Advances in Infectious Diseases: New Directions for Primary Care

Antibiotic Allergies

Daniel Deck, PharmD
Infectious Diseases Clinical Pharmacist
San Francisco General Hospital

Disclosure

• I have received honorarium from Merck.

Overview

• Adverse drug reaction versus allergy
• Types of allergic reactions
• Beta-lactam allergy and cross-reactivity
• Sulfonamide allergy and cross-reactivity
• Management principles
  – History taking
  – Skin Testing
  – Densensitization
  – Graded Challenge (drug provocation)

A common scenario

A 67 year old woman new to your clinic presents with 3 days of dysuria. She reports a history of multiple UTIs, last episode 9 months ago when she was treated with ciprofloxacin. She has no other complaints. PMH: hypertension and DM for which she takes lisinopril and metformin. She states she is allergic to penicillin (hives) and sulfa (rash). You obtain a urine culture & prescribe her ciprofloxacin. She returns two days later with continued UTI symptoms and is febrile to 39.6F although otherwise non-toxic. The urine culture returns >100K E.coli. Resistant: ampicillin, ciprofloxacin Sensitive: cefazolin, ceftriaxone, gentamicin, TMP/SMX. Now what?
What would you prescribe?

1) Cephalexin
2) Cefpodoxime
3) TMP/SMX
4) IV Ceftriaxone
5) IV Gentamicin
6) None of the above

Adverse Drug Reactions (ADR)

- Type A (85-90%)
  - Predictable, dose-dependent
  - Related to known pharmacological action
  - Occur in otherwise normal patients
  - "Side Effect"
- Type B (10-15%)
  - Unpredictable
  - Not related to pharmacological action
  - Occur in only a small proportion of the population
  - Allergic reactions, idiosyncratic reactions, drug intolerance
  - Allergic reactions are immunologically mediated

Antibiotic Allergy

- Small proportion of all reported ADRs
  - 2.2% frequency of cutaneous drug reactions among hospitalized patients
  - 75% of these reactions attributed to an antibiotic
- Associated with substantial morbidity, mortality, and increased health care costs
- Use of less efficacious or more toxic alternative antibiotics
  - Inpatients with a reported PCN allergy more likely to receive vancomycin (40% vs. 17%) or a quinolone (22% vs. 8%)

Classification of Allergic Reactions

<table>
<thead>
<tr>
<th>Classification</th>
<th>Time of onset</th>
<th>Mediator(s)</th>
<th>Pathologic Characteristic</th>
<th>Clinical Symptoms</th>
<th>Skin Testing Useful</th>
</tr>
</thead>
<tbody>
<tr>
<td>Type I</td>
<td>&lt; 1 hr</td>
<td>IgE</td>
<td>Mast cell degranulation</td>
<td>Anaphylaxis, hypotension, angioedema, urticaria, wheezing</td>
<td>Yes</td>
</tr>
<tr>
<td>Type II</td>
<td>&gt; 72 hr</td>
<td>IgG/IgM</td>
<td>Full-dependent cell destruction</td>
<td>Hemolytic anemia, thrombocytopenia, proteinuria, hematuria</td>
<td>No</td>
</tr>
<tr>
<td>Type III</td>
<td>10-21 days</td>
<td>IgG/IgM</td>
<td>Immune complex deposition</td>
<td>Serum sickness, vasculitis, tissue injury, eosinophilia, renal failure</td>
<td>No</td>
</tr>
<tr>
<td>Type IV</td>
<td>2-4 or more days</td>
<td>T cells, cytokines</td>
<td>Delayed/cellular hypersensitivity</td>
<td>Maculopapular, bullous, or purpuric exanthema, eosinemia, SJS/TEN</td>
<td>No</td>
</tr>
</tbody>
</table>
Clinical Features of Allergic reactions

- Immediate reaction (Type I anaphylaxis)
  - Rare but life threatening
  - Requires sensitization, do not occur with first dose
- Delayed reactions (Type II, III, IV)
  - Any organ may be affected but skin is most common
  - Occur days to weeks after initial exposure
  - Secondary exposure reaction may occur in minutes or hours
    - Examples
      - Maculopapular skin eruptions
      - DRESS syndrome (fever, eosinophilia, internal organ involvement)
      - Stevens-Johnson Syndrome/ Toxic Epidermal Necrolysis
      - Hemolysis, cytopenias,

Special Populations

- HIV-infected
  - Higher frequency of allergic reactions
  - TMP/SMX hypersensitivity rates 20-80% vs 1-3%
  - Altered drug metabolism, decreased glutathione levels
- Cystic Fibrosis
  - Antibiotic allergies reported in up to 30% of patients
  - Repeated exposure and immune hyperresponsiveness
- Infectious Mononucleosis
  - Increase in cutaneous reactions to penicillin, aminopenicillins
  - Viral infection may alter immune status of host
  - Implicated antibiotic may be safely readministered

Allergy management algorithm

- Reported antibiotic allergy
- History and physical examination
- True allergy suspected?
- Nonimmune-mediated ADR
  - Rechallenge if necessary
- Immediate reaction
  - Presumed IgE-mediated anaphylaxis
  - Skin Testing (if available and indicated)
  - Desensitization (when indicated)
- Education
- Communication

- Delayed reaction
  - Differentiate mild vs severe reactions
  - Graded challenge (mild reactions only)
  - Drug avoidance (severe reactions)
  - Education
  - Communication

Allergy History Taking

- What was the patient’s age at the time of the reaction? Does the patient recall the reaction?
- Was this a first-dose reaction?
- What were the characteristics of the reaction?
- What was the time course of the reaction?
- Why was the patient taking the medication?
- Was the patient taking other medication (including OTCs) at the time of the reaction?
- Has the patient taken similar medication before or after the reported reaction?
Penicillin allergy facts

- Up to 10% of patients report an allergy to penicillin
- Type I reactions occur in 1 in 5000 to 10000 courses of therapy
- 80 to 90% of patients who claim to be allergic will have a negative skin test for an IgE-mediated allergy
  - Unacceptable history = 0/34
  - Vague history = 10/150 (6.7%)
  - Convincing history = 19/135 (14%)
- Patients with Type 1 reaction to aminopenicillins frequently demonstrate cross reactivity to penicillin on skin testing

Skin Testing

- May be used to detect allergen-specific IgE antibodies
- With the exception of penicillin the relevant immunogens are not known for most drugs
- Highly accurate for identifying Type 1 PCN reactions
  - Accurately identify 90-97% of patients
  - Penicilloyl polysine (Pre-Pen®) plus diluted Penicillin G
- Skin prick testing followed by intradermal test in 15 minutes
- If test is positive penicillin may be administered
- If positive use alternative drug or consider desensitization

Penicillin Antigenic Determinants

Skin testing: practical concerns

- In whom should penicillin skin testing be considered?
  - History of Type I penicillin allergy
  - Elective skin-testing for patients where treatment with penicillin (or a related antibiotic) is anticipated
    - Patients who require treatment with penicillin (or a related antibiotic) or when such an antibiotic is strongly preferred
- Is skin testing available and/or practical?
  - Outpatient referral to allergist
  - Inpatient availability
  - Are the necessary reagents available?
Desensitization

- Reaction presumed to be IgE mediated
- No other alternative medications are appropriate
- Inpatient, trained staff, rescue meds bedside
- Amount of drug increased over a period of hours
  - Starting dose in micrograms
  - Doses doubled every 15 to 30 minutes
  - Therapeutic dose reached in 4 to 12 hours
  - IV or PO, PO considered safer
- Patient must remain on drug continuously through course of therapy or process must be repeated

Graded Challenge (Drug Provocation)

- For reactions that are not considered IgE-mediated
- Contraindicated with history of serious reaction such as Stevens Johnson, TEN, DRESS
- Useful for history of maculopapular eruptions
- Starting doses higher than in desensitization
- Interval for redosing varies (hours to days)
- May treat through mild skin reactions with antihistamines, corticosteroids, or both if needed

Oral Penicillin Desensitization Protocol

<table>
<thead>
<tr>
<th>Penicillin suspension</th>
<th>Concentration (units/ml)</th>
<th>Vol (ml)</th>
<th>Cumulative dose (units)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>1000</td>
<td>0.1</td>
<td>100</td>
</tr>
<tr>
<td>2</td>
<td>1000</td>
<td>0.2</td>
<td>200</td>
</tr>
<tr>
<td>3</td>
<td>1000</td>
<td>0.4</td>
<td>400</td>
</tr>
<tr>
<td>4</td>
<td>1000</td>
<td>0.8</td>
<td>800</td>
</tr>
<tr>
<td>5</td>
<td>1000</td>
<td>1.6</td>
<td>1,600</td>
</tr>
<tr>
<td>6</td>
<td>1000</td>
<td>3.2</td>
<td>3,200</td>
</tr>
<tr>
<td>7</td>
<td>1000</td>
<td>6.4</td>
<td>6,400</td>
</tr>
<tr>
<td>8</td>
<td>10,000</td>
<td>1.2</td>
<td>12,000</td>
</tr>
<tr>
<td>9</td>
<td>10,000</td>
<td>2.4</td>
<td>24,000</td>
</tr>
<tr>
<td>10</td>
<td>10,000</td>
<td>4.8</td>
<td>48,000</td>
</tr>
<tr>
<td>11</td>
<td>80,000</td>
<td>1.0</td>
<td>80,000</td>
</tr>
<tr>
<td>12</td>
<td>80,000</td>
<td>2.0</td>
<td>160,000</td>
</tr>
<tr>
<td>13</td>
<td>80,000</td>
<td>4.0</td>
<td>320,000</td>
</tr>
<tr>
<td>14</td>
<td>80,000</td>
<td>8.0</td>
<td>640,000</td>
</tr>
</tbody>
</table>

Interval between doses of 15 to 30 minutes
Elapsed time 4-8 hours
Each dose diluted in 30 ml of water and given orally
30 minutes between last dose and first dose of IV penicillin

Desensitization vs Graded Challenge

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Graded challenge</th>
<th>Desensitization</th>
</tr>
</thead>
<tbody>
<tr>
<td>IgE-mediated allergy</td>
<td>Unlikely</td>
<td>Proven or highly suspected</td>
</tr>
<tr>
<td>Reason to perform</td>
<td>Disprove hypersensitivity</td>
<td>No other alternative antibiotics</td>
</tr>
<tr>
<td>Goal</td>
<td>Confirm ability to receive drug</td>
<td>Generate temporary tolerance</td>
</tr>
<tr>
<td>Contraindication</td>
<td>Non-IgE life threatening reaction</td>
<td>Non-IgE life threatening reaction</td>
</tr>
<tr>
<td>Starting dose</td>
<td>1:100 of therapeutic dose</td>
<td>1,000,000 of therapeutic dose</td>
</tr>
<tr>
<td>Steps to complete</td>
<td>3 to 5</td>
<td>10 to 20</td>
</tr>
<tr>
<td>Interval between steps</td>
<td>Variable</td>
<td>15 to 30 mins</td>
</tr>
<tr>
<td>Location</td>
<td>Clinic or Inpatient</td>
<td>Inpatient (usually ICU)</td>
</tr>
<tr>
<td>IV access</td>
<td>Not needed</td>
<td>Usually indicated</td>
</tr>
<tr>
<td>Disposition</td>
<td>Able to treat patient</td>
<td>Continue administration of drug</td>
</tr>
<tr>
<td>Sustainability</td>
<td>Yes once allergy disproven</td>
<td>Temporary tolerance only</td>
</tr>
</tbody>
</table>
Beta-Lactam Antibiotics

All share the 4-membered beta-lactam ring

Beta-lactam ring may be fused to another 5 or 6 membered ring to yield:
- Penicillins
- Cephalosporins
- Carbapenems
- Monobactam (no second ring)

Each of these compounds can be further modified by various substituents at the R1 position. Cephalosporins also have a second R2 position. The side chain differentiate the activity and metabolic parameters of individual drug in each class.

Cephalosporin allergy and cross-reactivity

- Allergic reactions occur in 1-3% of patients
- Risk of anaphylaxis is low (0.001 – 0.1%)
- 4-fold increase in risk with reported penicillin allergy
- 10 -20% cross-reactivity rate is inaccurate
  - Non-allergic ADRs reported as allergy
  - Received primarily 1st generation cephalosporins
  - Changes in manufacturing process over time
  - Chemical changes in later generation cephalosporins make them less similar to penicillin and aminopenicillins
- Similarities in R1 side chains implicated in cross-reactivity

Chemical Similarities of R-1 side chain

<table>
<thead>
<tr>
<th>Penicillin 6</th>
<th>Ampicillin</th>
<th>Cefoxitin</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cephalothin 1st</td>
<td>Amoxicillin</td>
<td>Cefotaxime (3rd)</td>
</tr>
<tr>
<td>Cefoxitin 2nd</td>
<td>Cephalaxin (1st)</td>
<td>Cefradixin (3rd)</td>
</tr>
<tr>
<td>Cefadroxil (3rd)</td>
<td>Cefoaxime (3rd)</td>
<td></td>
</tr>
<tr>
<td>Cefprozil (2nd)</td>
<td>Cefepime (4th)</td>
<td></td>
</tr>
<tr>
<td>Cefaclor (2nd)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Cephalosporin with R-1 Side Chains Chemically Unrelated to Penicillins

- 1st generation: Cefazolin
- 2nd generation: Cefuroxime, Cefotetan, Cefamandole
- 3rd generation: Ceftazidime, Cefixime, Cefitubin, Cefdinir

Approach to prescribing cephalosporin in a penicillin allergic patient

- Avoid 1st generation unless further testing done
- History not consistent with IgE-mediated reaction
  - Low risk; may give 2nd, 3rd, and 4th generation
- Convincing history for IgE-mediated reaction
  - Use non beta-lactam antibiotic
  - Consider desensitization
  - Skin test for PCN allergy
    - Negative result – ok to administer cephalosporins (any generation)
    - Positive result – Avoid 1st and 2nd generation, cautious approach to prescribing 3rd and 4th generation cephalosporins
**Carbapenem and monobactams**

- **Carbapenems**
  - Cross-reactivity of 50% in initial study
  - Retrospective studies estimated 10% rate of
  - Prospective studies suggest rate is around 1%
  - Similar approach as with cephalosporins
- **Monobactams (Aztreonam)**
  - Clinical trials show no cross-reactivity to penicillin
  - May be safely administered to penicillin allergic patients
  - Ceftazidime shares the same R1 side chain, reports of cross-reactivity so aztreonam should be avoided

---

**Sulfonamide antibiotic allergy**

- **Adverse reactions relatively common**
  - Occur in 3% of all courses
  - Only a small percent of these are true allergies
- **Rash is most common allergic presentation**
  - More severe derm reactions (SJS/TEN) uncommon but well described
  - IgE-mediated reactions are rare
- **Cross-reactivity with other sulfonamide drugs has historically been a concern but...**

---

**“Sulfa” allergy**

- Use of the term *sulfa allergy* is imprecise, often misleading, and should be abandoned
- Attempt to classify diverse compounds containing a sulfonamide moiety into one group
- Sulfonamide antibiotics (sulfonylarylamines) are distinct from nonarylamine (nonantimicrobial) sulfonamides and sulfones:
  - Antibiotics: sulmethoxazole, sulfadiazine
  - Nonantibiotics: furosemide, HCTZ, glyburide, acetazolamide
  - Sulfone: dapsone

---

**Sulfonamide moiety**

**Sulfonylarylamine**

**Sulfamethoxazole**

**Furosemide**

**Dapsone**
Large observational study (969 patient with sulfonamide abx allergy & 19,257 w/o a sulfonamide abx allergy

Patients with a history of sulfonamide allergy had an increased risk of an allergic reaction to non-sulfonamide antibiotics compared to patient w/o history (OR 2.8, 95%CI 2.1-3.7)

But were even more likely to have a reaction to penicillin (OR 3.9, 95%CI 3.5-4.3)

Conclusion: increased reactions attributable to predisposition to allergic reaction in general as opposed to cross-reactivity

Case revisited

After taking a thorough allergy history you find out that she can’t recall her penicillin allergy but her mom told her that she had hives as a child when treated for a tonsil infection. Her “sufa” allergy turned out to be a rash that she developed when taking a blood pressure called “HCTZ”.

Penicillin allergy: vague but somewhat concerning for an IgE-mediated reaction

Sulfonamide antibiotic allergy: rejected on the basis of her history and evidence that cross-reactivity is unlikely

What would you prescribe?

1) Cephalexin – 1st generation CPH generally avoided unless she is skin tested for PCN allergy
2) Cefpodoxime – 3rd generation CPH so less chance for cross-reactivity, preferred to skin test for PCN allergy before giving
3) TMP/SMX – safe to prescribe, oral step-down if she requires initial IV course
4) IV Ceftriaxone – similar to cefpodoxime, since she is in a monitored inpatient setting may consider challenge is skin test not available
5) IV Gentamicin – no contraindication but age and comorbidities may increase risk for nephrotoxicity
6) None of the above - another option would be IV aztreonam

Final Questions?

• Contact Info
• Extension: 415-206-5574
• Email: daniel.deck@sfdph.org

SFGH “As real as it gets”
References

8) Breslau CG, Singh H, Illoca JH. Likelihood and mechanisms of cross-allergenicity between sulfonamide antibiotics and other drugs containing a sulfonamide functional group. Pharmacotherapy. 2004;24(7):856-70