $137 versus $75
  - Equivalent of $241.61/hospital stay

- Duration of hospital stay
  - 0.59 days longer than control subjects

- Potential cost savings for penicillin skin testing compared to extended hospital stay
  - Calculated as $60 million during 3 year study period

- Multiply cost savings over patient’s lifetime
Clinical Outcomes of Allergy Label

- 12,000 inpatients who received 1 antimicrobial
- 11% (1324) with antimicrobial allergy label

Adjusted Outcomes:
- Length of stay was 1.16 days longer
- ICU admission 1.4 times greater (aOR)
- Receipt of >1 course of antibiotics 1.6 (aOR)
- Increased risk of death 1.56 (aOR)
- NOT associated: readmission within 4 weeks of discharge

Charneski et al. Pharmacotherapy, 2012
Persistence of EMR Labeling

- Persistence of penicillin allergy label (PAL) in an EMR despite documented penicillin tolerance
- Ambulatory Patients >18 years or older with >3 visits
  - 67% were labeled upon entry into the EMR
  - 96% remained persistently labeled
- 39% (4321/11,216) had EMR documentation of having received and tolerated a penicillin
- Increased prevalence of C. difficile infection
- Greater broad spectrum antibiotic utilization

Gerace et al. JACI 2015
Survey on Prescriber Understanding

- 276 prescribers surveyed early 2016
  - Advanced practice providers & attending physicians
- Only 30% correctly identified that 90% of patients with PAL would tolerate penicillin
- 80% of prescribers consult allergy 0-1 time a year
- 42% believed penicillin allergy does not resolve with time

Antibiotic Stewardship

- Less than 0.1% of subjects with history of penicillin allergy undergo allergy testing in the US annually (Macy et al, JACI 2014)
- Skin test is rarely used to undiagnose allergy
- Choosing Wisely: Don’t overuse non-beta lactam antibiotics in patients with a history of penicillin allergy, without an appropriate evaluation
- Antibiotic Stewardship Programs: should promote [antibiotic] allergy assessments and penicillin skin testing when appropriate
Proof of Concept

- Prospective case controlled study 2010-2012
- Penicillin allergy testing, primarily done in the outpatient setting, resulted in (per coverage year):
  - 0.09 fewer outpatient visits
  - 0.13 fewer ED visits
  - 0.55 fewer hospital days ($P < .001$)
- Cost savings:
  - $1915 per patient per year
  - $2 million in 3.6 year study span

Macy et al. JACI In Practice 2017
Immune System Overview
Immune System Overview

- Network of cells, tissues and organs that work together to defend the body against attack by foreign invaders
- Bacteria, viruses, parasites
- **Innate Immunity**
  - Provides early, rapid response
  - Responds the same way each time
  - Alerts and recruits adaptive immunity

- **Adaptive Immunity**
  - Recognizes and reacts, with specificity and memory
  - Microbial and nonmicrobial antigens
  - Components
    - B cells
    - T cells

"I attack invaders outside the cells." (B-Cells)
"I attack invaders inside the cells." (T-Cells)
(a) Innate defenses
- Surface barriers
  - Skin
  - Mucous membranes
- Internal defenses
  - Phagocytes
  - Fever
  - NK cells
  - Antimicrobial proteins
  - Inflammation

(b) Adaptive defenses
- Humoral immunity
  - B cells
- Cellular immunity
  - T cells
Antibodies

- Immunoglobulins (Ig) or antibodies (Ab) are Y shaped proteins produced by B cells.
- They are used by the immune system to neutralize pathogenic bacteria and viruses.
- The antibody binding site recognizes a specific epitope on an antigen.
Types of Antibodies

ANTIBODY CLASSIFICATION

- **IgG**
- **IgE**
- **IgD**
- **IgM**
- **IgA**
Antigen

- Unique molecular pattern on a pathogen or protein that stimulates an immune response
Mast Cells and Anaphylaxis

- Mast cells are granulocytes that contain:
  - Histamine, heparin, tryptase, cytokines

- IgE, produced in response to an initial exposure to an allergen, is bound to mast cells

- Upon the 2\textsuperscript{nd} exposure, allergen cross links IgE primed mast cells, causing degranulation

- Anaphylaxis: body wide degranulation, leading to vasodilation:
  - Urticaria and angioedema
  - Bronchospasm
  - Rhinitis, conjunctivitis
  - Hypotension
Pathophysiology of β-Lactam Allergy
β-Lactam Antibiotics

- 2 major classes:
  - Penicillins
  - Cephalosporins

- 4 minor classes:
  - Monobactams, carbpenems, oxacephems, beta-lactamase inhibitors
Allergenicity of Penicillin

- Chemically inert in natural state
- Reactive intermediate
- Hapten-carrier effect
  - Hapten: penicillin degradation product
  - Carrier: protein
- IgE forms to penicillin-self protein complex
Cephalosporin allergy

- Cephalosporins are β-lactams that also bind to proteins
  - Haptenization is slower and less efficient
  - R2 is lost after the opening of the BL ring
- IgE antibodies recognize
  - R1 side chain and part of the BL ring structure
- Cross-reactivity between cephalosporins is explained through similarity of R1 side chain
Penicillin Skin Testing
Penicillin Skin Testing

- Skin testing detects specific IgE on a patient’s mast cells
  - Allergen introduced into the skin, comes into contact with cutaneous mast cells
  - Allergen cross links specific IgE bound to mast cells, and the cells are activated
  - Mast cell activation results in a transient wheal and flare reaction

- Sensitization: detectable penicillin specific IgE
  - High risk for immediate hypersensitivity reaction

- Most rapid, sensitive and cost effective testing modality
Indications for Skin Testing

- History of immediate hypersensitivity reaction
- Unclear histories of past penicillin reactions
  - Isolated urticaria, isolated angioedema, or unspecified rash
- Ideally performed when the patient is well and not in urgent or immediate need of antibiotic therapy
- Trend for testing even if they have alternatives to penicillin or beta-lactam therapy
- Special populations
  - Subjects in ICU, children and pregnant women
Contraindications for Skin Testing

- History of severe blistering skin reactions, such as Stevens Johnson syndrome or toxic epidermal necrolysis (TEN)
- History of non-IgE mediated reaction
  - Hemolytic anemia, interstitial nephritis
- Over-reactive skin conditions
  - CIU, dermatographia
- Inability to temporarily hold medications which interfere with skin testing or interfere with treatment of anaphylaxis
- Delay testing for 4 weeks following acute reaction
Skin Testing Reagants

- Major determinant
  - Penicilloyl-polylysine (PPL)

- Minor determinants
  - Benzylpenicillin/Penicillin G (10,000 units/mL)
  - Penilloate (0.01 M)
  - Penilloate (0.01M)  
    - MDM: minor determinate mixture

- Ampicillin or amoxicillin

- Positive and Negative controls

- Full strength skin prick, followed by intradermal injections, in duplicate
  - Dilute 1:10, 1:100 for history of severe allergic reaction
Skin Prick

Photographs courtesy of Laurianne Wild, MD
Intradermal Testing

**Controls**
- Saline
- Histamine

**Penicillin**
- Pen G 10,000 units/ml
- Minor determinants
- Pre Pen
Predictive Values

- **Positive Predictive Value**
  - Studies limited due to ethical concerns
  - Avoid natural, amino (ampicillin, amoxicillin) and semisynthetic penicillin

- **Negative Predictive Value with minor determinant: 97-99%**
  - 1-3% of penicillin skin test negative patients develop reactions upon drug challenge
  - Absence of MDM: potentially misses 1-10%
  - Current NPV without MDM: 90-93%

- Confirmatory oral challenge after negative skin test

- In vitro testing: unknown predictive value
Patient with negative penicillin skin testing and oral challenge will have new penicillin associated ADR rates similar to the general population:
- 0.5 – 5.0%
- Dependent on gender and other drug “allergy” history
- Higher rates
  - Parenteral administration
  - Female subjects
  - Multiple-drug intolerance syndrome (MDIS)
    - Increased overall health care use
    - No increase in mortality rate
- No need for repeat skin testing
43 year old male, PMH of asthma, active IVDU and adverse reaction to penicillin, found to have MSSA bacteremia

- Treated with vancomycin, unable to achieve therapeutic trough level, transitioned to daptomycin
- Serial blood cultures MSSA positive

Penicillin Allergy

- Gum and facial swelling and respiratory compromise, age 3-4

ID: nafcillin is the therapeutic agent of choice
Skin Test Results: No evidence of penicillin specific IgE on prick and intradermal skin testing with major determinant and Pen G. Patients with negative skin testing will tolerate penicillin, at the time of testing, without the risk of an IgE mediated reaction with 90-93% certainty.

Proceeded with oral ingestion challenge.
Oral Ingestion Challenge

- Amoxicillin 250 mg/5 mL oral suspension
- Small amount was applied to patient's lower lip mucosa
- After 15 minutes, patient reported some throat discomfort. Patient was examined, and physical exam was negative for lip, tongue or gum edema, posterior oropharynx erythema, inspiratory or expiratory wheezing
- Patient proceeded with full dose oral challenge, and was observed for 60 minutes. Patient tolerated procedure well, and remained at baseline
Results

- Penicillin allergy was removed from the patient's listed allergies
- Patient has risk of future acute reaction and delayed reaction to penicillin equivalent to the standard population
- Nafcillin therapy was initiated
Post-Penicillin Rash

- Over the next 3 days, the patient developed progressively worsening morbilliform eruption
  - Present on back prior to nafcillin
  - Spread to abdomen, upper & lower extremities

- Pruritus improved with 2nd generation antihistamine, bid

- Possible etiologies
  - Delayed hypersensitivity reaction to current or prior Abx
  - Viral induced
  - Heat induced dermatitis

- Counseled and continued therapy
  - Resolved
Skin Testing in Sub-Populations
Skin Testing in Pregnant Women

- Study examined safety and utility of PST in pregnant women with a history of penicillin allergy & GBS colonization.

- 56 pregnant women were skin tested, and if negative, penicillin class antibiotics were recommended for intrapartum GBS prophylaxis.

- 2 reactions associated with PST:
  - generalized pruritus (hives, +); fainting (fainting, -)

- 3 positive PSTs.

- 47/53 PST negative patients received intrapartum PCN:
  - 2 delayed onset rashes
  - 1 immediate onset rash with vancomycin.

Macy, Annals of AAI 2006
Skin Testing in Hospitalized Patients

- NIAID collaborative clinical trial to evaluate the predictive value of penicillin skin testing, with major and minor determinants, in hospitalized adults

- 1539 patients: 11.4% positive skin tests
  - 825 history positive: 18% positive PST
  - 104 unsure: 4% positive PST
  - 616 history negative: 4% positive PST

- 1.2% immediate reactions to penicillin: all history +/-PST-

- NPV with PPL and MDM: 99%
  - 16% reacted to solely MDM

Sogn, Arch Internal Medicine 1992
Penicillin skin testing is a safe and effective tool for evaluating penicillin allergy in the pediatric population.

778 children <18 yo underwent skin testing with PPL, Pen G, amoxicillin and penicilloate (institution produced)
- 90.4% negative
- 8.5% positive
- No adverse reaction to SPT

50% of patients with negative SPT had oral challenge
- 3.8% mild adverse reaction
Cephalosporin Allergy
Cephalosporin Use

- Most common antibiotic class in both penicillin allergic and control subjects
- CDC: 2.5% cross reactivity, primarily in cephalosporins which share identical R-group side chains to penicillins
  - “Negligible” for most 2nd and all 3rd generation cephalosporins
- Cross reactivity amongst cephalosporins related to R-1 side chain determinants
- In penicillin-allergic subjects, >30% cross-reactivity when cephalosporins has identical side chains to penicillin
  - <1% cross-reactivity between penicillins and carbapenems or aztreonam

Romano, Curr Allergy Asthma Rep 2016
### Groupings By R Side Chain

<table>
<thead>
<tr>
<th>Amino</th>
<th>Amino</th>
<th>Methoxyimino</th>
</tr>
</thead>
</table>

#### Table 16. Groups of β-Lactam Antibiotics That Share Identical R₁-Group Side Chains

<table>
<thead>
<tr>
<th>Amoxicillin</th>
<th>Ampicillin</th>
<th>Ceftriaxone</th>
<th>Cefoxitin</th>
<th>Cefamandole</th>
<th>Ceftazidime</th>
<th>Aztreonam</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cefadroxil</td>
<td>Cefaclor</td>
<td>Cefotaxime</td>
<td>Cephaloridine</td>
<td>Cefonicid</td>
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<tr>
<td>Cefprozil</td>
<td>Cephalexin</td>
<td>Cepodoxime</td>
<td>Cephalothin</td>
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<td></td>
</tr>
<tr>
<td>Cefatrizine</td>
<td>Cephradine</td>
<td>Cefditoren</td>
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</tr>
<tr>
<td></td>
<td>Cephaloglycin</td>
<td>Cefizoxime</td>
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<td></td>
</tr>
<tr>
<td></td>
<td>Loracarbef</td>
<td>Cefmenoxime</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*Tolerated cefaclor, and cefazolin, cefibuten*

Aminocephalosporins tolerated cefuroxime, ceftriaxone, cefazolin, cefibuten

#### Table 17. Groups of β-Lactam Antibiotics That Share Identical R₂-Group Side Chains

<table>
<thead>
<tr>
<th>Cephalexin</th>
<th>Cefotaxime</th>
<th>Cefuroxime</th>
<th>Cefotetan</th>
<th>Cefaclor</th>
<th>Cefibuten</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cefadroxil</td>
<td>Cephalothin</td>
<td>Cefoxitin</td>
<td>Cefamandole</td>
<td>Loracarbef</td>
<td>Ceftizoxime</td>
</tr>
<tr>
<td>Cephradine</td>
<td>Cephaloglycin</td>
<td>Cefimetazole</td>
<td>Cefpiramide</td>
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</tr>
<tr>
<td></td>
<td>Cephapirin</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*a Each column represents a group with identical R₁ side chains.*

*a Each column represents a group with identical R₂ side chains.*
Conclusions

- Penicillin testing is safe, reproducible and effective in delabeling up to 90% of individuals with beta-lactam allergy
- Less health care utilization
- Fewer broad spectrum antibiotics
- High yield patients
  - Remote history of any adverse reaction to penicillin
  - Multiple listed antibiotic allergies
  - Penicillin allergy label + higher risk of infection:
    - Diabetes, HIV, malignancy, immunosuppression
  - Inpatients with PAL when the therapeutic agent of choice is a beta lactam
Sources


