Practical Approaches to Drug Allergy

David A. Khan, MD
Professor of Medicine and Pediatrics
Allergy & Immunology Program Director

Disclosures

- No relevant disclosures
Objectives

- Gain an understanding of the spectrum of drug allergies
- Be able to identify historical features suggestive of a low likelihood for drug allergy
- Gain an understanding of when diagnostic testing or desensitization procedures are indicated

Adverse Drug Reactions ≠ Drug Allergy

Key Point 1
There are Many Types of Drug Allergies!

Key Point #2
Different Types of Drug Rashes Mean Different Things

Key Point #3

Case RT

- 17 yo with history of acne on TMP-SMX for 6 weeks developed some cold symptoms, then fever (101° F) and cervical lymphadenopathy. Started on azithromycin by pediatrician with no change in fever and 3 days later developed a rash, some facial edema and was admitted.
- In ED treated with epinephrine and single dose of steroids
Case RT

- Initial Labs
  - Eosinophilia (total eosinophil count ~4,000)
  - Elevated liver function tests
    - ALT 230, AST 123, T Bili 1.6
- Diagnosed with viral illness and steroids discontinued
- No improvement in symptoms after 2 more days with worsening labs
  - ALT 461, AST 269, T Bili 1.6, INR 1.3
Case RT

- Mother spoke with her cousin, a pediatrician in Maryland, the wife of an allergist at NIH who suspected DRESS
- Steroids reinitiated with prompt improvement and discharged to f/u at UTSW
- We agreed with diagnosis of DRESS from sulfonamide antibiotic
- Systemic steroids tapered over 2 months with resolution of rash, and all laboratory abnormalities

DRESS

- Drug Reaction with Eosinophilia and Systemic Symptoms
- Other Terminology
  - Phenytoin Hypersensitivity Syndrome
  - Antiepileptic Drug Hypersensitivity Syndrome
  - Drug Hypersensitivity Syndrome
  - Drug Induced Hypersensitivity Syndrome (DiHS)
DRESS

- Pathogenesis not well understood
- Drug-specific T cells and reactivation of human herpesvirus 6 may also be involved

RegiSCAR Scoring for DRESS

<table>
<thead>
<tr>
<th></th>
<th>No</th>
<th>Yes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fever ≥ 38.5°C</td>
<td>-1</td>
<td>0</td>
</tr>
<tr>
<td>Lymphadenopathy</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Eosinophilia</td>
<td>0</td>
<td>700-1500 cells/mm$^3$=1</td>
</tr>
<tr>
<td></td>
<td></td>
<td>&gt;1500= 2</td>
</tr>
<tr>
<td>Atypical Lymphocytes</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Skin rash</td>
<td>-1</td>
<td>&gt;50% BSA=1</td>
</tr>
<tr>
<td>Organ involvement</td>
<td>0</td>
<td>Single organ=1</td>
</tr>
<tr>
<td></td>
<td></td>
<td>≥2 organs=2</td>
</tr>
<tr>
<td>Resolution ≥ 15 days</td>
<td>-1</td>
<td>0</td>
</tr>
</tbody>
</table>

Total Score: <2 no case; 2-3 possible case; 4-5 probable; ≥5 definite

Unique Aspects of DRESS

- Reaction occurs after 2-8 weeks of therapy
- Symptoms may worsen after drug discontinued
- Symptoms may last weeks to even months after drug discontinued

Medications Linked to DRESS

- Causative Medications
  - Anticonvulsants, sulfonamides, allopurinol, minocycline, dapsone, sulfasalazine, abacavir, nevirapine, hydroxychloroquine, vancomycin
- Less common medications
  - celecoxib, efalizumab etc.
### Urticaria & Angioedema

<table>
<thead>
<tr>
<th>Common cutaneous drug reactions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Exanthems</td>
</tr>
<tr>
<td>Urticaria</td>
</tr>
<tr>
<td>Angioedema</td>
</tr>
<tr>
<td>Fixed drug eruption</td>
</tr>
<tr>
<td>Pruritus</td>
</tr>
<tr>
<td>Acniform</td>
</tr>
<tr>
<td>SCARs</td>
</tr>
<tr>
<td>DRESS</td>
</tr>
<tr>
<td>SJS/TEN</td>
</tr>
<tr>
<td>AGEP</td>
</tr>
</tbody>
</table>

#### Less common cutaneous drug reactions

- Acanthosis nigricans
- Alopecia
- Aphthous stomatitis
- Black hairy tongue
- Bullous eruptions
- Erythema nodosum
- Exfoliative dermatitis
- Gingival hyperplasia
- Lichenoid eruptions
- Lupus erythematosus
- Phototoxic/photoallergic
- Pigmentation
- Pityriasis rosea-like eruptions
- Psoiasis
- Purpura
- Vasculitis

Drug-Induced Urticaria and Angioedema

- IgE Mediated
- Pseudoallergic Reactions
- Serum Sickness
- Bradykinin-mediated
- Other

IgE Mediated Reactions

- Onset
  - Usually minutes to hour after drug exposure
  - Requires prior exposure to drug or cross-reacting drug (sensitization)
- Symptoms
  - Urticaria, flushing, pruritus, angioedema, anaphylaxis
- Rash resolves without peeling, or changes in pigmentation
Pseudoallergic Reactions

- Resemble true IgE allergic reactions but IgE not involved
- Pathophysiology
  - Non-specific mast cell degranulation
  - Activation of MRGPRX2 receptor
- Onset usually minutes to hour after exposure (like IgE)
  - May occur with 1st exposure
- Urticaria, flushing, pruritus, rarely hypotension
- Examples
  - Opiates, vancomycin, ciprofloxacin
- Premedication with antihistamines is helpful

Drug Exanthems (Maculopapular Eruptions)

- Most common drug allergic reaction
- Pathophysiology mixed
  - Often T-cell mediated
- Onset variable often within days or longer
- Pruritic, usually starts on trunk and spreads to extremities in a symmetric fashion
- Often resolves with scaling/peeling
- **Does not evolve into anaphylaxis**
Maculopapular Drug Exanthem

Hospital

4 Days later

Cutaneous Drug Eruptions
Severe Cutaneous Adverse Drug Reactions

- SJS/TEN, DRESS, AGEP
- Patients are ill
  - Fever, other systemic symptoms
- Mortality 5 to >30%
- Require multidisciplinary care

SJS

Serum Sickness-Like Reactions (SSLR)

- Symptoms of fever, rash, arthralgia ~ 7 days after medication started
  - Antibiotics and monoclonal antibodies frequent causes
- Unlike serum sickness, SSLR usually lack features of immune complexes, hypocomplementemia, vasculitis, renal disease
- Cefaclor most common cause in children
  - Altered metabolism leading to toxic reactive intermediates
### Non-Cutaneous Organ Specific Drug Allergic Reactions

<table>
<thead>
<tr>
<th>Clinical Features</th>
<th>Examples of causative agents</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hematologic</td>
<td>hemolytic anemia, thrombocytopenia, granulocytopenia</td>
</tr>
<tr>
<td></td>
<td>penicillin, quinine, sulfonamides</td>
</tr>
<tr>
<td>Hepatic</td>
<td>hepatitis, cholestatic jaundice</td>
</tr>
<tr>
<td></td>
<td>para-aminosalicylic acid, sulfonamides, phenothiazines</td>
</tr>
<tr>
<td>Pulmonary</td>
<td>pneumonitis, fibrosis</td>
</tr>
<tr>
<td></td>
<td>nitrofurantoin, bleomycin, methotrexate</td>
</tr>
<tr>
<td>Renal</td>
<td>interstitial nephritis, membranous glomerulonephritis</td>
</tr>
<tr>
<td></td>
<td>penicillin, sulfonamides, gold, penicillamine, allopurinol</td>
</tr>
</tbody>
</table>


### History Taking in Drug Allergy
Vast Majority of Patients with Drug Allergy Histories are Not Allergic

Drug Challenges confirm “not allergic”: ok to treat with drug
Skin tests and history confirm “allergic”: avoid drug or desensitize

Key Features of Drug Allergy History

<table>
<thead>
<tr>
<th>Question</th>
<th>Relevance</th>
</tr>
</thead>
<tbody>
<tr>
<td>How long ago was reaction?</td>
<td>Some drug allergies tend to wane over time (e.g. penicillin)</td>
</tr>
</tbody>
</table>
| Description of “rash” or “hives” (seeing pictures helps; showing pictures doesn’t) | Most patients can’t differentiate urticaria from other rashes
Urticaria more suggestive of IgE-mediated reaction |
| Symptoms objective or subjective?             | Subjective symptoms often anxiety-related                                  |
| When did reaction occur?                      | Immediate vs. delayed reaction                                             |
| What therapy required?                        | Gauge of severity                                                          |
| Similar symptoms in absence of drug?          | Underlying disease not drug allergy (e.g. chronic urticaria)               |

Features Suggestive of True Drug Allergy

- Objective findings
  - Rash
  - Wheezing, hypoxia
  - Hypotension
- Rational temporal relationship to drug
- “allergy-prone” drug
- Resolution with discontinuation

Features Less Suggestive of Drug Allergy

- Subjective symptoms only
  - “swelling”, pruritus
  - isolated throat symptoms
- High number of listed drug allergies
- Stereotypical reactions
- History of a childhood reaction
Testing in Drug Allergy

Testing:
Genetic Screening
Skin Testing
Drug Challenges

Immediate Drug Skin Testing

Penicillin is the only drug with reliable and validated skin testing

- **Always**
  - Penicillin
  - Platinum based chemotherapeutics
  - Perioperative agents
  - Local Anesthetic*
  - Drug anaphylaxis
  - Insulin
  - Corticosteroids

- **Maybe**
  - Other antibiotics
  - Biologics
  - PPIs

- **Never**
  - Anti-hypertensives
  - Lipid lowering agents
  - Anti-seizure agents
Most patients who think they are allergic to penicillin are not

Key Point #4

Most patients who really were allergic to penicillin in the past, lose their allergy over time

Key Point #5
Updates on Penicillin Allergy Disease

Penicillin (PCN) Allergy in the 1970’s at Wash U.

**TABLE I. Results of penicillin skin testing**

<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n</td>
<td>%</td>
<td>n</td>
<td>%</td>
<td>n</td>
</tr>
<tr>
<td>Patients tested</td>
<td>450</td>
<td>72.2</td>
<td>290</td>
<td>49.7</td>
<td>740</td>
</tr>
<tr>
<td>Patients positive</td>
<td>325</td>
<td></td>
<td>144</td>
<td></td>
<td>469</td>
</tr>
<tr>
<td>Males tested</td>
<td>214</td>
<td></td>
<td>134</td>
<td></td>
<td>348</td>
</tr>
<tr>
<td>Males positive</td>
<td>155</td>
<td>72.4</td>
<td>66</td>
<td>49.3</td>
<td>221</td>
</tr>
<tr>
<td>Females tested</td>
<td>236</td>
<td></td>
<td>156</td>
<td></td>
<td>392</td>
</tr>
<tr>
<td>Females positive</td>
<td>170</td>
<td>72.0</td>
<td>78</td>
<td>50.0</td>
<td>248</td>
</tr>
<tr>
<td>Inpatients tested</td>
<td>265</td>
<td></td>
<td>191</td>
<td></td>
<td>456</td>
</tr>
<tr>
<td>Inpatients positive</td>
<td>191</td>
<td>72.1</td>
<td>70</td>
<td>36.6</td>
<td>261</td>
</tr>
<tr>
<td>Outpatients tested</td>
<td>185</td>
<td></td>
<td>99</td>
<td></td>
<td>284</td>
</tr>
<tr>
<td>Outpatients positive</td>
<td>134</td>
<td>72.4</td>
<td>74</td>
<td>74.7</td>
<td>208</td>
</tr>
</tbody>
</table>

10/02/2017

Changing Epidemiology of Penicillin Allergy

<table>
<thead>
<tr>
<th>Time period</th>
<th>No. of subjects tested</th>
<th>Positive (%)</th>
<th>Age (mean years ± SD)</th>
<th>Time since reaction (mean years ± SD)</th>
<th>Average Health Plan patient age (years)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1994</td>
<td>25</td>
<td>10 (40.0)</td>
<td>30.7 ± 25.3</td>
<td>13.6 ± 15.9</td>
<td>35.7</td>
</tr>
<tr>
<td>1995</td>
<td>253</td>
<td>39 (15.4)</td>
<td>38.8 ± 22.3</td>
<td>13.8 ± 15.8</td>
<td>35.6</td>
</tr>
<tr>
<td>1996</td>
<td>196</td>
<td>19 (9.2)</td>
<td>39.4 ± 23.0</td>
<td>15.0 ± 15.6</td>
<td>35.8</td>
</tr>
<tr>
<td>1997</td>
<td>250</td>
<td>20 (8.0)</td>
<td>39.8 ± 21.3</td>
<td>14.9 ± 14.8</td>
<td>35.6</td>
</tr>
<tr>
<td>1998</td>
<td>219</td>
<td>2 (0.9)</td>
<td>38.9 ± 20.9</td>
<td>13.9 ± 15.7</td>
<td>35.6</td>
</tr>
<tr>
<td>1999</td>
<td>171</td>
<td>17 (10.0)</td>
<td>45.0 ± 20.5</td>
<td>16.5 ± 16.4</td>
<td>36.0</td>
</tr>
<tr>
<td>2000</td>
<td>150</td>
<td>19 (12.7)</td>
<td>40.1 ± 21.6</td>
<td>14.2 ± 16.7</td>
<td>36.5</td>
</tr>
<tr>
<td>2001</td>
<td>231</td>
<td>25 (10.8)</td>
<td>43.9 ± 25.4</td>
<td>18.3 ± 17.1</td>
<td>37.0</td>
</tr>
<tr>
<td>2002</td>
<td>330</td>
<td>29 (8.8)</td>
<td>56.5 ± 22.0</td>
<td>28.9 ± 18.6</td>
<td>37.4</td>
</tr>
<tr>
<td>2003</td>
<td>492</td>
<td>28 (4.7)</td>
<td>52.9 ± 21.2</td>
<td>24.1 ± 17.8</td>
<td>37.9</td>
</tr>
<tr>
<td>2004</td>
<td>435</td>
<td>2 (0.4)</td>
<td>50.9 ± 22.5</td>
<td>26.2 ± 19.3</td>
<td>38.3</td>
</tr>
<tr>
<td>2005</td>
<td>358</td>
<td>14 (4.5)</td>
<td>50.9 ± 24.3</td>
<td>26.3 ± 20.5</td>
<td>38.4</td>
</tr>
<tr>
<td>2006</td>
<td>168</td>
<td>7 (4.1)</td>
<td>47.9 ± 22.4</td>
<td>20.7 ± 16.6</td>
<td>38.4</td>
</tr>
<tr>
<td>2007</td>
<td>176</td>
<td>6 (3.4)</td>
<td>46.8 ± 22.7</td>
<td>23.9 ± 19.6</td>
<td>38.5</td>
</tr>
<tr>
<td>Total</td>
<td>3469</td>
<td>255 (7.3)</td>
<td>46.9 ± 23.3</td>
<td>21.1 ± 16.6</td>
<td>38.1</td>
</tr>
</tbody>
</table>


Low Current Rate of PCN Allergy

- Latest study from Kaiser of 500 consecutive patients with PCN allergy histories tested between 2010-2012
  - **1.6% had evidence of PCN allergy**
    - 0.8% + PCN skin tests
    - 0.8% + amoxicillin challenge

Decline in PCN allergy may be due to less parenteral PCN therapy

Why Do Patients “Lose” Their Drug Allergy?

- They were never allergic in 1st place
  - Most rashes with beta-lactams in children due to viral exanthem
- Loss of sensitivity over time
  - After 5 years 50% lose IgE to penicillin and cephalosporins

Is the Antibiotic to Blame?

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

Jean-Christoph Caubet, MD, * Laurent Kaiser, MD, † Barbara Lemaitre, MS, ‡ Benoît Fellay, PhD, § Alain Gervaix, MD, † and Philippe A. Eigenmann, MD †
Geneva and Fribourg, Switzerland

- Studied children 0-16 with urticarial or maculopapular rashes during or up to 72 hrs after β-lactam treatment
- Excluded rashes clearly suggestive of childhood infections (e.g. rubella, measles, chicken pox, etc)
- Serologies for EBV, HHV6, CMV, parvo B19 performed
- Throat swab for PCR to respiratory viruses included picorna, corona, human metapneumovirus, bocavirus, influenza, and parainfluenza viruses
6.8% positive oral challenges


Viral Exanthems Likely Source of “Drug Rashes”

- 55% children had + viral PCR
- Positive viral serologies
  - 50% in those with + oral challenges
  - 16% in those with – oral challenges

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

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 via EMR
Selection of Inpatients to Undergo Penicillin Testing

Outcomes of Proactive In Patient Penicillin Testing

Changes in Antibiotics Due to Penicillin Allergy Testing

A

Inpatient Antibiotic Orders Before and After a Negative Penicillin Allergy Test


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-Noél Primeau, MD; Elaine Medoff, MD; Christine Lester, MD; Andrew O’Keeffe, MD; Elena Nitchania, MD; Aliza 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)

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, Laurens Kaiser, MD, Barbara Lemaître, MS, Benoît Fellay, PhD, Alain Gervaix, MD, and Philippe A. Eigemmann, MD

Geneva and Fribourg, Switzerland

Original Article

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

Ronit Confino-Cohen, MD; Yossi Roisman, MD; Karen Meir-Shafir, MD; Tali Stauber, MD; Idit Lachover-Roth, MD; Alon Harshko, MD; and Amon Goldberg, MD

Rishon-Le-Zion 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; Chad M. Lomas, MD; Nanda Ramchandar, MD; and Jeremy D. Waldram, MD

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

Cross-Reactivity Between Penicillin and other Beta-lactams is Very Low

Key Point #6

Structural Similarities and Differences in Penicillin and Cephalosporin

Risk of reacting to cephalosporins in a patient with a history of a non-severe penicillin allergy is ~ 0.2% 


Carbapenems and PCN Allergy 

- Earlier retrospective studies suggested risk of reaction of 6-11% when administering carbapenem to patient with history of PCN allergy 
- Prospective studies of 602 PCN ST + patients (majority anaphylaxis to PCN) reveal: 
  - ~1% have + carbapenem skin tests 
  - 98% negative predictive value for carbapenem skin test 
  - If skin test negative, no need for graded challenge 

Drug Challenge

Gold standard for determining drug tolerance

Drug Challenges

- Intended for patients who are unlikely to be allergic to the given drug
- May be done in a graded manner or 1 step (full dose)
  - Graded challenges often start at \( \frac{1}{10} \)th of final dose with full dose administered 30-60 minutes later
- The intention of a drug challenge is to verify that a patient will not experience an adverse reaction to a given drug

Safety of Drug Challenges

Adverse reactions during drug challenges: a single US institution’s experience
Leon Kao, MD; Jessica Rajan, MD; Lonnie Roy, PhD; Eric Kavosh, MD; and David A. Khan, MD

- 1/123 challenges positive (no treatment required)
- Subjective symptoms in 20 and were higher with
  - Historically subjective symptoms
  - Female gender
  - >10 listed drug allergies associated

Only 16% skin tests/challenges were positive
Reactions to challenges typically mild and treated with antihistamines and steroids; 2 SSLRs were more severe
Contraindications to Drug Challenges

<table>
<thead>
<tr>
<th>Autoimmune Diseases</th>
<th>Drug Induced Vasculitis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bullous pemphigoid</td>
<td>Leukocytoclastic vasculitis</td>
</tr>
<tr>
<td>Pemphigus vulgaris</td>
<td>Churg Strauss</td>
</tr>
<tr>
<td>Linear IgA bullous disease</td>
<td>Organ Specific Drug Reactions</td>
</tr>
<tr>
<td>Drug induced lupus</td>
<td>Cytopenias</td>
</tr>
<tr>
<td>Neutrophilic Dermatosis</td>
<td>Hepatitis</td>
</tr>
<tr>
<td>AGEP</td>
<td>Nephritis</td>
</tr>
<tr>
<td>Sweet's syndrome</td>
<td>Pneumonitis</td>
</tr>
<tr>
<td>Severe Cutaneous Drug Reactions</td>
<td>Serum Sickness</td>
</tr>
<tr>
<td>SJS/TEN</td>
<td>SSLR may be amenable to challenge</td>
</tr>
<tr>
<td>DRESS</td>
<td></td>
</tr>
<tr>
<td>Exfoliative Dermatitis</td>
<td></td>
</tr>
</tbody>
</table>

Graded Challenge Vs. Desensitization

- Clinical Question: **Will this patient tolerate this drug?**
  - Graded challenge will answer this question

- Clinical Question: **How do I treat this patient who is allergic to this drug?**
  - Drug desensitization is a procedure to address this question
Managing Beta-Lactam Allergy Without Skin Testing or Allergists


Contents lists available at ScienceDirect

Impact of a clinical guideline for prescribing antibiotics to inpatients reporting penicillin or cephalosporin allergy

Kimberly G. Blumenthal, MD 1,3,5; Erica S. Shenoy, MD, PhD 1,3,5; Christy A. Varughese, PharmD 1,6; Shelley Hurwitz, PhD 1,5; David C. Hooper, MD 1,3,5; and Aleena Banerji, MD 1,6

1 Division of Rheumatology, Allergy, and Immunology, Department of Medicine, Massachusetts General Hospital, Boston, Massachusetts
2 Medical Practice Evaluation Center, Massachusetts General Hospital, Boston, Massachusetts
3 Harvard Medical School, Boston, Massachusetts
4 Division of Nephrology, Department of Medicine, Massachusetts General Hospital, Boston, Massachusetts
5 Infection Control Unit, Massachusetts General Hospital, Boston, Massachusetts
6 Department of Medicine, Brigham and Women’s Hospital, Boston, Massachusetts

Type I (IgE-mediated) HSR

- Anaphylaxis
- Angioedema
- Wheezing
- Laryngeal edema
- Hypotension
- Hives/urticaria
- OR
- Unknown reaction WITHOUT mucosal involvement, skin desquamation or organ involvement

Type II-V HSR

- Serum sickness
- Stevens-Johnson Syndrome
- Toxic Epidermal Necrolysis
- Acute Interstitial Nephritis (AIN)
- Drug Rash Eosinophilia Syndrome
- Hemolytic anemia

Mild Reaction

- Itching
- Minor rash (not hives)
- Maculopapular rash (mild Type IV HSR)
- EMR lists allergy, but patient denies

Avoid using PCN or cephalosporin; use alternative agents by microbial coverage.

OK to:

- Use 3rd/4th generation cephalosporins or carbapenems by Test Dose Procedure
- Use alternative agent by microbial coverage
- Astrocene

If KD consult determines that PCN or a 1/2/3rd generation cephalosporin is the preferred therapy, or that one of the alternative agents is substandard, consult Allergy.

OK to:

- Use full dose 3rd/4th generation cephalosporin
- Use penicillin or 1/2/3rd generation cephalosporin by Test Dose Procedure
- Use carbapenem

Impact of Drug Challenges by non-allergists on Antimicrobial Therapy

Test doses improved antimicrobial therapy after guideline adoption (n = 183)

<table>
<thead>
<tr>
<th>Antibiotic or class of antibiotic, n (%)</th>
<th>Before test dose</th>
<th>After test dose</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Penicillins&lt;sup&gt;b&lt;/sup&gt;</td>
<td>3 (2)</td>
<td>35 (19)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Piperacillin–tazobactam</td>
<td>4 (2)</td>
<td>2 (1)</td>
<td>&gt;.5</td>
</tr>
<tr>
<td>Cephalosporins&lt;sup&gt;c&lt;/sup&gt;</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>First generation</td>
<td>1 (0.6)</td>
<td>18 (10)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Third generation</td>
<td>9 (5)</td>
<td>54 (30)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Fourth generation</td>
<td>12 (7)</td>
<td>58 (32)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Aztreonam</td>
<td>21 (12)</td>
<td>1 (0.6)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Carbapenems</td>
<td>18 (10)</td>
<td>11 (6)</td>
<td>.21</td>
</tr>
<tr>
<td>Clindamycin</td>
<td>3 (2)</td>
<td>2 (1)</td>
<td>&gt;.5</td>
</tr>
<tr>
<td>Daptomycin</td>
<td>2 (1)</td>
<td>2 (1)</td>
<td>&gt;.5</td>
</tr>
<tr>
<td>Fluoroquinolone</td>
<td>28 (15)</td>
<td>6 (3)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Gentamycin</td>
<td>11 (6)</td>
<td>2 (1)</td>
<td>.004</td>
</tr>
<tr>
<td>Linezolid</td>
<td>7 (4)</td>
<td>4 (2)</td>
<td>.45</td>
</tr>
<tr>
<td>Vancomycin</td>
<td>125 (68)</td>
<td>68 (37)</td>
<td>&lt;.001</td>
</tr>
</tbody>
</table>

Key Point #7

When There is No Alternative A Drug Desensitization May Be Considered But It is Not Permanent
Drug Desensitizations

- Indicated for patients with:
  - High likelihood or confirmed drug allergy
  - In need of culprit drug where no alternative therapy exists
- Many Rapid Drug Desensitizations
  - Antibiotics
  - Chemotherapeutics
  - Monoclonals
  - Others

Rapid Drug Desensitization

- Typical starting dose is \(1/10,000^{th}\) of target therapeutic dose
- Can also use calculated dose from skin test as starting point
- Further dosage increases are typically twice the previous dose
- Administered at 15-20 minute intervals until therapeutic dosage achieved
- Can be performed with oral or IV medications
Conclusions

- There are many types of drug allergic reactions, cutaneous features can help determine testing/management/prognosis
- Most patients labeled with drug allergy are not allergic
- The label of penicillin allergy is associated with adverse health outcomes and can be removed through testing in >98% cases
- Drug challenges can be performed with antibiotics to prove tolerance, even by non-allergists
- Drug desensitizations can be used for truly allergic patients who require a specific drug but is a temporary effect