Drug Hypersensitivity Reactions: Tall Tales from Texas
David A. Khan, MD
Professor of Medicine and Pediatrics
Allergy & Immunology Program Director
UT Southwestern, Dallas, TX

Disclosures

- Research Grants
  - NIH
- Honoraria
  - UpToDate, Genentech
- Consulting
  - Aimmune (DSMB)
- Organizations:
  - Joint Task Force on Practice Parameters
  - AAAAI BOD
Objectives

- By attending this lecture the participant should be able to:
  - Gain an understanding of the benefits and limitations of pharmacogenetics in drug allergy
  - Gain an understanding of the spectrum of cutaneous drug reactions
  - Be able to recognize clinical features of specific drug hypersensitivity syndromes and mimics of drug allergy
Outline

- Drug Allergy Updates
  - Pharmacogenomics
  - AERD
  - Penicillin Allergy
- Drug Allergy Cases

Updates in Pharmacogenomics of Drug Allergy
Definitions

- Pharmacogenetics
  - Any influence that genetics may have on drug therapy
  - Usually deals with **single drug-gene** interactions

- Pharmacogenomics
  - Similar to pharmacogenetics but incorporates genomics and epigenetics to evaluate effect of **multiple genes** on drug responses

---

Clinical reviews in allergy and immunology

**Pharmacogenomics and adverse drug reactions:**
Primetime and not ready for primetime tests

![Timeline Diagram]

Pharmacogenetics in SJS

- Incidence of SJS is higher in Han Chinese with carbamazepine (CBZ) being the most common drug in Asians
- Pharmacogenetic study in a Han Chinese population including 44 CBZ-SJS patients and controls
- HLA-B*15:02 was found in 100% of CBZ-SJS pts and only 3% of CBZ-tolerant pts and 8.6% of general population
  - OR: CBZ-SJ/CBZ-tolerant: **2504** p=3.13 x 10^{-27}
Carbamazepine-Induced Toxic Effects and HLA-B*1502 Screening in Taiwan

Pei Chen, Ph.D., Juei-Jueng Lin, M.D., Chin-Song Lu, M.D., Cheung-Ter Ong, M.D., Peiyuan F. Hsieh, M.D., Chih-Chao Yang, M.D., Chih-Ta Tai, M.D., Shey-Lin Wu, M.D., Cheng-Hsien Lu, M.D., Yung-Chu Hsu, M.D., Hsiang-Yu Yu, M.D., Long-Sun Ro, M.D., Chung-Ta Lu, M.D., Chun-Che Chu, M.D., Jing-Jane Tsai, M.D., Yu-Hsiang Su, M.D., Sheng-Hsing Lan, M.D., Sheng-Feng Sung, M.D., Shu-Yi Lin, M.S., Hui-Ping Chuang, B.S., Li-Chen Huang, B.S., Ying-Ju Chen, M.S., Pei-Joung Tsai, M.S., Hung-Ting Liao, M.S., Yu-Hsuan Lin, M.S., Chen-Hsien Chen, Ph.D., Wen-Hung Chung, M.D., Ph.D., Shuen-Iu Hung, Ph.D., Jer-Yuan Wu, Ph.D., Chi-Feng Chang, Ph.D., Luke Chen, Ph.D., Yuan-Tsong Chen, M.D., Ph.D., and Chen-Yang Shen, Ph.D., for the Taiwan SJS Consortium


Table 2. Adverse Events during the 2-Month Follow-up.

<table>
<thead>
<tr>
<th>Adverse Event</th>
<th>HLA-B*1502-Positive with Alternative Medication (N=215)</th>
<th>HLA-B*1502-Negative with Carbamazepine (N=4120)</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>number of events</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mild cutaneous events</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rash and itching</td>
<td>5</td>
<td>206</td>
<td>211</td>
</tr>
<tr>
<td>Rash, itching, and blisters</td>
<td>1†</td>
<td>20</td>
<td>21</td>
</tr>
<tr>
<td>Rash, itching, and oral ulcers</td>
<td>0</td>
<td>14</td>
<td>14</td>
</tr>
<tr>
<td>Rash, itching, blisters, and oral ulcers</td>
<td>0</td>
<td>7</td>
<td>7</td>
</tr>
<tr>
<td>Itching, blisters, and oral ulcers</td>
<td>0</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>Blisters and oral ulcers</td>
<td>0</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Severe cutaneous events</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Maculopapular eruption</td>
<td>0</td>
<td>3</td>
<td>3</td>
</tr>
<tr>
<td>Hypersensitivity syndrome</td>
<td>0</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>Urticaria</td>
<td>1‡</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>Stevens-Johnson syndrome or toxic epidermal necrolysis</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

Reduced Carbamazepine-Induced SJS Compared to Historical Incidence


<table>
<thead>
<tr>
<th>Variable</th>
<th>2002</th>
<th>2003</th>
<th>2004</th>
</tr>
</thead>
<tbody>
<tr>
<td>New recipients of carbamazepine (no.)</td>
<td>50,917</td>
<td>48,522</td>
<td>49,670</td>
</tr>
<tr>
<td>Subjects with ICD-9-CM diagnostic code 695.1 (no.)</td>
<td>1441</td>
<td>1261</td>
<td>1354</td>
</tr>
<tr>
<td>Carbamazepine-induced SJS–TEN (no.)</td>
<td>123</td>
<td>108</td>
<td>116</td>
</tr>
<tr>
<td>Incidence of carbamazepine-induced SJS–TEN (%)</td>
<td>0.24</td>
<td>0.22</td>
<td>0.23</td>
</tr>
<tr>
<td>P value for comparison between historical incidence and incidence among study subjects*</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

Prospective Screening for HLA-B*5701 Reduces Hypersensitivity Reactions to Abacavir


Immunologically confirmed via abacavir patch testing

<table>
<thead>
<tr>
<th>Drug-Reaction</th>
<th>Genotype</th>
<th>Ethnicity</th>
<th>No. Positive/Total Cases vs. Controls</th>
<th>Odds Ratio</th>
<th>Type of Evidence</th>
<th>Screening Recommended by FDA</th>
</tr>
</thead>
<tbody>
<tr>
<td>Carbamazepine- SJS</td>
<td>HLA-B*1502</td>
<td>Han Chinese</td>
<td>102/109 vs. 40/384</td>
<td>115.3</td>
<td>Meta-analysis (5 studies)</td>
<td>Yes</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Thai</td>
<td>43/48 vs. 13/84</td>
<td>54.4</td>
<td>Meta-analysis (2 studies)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Malaysian</td>
<td>6/6 vs. 0/8</td>
<td>221</td>
<td>Single study</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Indian</td>
<td>6/8 vs. 0/10</td>
<td>70.4</td>
<td>Single study</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Korean</td>
<td>1/7 vs. 0/50</td>
<td>23.3</td>
<td>Single study</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Japanese</td>
<td>0/3 vs. 0/33</td>
<td>NA</td>
<td>Single study</td>
<td></td>
</tr>
<tr>
<td>Carbamazepine- DRESS</td>
<td>HLA-A*3101</td>
<td>Europeans</td>
<td>18/139 vs. 22/579</td>
<td>24.1</td>
<td>Meta-analysis (3 studies)</td>
<td>No</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Asians</td>
<td>40/80 vs. 69/712</td>
<td>10.3</td>
<td>Meta-analysis (5 studies)</td>
<td></td>
</tr>
<tr>
<td>Carbamazepine- SJS/TEN</td>
<td>HLA-A*3101</td>
<td>Europeans</td>
<td>9/36 vs. 22/579</td>
<td>7.9</td>
<td>Meta-analysis (3 studies)</td>
<td>No</td>
</tr>
</tbody>
</table>

Pharmacogenetic Associations and Severe Cutaneous Adverse Reactions

<table>
<thead>
<tr>
<th>Drug-Reaction</th>
<th>Genotype</th>
<th>Ethnicity</th>
<th>No. Positive/Total Cases vs. Controls</th>
<th>Odds Ratio</th>
<th>Type of Evidence</th>
<th>Screening Recommended by FDA</th>
</tr>
</thead>
<tbody>
<tr>
<td>Abacavir hypersensitivity syndrome</td>
<td>HLA-B*5701</td>
<td>Multi-ethnic</td>
<td>484/1223 (broad clinical criteria) 57/2869 (strict clinical criteria)</td>
<td>32.1</td>
<td>Meta-analysis (11 studies)</td>
<td>Yes</td>
</tr>
<tr>
<td>Allopurinol SJS/TEN</td>
<td>HLA-B*5801</td>
<td>Asian</td>
<td>54/55 (matched controls) 74/678 (patch test criteria)</td>
<td>96.6</td>
<td>Meta-analysis (4 studies)</td>
<td>No</td>
</tr>
<tr>
<td>Dapsone hypersensitivity syndrome</td>
<td>HLA-B*1301</td>
<td>Han Chinese</td>
<td>65/76 140/1034</td>
<td>20.5</td>
<td>Single study</td>
<td>No</td>
</tr>
</tbody>
</table>

Pharmacogenetic Associations and Severe Cutaneous Adverse Reactions


Carbamazepine-Induced Severe Cutaneous Adverse Reactions

### Issues with Genotype Screening

- Low positive predictive value for many genotypes
  - HLA-B*58:01 for allopurinol-induced SJS/TEN only 3%
- Screening based only on HLA genotyping will result in denial of therapies that would be beneficial and tolerated by many patients
- Data not always reproducible
  - HLA-A*31:01 and carbamazepine SJS/TEN in Europeans


---

### Updates in Aspirin Exacerbated Respiratory Disease (AERD)
Aspirin/NSAID Hypersensitivity Phenotypes

<table>
<thead>
<tr>
<th>Hypersensitivity Reaction</th>
<th>Cross-Reactivity</th>
<th>Onset</th>
<th>Clinical Features</th>
<th>Underlying Disease</th>
<th>Mechanism</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aspirin Exacerbated Respiratory Disease (AEDR)</td>
<td>Yes</td>
<td>Immediate</td>
<td>Naso-ocular Respiratory (GI, skin less often)</td>
<td>Asthma, nasal polyps</td>
<td>COX-1 Inhibition</td>
</tr>
<tr>
<td>Aspirin Exacerbated Cutaneous Disease</td>
<td>Yes</td>
<td>Immediate</td>
<td>Urticaria/Angioedema</td>
<td>Chronic urticaria</td>
<td>COX-1 Inhibition</td>
</tr>
<tr>
<td>Multiple NSAID-Induced Urticaria</td>
<td>Yes</td>
<td>Immediate</td>
<td>Urticaria/Angioedema</td>
<td>None</td>
<td>COX-1 Inhibition</td>
</tr>
<tr>
<td>Single NSAID-Induced Urticaria/Anaphylaxis</td>
<td>No</td>
<td>Immediate</td>
<td>Urticaria/Angioedema</td>
<td>None</td>
<td>IgE mediated ?</td>
</tr>
<tr>
<td>Delayed Hypersensitivity</td>
<td>No</td>
<td>Delayed</td>
<td>Fixed drug eruption, SJS/TEN, MP exanthem, Hypersensitivity pneumonitis, aseptic meningitis</td>
<td>None</td>
<td>T cell mediated ?</td>
</tr>
</tbody>
</table>

New Theories in AEDR

Mechanisms of allergy and clinical immunology

Prostaglandin E₂ resistance in granulocytes from patients with aspirin-exacerbated respiratory disease

Tanya M. Laidlaw, MD, a,b Anya J. Cutler, a Molly S. Kidder, b Tao Liu, PhD, b Juan Carlos Cardet, MD, a,b Heng Chhuy, b Chunli Feng, MD, b and Joshua A. Boyce, MD, a,b

Neutrophils and Platelets are important in AEDR

Role of PGE₂ in AERD

- Aspirin-exacerbated respiratory disease (AERD) is characterized by overproduction of leukotrienes.
- Leukotriene production can be suppressed by PGE₂ and the cAMP dependent protein kinase A (PKA).
- PGE2 effects are mediated via EP receptors.

Granulocyte PKACγ Activity is Reduced in AERD

- The graph shows the PKACγ activity corrected for GAPDH in nonasthmatic control, ATA control, and AERD groups. The activity is reduced in the AERD group compared to controls.

* p < 0.05
Platelet-adherent Neutrophils Correlate with Increased LTB4 and Less LTB4 Inhibition

A

Baseline LTB4

LTB4 production (pg/mL)

r = 0.80
P = 0.01

B

PGE2 (1 µM)

LTB4 inhibition (%)

r = 0.65
P < 0.05

C

Aspirin-tolerant


+ + +
cAMP PKA S-LO

LTB4 LTA4 LTA4

AERD


Platelet

PKA AA S-LO

LTB4 LTA4 LTA4

FIG. 2: Signaling mechanisms by which EP2, EP4, and EP3 receptors may control granulocyte PKA activity and LT production in controls (A) and patients with AERD (B).
Future Therapies in AERD

- **Prasugrel**
  - ADP receptor inhibitor
  - Reduces aggregation of platelets by binding to P2Y<sub>12</sub> receptors
  - Study by Laidlaw et al. of 50 AERD patients treated with 4 weeks of prasugrel
    - Primary outcome was difference in provocative dose of aspirin
    - Overall no change in provocative dose, platelet activation, granulocyte adherence
    - 5 of 40 patients did not react on prasugrel

Ifetroban (thromboxane receptor antagonist) in AERD

Phase 2 studies ongoing

Alcohol May Trigger AERD

Original Article

Alcohol-induced Respiratory Symptoms Are Common in Patients With Aspirin Exacerbated Respiratory Disease

Alcohol can inhibit catabolism of cys-leukotrienes

Reported Prevalence of Alcohol-Induced Rhinitis


Reported Prevalence of Alcohol-Induced Wheezing/Dyspnea

Aspirin Desensitization for AERD

Benefits of ASA Desensitization

- Long-term observational studies reveal
  - ↓ sinus infections
  - ↓ oral steroid bursts
  - ↓ anosmia
  - ↓ rhinitis
  - ↓ asthma symptoms

- After 1 yr therapy
  - Good-excellent improvement (78%) 115/148 pts

- Discontinuation due to side effects
  - 14% in 1st year (mostly epigastric pain)
Candidates for ASA Desensitization

- Patients with AERD who have moderate or severe asthma, intractable nasal congestion, or both on the basis of their AERD who have failed medical therapy
- Patients with AERD who are multiple nasal polyp formers
- Patients requiring systemic corticosteroids for control of AERD
- Patients with AERD who require aspirin for other diseases


An Hourly Dose-Escalation Desensitization Protocol for Aspirin Exacerbated Respiratory Disease

Justin R. Chen, MD, Brett L. Buchmiller, MD, and David A. Khan, MD

Dallas, Tex.

What is already known about this topic? Aspirin desensitization therapy using multiday protocols followed by maintenance dosing effectively treats upper and lower airway symptoms in patients with aspirin-exacerbated respiratory disease (AERD) who are inadequately controlled on inhaled glucocorticoids and leukotriene-modifying agents.

What does this article add to our knowledge? Patients reacting to aspirin or nonsteroidal anti-inflammatory drugs within 1 hour of ingestion can be safely desensitized using a protocol of hourly dose escalations that in many cases can be accomplished in a single day.

How does this study impact current management guidelines? Our findings support shortening the dosing intervals for patients without delayed reactions to aspirin, which applies to the majority of patients undergoing desensitization for AERD. This would reduce the need for prolonged observation and benefits both patients and practitioners.


UT Southwestern AERD Desensitization Protocol

<table>
<thead>
<tr>
<th>Time</th>
<th>Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>08:00</td>
<td>40 mg (20 mg if history of serious reaction)</td>
</tr>
<tr>
<td>09:00</td>
<td>81 mg</td>
</tr>
<tr>
<td>10:00</td>
<td>120 mg</td>
</tr>
<tr>
<td>11:00</td>
<td>162 mg</td>
</tr>
<tr>
<td>12:00</td>
<td>325 mg</td>
</tr>
<tr>
<td>13:30</td>
<td>Observation period</td>
</tr>
</tbody>
</table>

UT Southwestern Protocol

- Indicated for patients with a history of reactions to ASA or NSAIDs within 1 hour
- 57 hourly dose-escalation aspirin desensitizations performed in AERD subjects
- All but 1 patient successfully desensitized
  - 40% completed in 1 day
  - 60% in 2 days


Aspirin Therapy Post-Desensitization

- Typical initial dose of aspirin is 650 mg twice daily
- After 1-3 months, aspirin dose usually reduced to 325 mg twice a day
- Doses less than this rarely provide benefit for sinopulmonary disease
- Patients need to be maintained on aspirin therapy indefinitely
Urgent Need for Aspirin

- Many studies have performed “aspirin desensitizations” in patients with histories of both cutaneous and respiratory reactions to aspirin, all with similar high rate of success (>80%)
- Patients with chronic urticaria have higher failure rate
- Surprisingly good results in AERD patients
  - Likely due to lower doses used


Are These Really Desensitizations?

- Patients in these studies never had confirmatory challenges to determine if truly allergic to aspirin
- **Whether** these protocols truly induce drug tolerance or are simply a multi-stepped graded challenge is unclear
Rapid Aspirin “Desensitization” Protocol

<table>
<thead>
<tr>
<th>Time</th>
<th>Aspirin dose, mg</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>0.1</td>
</tr>
<tr>
<td>15</td>
<td>0.3</td>
</tr>
<tr>
<td>30</td>
<td>1</td>
</tr>
<tr>
<td>45</td>
<td>3</td>
</tr>
<tr>
<td>60</td>
<td>10</td>
</tr>
<tr>
<td>75</td>
<td>20</td>
</tr>
<tr>
<td>90</td>
<td>40</td>
</tr>
<tr>
<td>105</td>
<td>81</td>
</tr>
<tr>
<td>120</td>
<td>162</td>
</tr>
<tr>
<td>135</td>
<td>325</td>
</tr>
</tbody>
</table>

*Dosing interval shown is 15 minutes but may also dose every 20 minutes with premedication with oral antihistamine.


Aspirin Challenge for Acute Cardiac Needs

1. Does patient have asthma that is worsened by ASA/NSAIDs (AERD)?
   - yes: Premedicate with montelukast, ICS/LABA, prednisone
   - no: Administer 40.5 mg aspirin

2. Observe 90 min & no reaction: ok to take 81 mg aspirin

### UT Southwestern Protocol for Urgent ASA Needs

<table>
<thead>
<tr>
<th>Historical Reaction to ASA/NSAID</th>
<th>Dosing strategy</th>
<th>Pretreatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>AERD</td>
<td>Split dosing, give 40.5 mg and wait 90 minutes then give another 40.5 mg</td>
<td>1 hr before: 40 mg prednisone, montelukast 10 mg, ICS/LABA</td>
</tr>
<tr>
<td>ASA-induced urticarial or angioedema</td>
<td>81 mg ASA</td>
<td>None</td>
</tr>
<tr>
<td>Vague</td>
<td>81 mg ASA</td>
<td>None</td>
</tr>
<tr>
<td>SJS or TEN to NSAID (not ASA)</td>
<td>81 mg ASA</td>
<td>None</td>
</tr>
</tbody>
</table>

### Updates on Penicillin Allergy Disease
Why Testing for PCN Allergy Matters?

- PCN allergic patients receive higher rates of vancomycin, fluoroquinolones, clindamycin, and aztreonam
- β-lactams superior to vancomycin for MSSA
- β-lactams less failure for gram neg bacteremia
- PCN allergy labeled patients have longer hospital stays and are readmitted more frequently

AAAAI Position Statement

Penicillin Allergy Testing Should Be Performed Routinely in Patients with Self-Reported Penicillin Allergy

Penicillin Allergy in Antibiotic Resistance Workgroup
Lang, DM, Castells MC, Khan DA, Macy EM, Murphy AW.


Original Article

A Proactive Approach to Penicillin Allergy Testing in Hospitalized Patients

Justin R. Chen, MD1, Scott A. Tarver, PharmD1, Kristin S. Alvarez, PharmD1, Trang Tran, PharmD1, and David A. Khan, MD2 * Dallas, Tex

Penicillin Allergy Testing Service (PATS)

- Established November 2014
- Collaboration between the UT Southwestern Division of Allergy & Immunology and Pharmacy Services at Parkland
- Utilizes a dedicated allergy pharmacist trained by A&I physicians
- Patients seen by referral from the primary team or through a selection process to be discussed in this presentation

Why a Pharmacist?

- Parkland Pharmacy Dept received funding from Medicaid 1115 waiver
- Other Reasons
  - highly educated/trained med professionals
  - greater understanding of drugs/names/adverse effects
  - used to protocols
  - accustomed to reviewing medications in detail
  - well equipped to educate patients after completion of testing
  - may also advise physicians on optimal posttest antibiotics
Selection of Inpatients to Undergo Penicillin Testing

Outcomes of Proactive In Patient Penicillin Testing

Changes in Antibiotics Due to Penicillin Allergy Testing


Reflexive Penicillin Allergy Testing with In-Hospital Aztreonam Use

Chen J et al. Abstract AAAAI 2017
**Reflexive Penicillin Allergy Testing with In-Hospital Aztreonam Use**

- Patients tested negative accumulated 46.8 inpatient days of penicillin and 25 days of cephalosporins
  - Direct cost $326.47
- Projected cost savings compared with use of aztreonam: 82-92%
- To show cost savings, targeting expensive antibiotics like aztreonam is a reasonable strategy

**Are Penicillin Skin Tests Needed in Children?**

*Research*

*Original Investigation*

**Assessing the Diagnostic Properties of a Graded Oral Provocation Challenge for the Diagnosis of Immediate and Nonimmediate Reactions to Amoxicillin in Children**

Christopher Mill, MPH; Marie-Noël Primeau, MD; Elaine Medoff, MD; Christine Lejnen, MD; Andrew O'Keefe, MD; Elena Netchiporoulou, MD; AlIZEE Dery, BSc; Moshe Ben Shoshan, MD, MSc

Challenge Protocol: 10% dose then 20 min later 90% dose amoxicillin

All immediate and delayed reactions were mild (few cases of SSL reactions)

No features predicted immediate reactions to challenge.

Children with histories of rashes persisting > 7 days (OR=4.8) and those with a parental history (OR=3.0) were more likely to have a delayed reaction
Other Studies of Challenge Only Penicillin Testing

The role of penicillin in benign skin rashes in childhood: A prospective study based on drug rechallenge

Jean-Christoph Caubet, MD, a Laurent Kaiser, MD, b Barbara Lemaitre, MS, b Benoît Fellay, PhD, b Alain Gervais, MD, b and Philippe A. Eigenmann, MD b Geneva and Fribourg, Switzerland

Original Article


Oral Challenge without Skin Testing Safely Excludes Clinically Significant Delayed-Onset Penicillin Hypersensitivity

Ronit Cohen-Cohen, MD a,b,c, Yosef Reiman, MD a,c, Kamei Meir-Shalev, MD a, Tal Stavitski, MD a; Idit Luchaver-Roth, MD a,b,c, Alan Hendroff, MD a,b,c, and Aaron Goldberg, MD a,b,c Kfar-Saba and Tel-Aviv, Israel

Amoxicillin challenge without penicillin skin testing in evaluation of penicillin allergy in a cohort of Marine recruits

Mark H. Tucker, MD a,b, Chad M. Lomas, MD a,b, Nanda Ramchandar, MD a,b, and Jeremy D. Waldram, MD a,b,c

J Allergy Clin Immunol Pract 2017;5:669-75


When to Skip Penicillin Skin Tests

- Histories not consistent with hypersensitivity (e.g. headache, GI upset)
- Children with amoxicillin reactions
- Benign rashes?
  - Only Australia has penicillin challenge without skin testing as part of a guideline
  - Reasonable but is it medicolegally sound?
Persistence of Penicillin Allergy in the Medical Record

- While penicillin allergy testing/challenge is an effective tool for proving tolerance to penicillin, the drug allergy listed in the medical record determines whether patients receive penicillins in the future.
- Multiple studies have shown that penicillin allergy labeling may persist in 36-49% of patients with negative penicillin allergy tests.


Effectiveness of Interventions to Maintain Penicillin Allergy Label Removal as Part of an Inpatient Penicillin Allergy Testing Protocol

Sheenal V. Patel, MD, Scott A. Tarver, PharmD, Kristin S. Alvarez, PharmD, Kristin Lutek, PharmD, James Schlebus, David A. Khan, MD

Oral Abstract AAAAI 2017
Interventions to Maintain Penicillin Allergy Label Removal

1. Pharmacist counseling at the time of negative test, active removal of allergy, procedure note documentation (began November 2014)
2. Pharmacist counseling at post-discharge visit (telephone call or face to face visit) (began June 2015)
3. Best practice advisory (pop-up alerts) in the electronic medical record alerting providers to negative penicillin allergy test result on attempt to add back allergy (began November 2015)
4. Wallet card given to patient at time of negative test documenting negative penicillin allergy testing (began April 2016)

Results

1545 EMR screens
- 12 with allergy removed by history
- 3 direct challenges
- 4 patients on beta blockers
- 16 patients with negative histamine control
- 3 patient with positive withdrawn
- 2 patients reporting N/V
- 2 patient withdrew consent for testing

348 patients evaluated
333 initiated tests
300 completed protocol

5 positive skin tests/challenge
304 negative skin tests/challenge (Allergy label removed)

225 allergy label removed and >90 days f/u

194 with persistence of allergy label removal (86.2%)
31 with relabel of penicillin allergy (13.8%)
Lessons Learned

- Partnering with hospital-based employees in leadership positions makes things happen quicker
  - Pharmacy partnership was key to our success
- Promoting penicillin allergy as part of antibiotic stewardship is important
  - Helps administrators choose good medical care without need to focus on $$
- Proving cost savings requires longer follow up or cherry-picking patients
- Allergists can be integral to an inpatient testing protocol without actually being in the hospital

Tales from the Great State of Texas
A 49-year-old woman with diabetes admitted due to a wound infection after inguinal hernia repair. She received a dose of cefazolin intraoperatively followed by ticarcillin/clavulanate and vancomycin. In addition she was started on fluoxetine for depression and hydrocodone as needed for pain. Three days later, cultures obtained at surgery revealed methicillin resistant Staphylococcus aureus and the ticarcillin/clavulanate was discontinued and she remained on vancomycin. On post-operative day nine, she received a dose of fluconazole for oral thrush and 30 minutes later she noted diffuse itching. Within hours she developed a diffuse, painful vesicular eruption. The Allergy & Immunology service was consulted for evaluation of fluconazole allergy.

Physical examination was notable for scattered erythematous papules, a few targetoid lesions, and tense blisters involving the arms, legs, palms, labia, and tongue with a few erosions on the gingiva.
What kind of drug reaction is this?
- SJS?

What drug was the culprit?
- Fluconazole?

Potential Culprits

- Onset of pruritus within 30 minutes of fluconazole may have been due to an IgE-mediated reaction, however the appearance of vesicular reactions within hours would make it highly unlikely that the fluconazole was the culprit drug.
- beta-lactams were considered unlikely due to their discontinuation 6-9 days prior.
- Hydrocodone is a common cause of pruritus from pseudoallergic reactions but vesicular eruptions would be rare.
- Fluoxetine is also rarely the cause of vesicular drug eruptions.
- Vancomycin is the most common cause of linear IgA bullous disease which may also affect mucosal surfaces and may also cause DRESS.
Case Epilogue

- Stevens Johnson syndrome was also a consideration due to the targetoid lesions and involvement of 2 mucosal sites.
- We recommended discontinuation of vancomycin.
- CBC with differential and comprehensive metabolic panel were normal
- Skin biopsy was performed with immunofluorescence and was consistent with a diagnosis of **linear IgA bullous dermatitis**
- She was started on systemic steroids due to worsening of the eruptions and painful lesions and had rapid improvement and eventual resolution of her symptoms

---

Linear IgA Bullous Dermatosis

- Most commonly with **vancomycin**
- Other medications
  - Captopril, furosemide, lithium, TMP/SMX
- Tense blisters that mimic bullous pemphigoid
- Generally occurs within 24 hours to 15 days following administration of the offending drug
- Vancomycin-induced LAD is not dose dependent and the severity of the reaction does not correlate with serum vancomycin levels

“Happy 40th Birthday!”

- A man who just turned 40 wanted to make a change in his life and decided to take an antibiotic to “clean me out”.
- He acquired some penicillin from a local street vendor of drugs.
- A few days after taking his penicillin he developed a diffuse rash.
What kind of Reaction is This?
- SJS?

What was the cause?
- Penicillin

Case Epilogue
- Patient reported a history of Bactrim allergy resulting in hyperpigmented patches on hands and penis
- This reaction started at same places but became more widespread
- Skin biopsy consistent with fixed drug eruption
- “Penicillin” was likely sulfamethoxazole
Fixed Drug Eruptions

- Common type of drug eruption but often unrecognized as such
  - Considered a T-cell mediated reaction
- Typically develops 1-2 weeks for initial reaction but sooner with later exposures
- Occur in same location with each subsequent exposure to drug
- Pleomorphic
  - eczema
  - erythematous papules
  - hyperpigmented areas
  - bullous
  - Urticarial
- May be diffuse with mucosal involvement
- Examples
  - Tetracycline, NSAIDs, carbamazepine

A Case of Chronic Hives

- A 25 yo F notes a > 2 yr history of daily urticaria and episodic angioedema, no physical triggers
- Prior laboratories have been unrevealing
- She has failed high doses of antihistamines including doxepin, hydroxyzine, cetirizine, fexofenadine as well as ranitidine, montelukast and alternative agents including dapsone and hydroxychloroquine
- She does feel that her urticaria flares in her premenstrual phase and will actually improve or go away several days after her period
Could her CU be related to her hormones?
How to test?
How to treat?
Progesterone skin testing

- Skin prick
  - 50 mg/ml
- Intradermal
  - 0.005, 0.05, 0.5 mg/ml diluted in benzyl alcohol or olive oil
- Irritant reactions can be seen with both diluents

TABLE II. Slow oral desensitization protocol for a prostaglandin.

<table>
<thead>
<tr>
<th>Day</th>
<th>Dose (Based on prostaglandin component)</th>
<th>Number of capsules × capsule dose on day</th>
<th>Total daily dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Day 1</td>
<td>1.25 mg AM, 1.25 mg PM</td>
<td>1 × 1.25 mg; 2 × 1.25 mg</td>
<td>3.75 mg</td>
</tr>
<tr>
<td>Day 2</td>
<td>1.25 mg AM, 1.25 mg PM</td>
<td>2 × 1.25 mg; 2 × 1.25 mg</td>
<td>5 mg</td>
</tr>
<tr>
<td>Day 3</td>
<td>1.25 mg AM, 1.25 mg PM</td>
<td>2 × 1.25 mg; 2 × 1.25 mg</td>
<td>3.75 mg</td>
</tr>
<tr>
<td>Day 4</td>
<td>1.25 mg AM, 1.25 mg PM</td>
<td>3 × 1.25 mg; 3 × 1.25 mg</td>
<td>7.5 mg</td>
</tr>
<tr>
<td>Day 5</td>
<td>1.25 mg AM, 1.25 mg PM</td>
<td>4 × 1.25 mg</td>
<td>5 mg</td>
</tr>
<tr>
<td>Day 6</td>
<td>1.25 mg AM, 1.25 mg PM</td>
<td>5 mg</td>
<td>2.5 mg</td>
</tr>
<tr>
<td>Day 7</td>
<td>2.5 mg AM, 2.5 mg PM</td>
<td>5 mg</td>
<td>2.5 mg</td>
</tr>
<tr>
<td>Day 8</td>
<td>500 µg</td>
<td>5 mg</td>
<td>2.5 mg</td>
</tr>
<tr>
<td>Day 9</td>
<td>500 µg</td>
<td>5 mg</td>
<td>2.5 mg</td>
</tr>
</tbody>
</table>

Target dose for this protocol: Nesiritide 1 mg/thrnil 0.02 mg.

TABLE III. IM progesterone desensitization protocol for IVF.

<table>
<thead>
<tr>
<th>Time</th>
<th>Dose (IM progesterone 50 mg/mL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0 min</td>
<td>1 mg</td>
</tr>
<tr>
<td>30 min</td>
<td>2 mg</td>
</tr>
<tr>
<td>60 min</td>
<td>4 mg</td>
</tr>
<tr>
<td>90 min</td>
<td>8 mg</td>
</tr>
<tr>
<td>120 min</td>
<td>16 mg</td>
</tr>
<tr>
<td>150 min</td>
<td>18.5 mg</td>
</tr>
<tr>
<td>Total dose</td>
<td>50 mg</td>
</tr>
</tbody>
</table>

Target daily dose: Intravaginal progesterone 90-180 mg (ie, 8% gel once or twice daily) or IM progesterone 50-75 mg daily, depending on IVF protocol.

Patients were premedicated with H1 and H2 blockers, completed in outpatients infusions center with registered nurses trained in desensitization.

TABLE V. Summary of patient management and outcomes

<table>
<thead>
<tr>
<th>Strategy</th>
<th>Medical management (N = 13)</th>
<th>Desensitization (N = 11)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Method</td>
<td>Hormone-based therapies (54%)</td>
<td>Oral protocol (73%)</td>
</tr>
<tr>
<td></td>
<td>Nonhormonal therapies (62%)</td>
<td>IM protocol (27%)</td>
</tr>
<tr>
<td>Outcome</td>
<td>Symptom improvement (92%)</td>
<td>Symptom improvement: dermatologic (88%); asthma/anaphylaxis (100%)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Tolerating IVF (3 of 3)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Pregnancy (2 of 3)</td>
</tr>
</tbody>
</table>

*Includes patients comanaged on OCPs.

The 2 anaphylaxis pts tolerated the slow 9 day oral protocol?!
Progestogen Hypersensitivity

- Autoimmune Progesterone Dermatitis is old term
- New term: Progestogen
  - Not all are due to progesterone
  - Some from synthetic derivatives
- Hypersensitivity
  - Not all dermatitis
  - Not all autoimmune

Case Epilogue

- Sera sent to University of Cincinnati with elevation of progesterone-specific IgE
- Referred to gynecology for treatment with GnRH agonist
- She received a dose of 11.25 mg of leuprolide (Lupron) but within a week was found to be pregnant
- Managed CU with antihistamines during pregnancy
- Started on omalizumab 300 mg every month in March 2016 with near complete control of hives
- Treated through a second pregnancy with omlaizumab
Aspirin Allergy?

- 39 yo F has a recent history of aspirin ingestion and within 20 minutes developed tongue numbness, tingling in her arms, chest pressure, and lightheadedness. She went to ED and was given another dose of aspirin and had worsening of her symptoms which resolved in 12-24 hrs.
- Past history notable for latex allergy with contact urticaria, and rhinitis symptoms when exposed to powdered gloves.
- Family history of CAD, HTN.

Case Continued

- In light of subjective symptoms with aspirin (tongue numbness and lightheadedness) and low likelihood of true allergy a placebo controlled challenge was performed.
Placebo Challenge Results

- 1 capsule (placebo) administered
  - 30 minutes later complained of tongue numbness
  - Physical exam normal
- 2 capsules (placebo administered) 15 minutes later
  - Tongue numbness increased and complained of lightheadedness (BP unchanged)
  - All symptoms spontaneously resolved after another 90 minutes

Aspirin Challenge

- Discussed results of placebo challenge and reassured her that her symptoms were not medication-induced and no sign of an allergic reaction
- Proceeded to open challenge with 325 mg aspirin
- Observed for an hour with no symptoms
Placebo Controlled Drug Challenges

- The choice of performing an open vs. a placebo controlled challenge is based on reaction type and patient characteristics
- Clinical features suggestive of needing a placebo challenge
  - Subjective symptoms of drug allergy (e.g. pruritus)
  - Anxiety level of patient regarding challenge to particular drug
  - Multiple drug allergy patients

Placebo Controlled Drug Challenges

- Techniques
  - Opaque capsules
  - Inert filler
  - Multiple placebos in highly anxious patients
  - For history of delayed reactions, consider full day of placebo followed by active drug on separate day
Placebo Tools

Symptoms with Placebo

- UT Southwestern study of drug challenges
- 19 patients underwent 21 placebo controlled challenges as an outpatient
- 57% of placebo challenges resulted in symptoms
- Signs/symptoms
  - Flushing
  - Pruritus
  - Tongue numbness
  - Throat tightness

Reactions to Placebo

97


Tips for the “Placebo Talk”

- Validate their reactions are legitimate
- Reassure them that anxiety is normal with drug challenges
- Inform them that anxiety reactions can mimic drug allergy and make it hard for you to discern
- Discuss that placebo challenges help you determine if reaction is anxiety or allergy
- Indicate that this is a routine practice
Tips for Management of Placebo/Subjective Reactions

- Examine the patient
- Take photos of “swelling”
- Reassure that reaction does not appear to be severe
- Delay next dose of challenge until symptoms resolved or nearly resolved
- Avoid medications
- Oxygen may be used if needed as a soothing measure

Multiple Drug Anaphylaxis Case

- 71 yo woman with *E. coli* UTI and bacteremia developed throat itching, swelling and dysphonia after 4th dose of ciprofloxacin
- Changed to meropenem and had similar reaction to 3rd dose
- History of multiple drug-induced anaphylaxis with throat closure and dysphonia including penicillin, cephalexin, sulfonamides, tetracycline and clarithromycin

Case

- Further questioning
  - No other symptoms with reactions
  - All symptoms localized to throat
  - No witnessed orofacial swelling

Case

- After baseline laryngoscopy, open ciprofloxacin IV challenge performed
- 15 minutes later developed throat itching, tightness and dysphonia
  - Symptoms identical to prior reactions
- Laryngoscopy showed paradoxical adduction of vocal cords with inspiration
- Patient informed about findings, taught throat relaxation methods and “anaphylactic” symptoms aborted in 5 minutes
Vocal Cord Dysfunction (VCD)

![Normal glottis vs. Adduction of vocal cords during VCD attack]

Drug-Induced Vocal Cord Dysfunction

- Histories usually described as “anaphylaxis”
- Symptoms localized to throat
- May have subjective swelling of lips/tongue but **lack objective evidence of orofacial swelling**
- May have multiple drugs involved
- Fiberoptic laryngoscopy is another useful tool in evaluating “drug allergy” patients

Conclusions

- Pharmacogenomics is still evolving in drug allergy
- Approach to aspirin allergy varies by urgency and nature of reaction but both ASA challenges and desensitizations can be done in the office
- Allergists are important to stamp out “Penicillin Allergy Disease”
- Ability to recognize patterns of cutaneous drug reactions will aid in timely and correct diagnosis and management of drug allergic reactions
- Placebo challenges are very helpful for subjective drug reactions