Antibiotic Allergies – Facts, Myths, and Half-truths

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Statement of Disclosures

• Meghan Jeffres has the following financial relationships.
  • Stock – Merck and Pfizer
Objectives

• Assess the validity of an allergy label on a patient’s medical record
• Analyze risk of cross-reactivity within and among antibiotic classes
• Given a case of a patient with one or more antibiotic allergies, create an appropriate antibiotic regimen

Big Picture

Adverse Reactions

- Unpredictable
- Predictable

Immediate – within 24 hours of receipt, typically within 1 hour
Delayed – anytime after 1 hour of receipt

Allergic 10%
Non-allergic 10%

Types of Allergic Drug Reactions

Immediate
- Type I: IgE Mediated
  - Anaphylaxis

Type II: IgG mediated cell destruction
- Hemolytic anemia, thrombocytopenia, neutropenia

Type III: IgG drug immune complex deposition/complement activation
- Serum sickness, vasculitis, drug fever

Type IV: T-Cell mediated
- Contact dermatitis, SJS, TEN, DIHS

Immediate Delayed
- Rare

Types
- Type I: Antibiotics, NMBA, Platinum chemotherapy, Chimeric antibodies
- Type II: Hemolytic anemia, antibiotics, NSAIDs, quinidine, Thrombocytopenia, heparin, sulfonamides, vancomycin, carbamazepine, Neutropenia, antimalarials, flecainide
- Type III: Vasculitis, antibiotics, loop and thiazide diuretics, phenytoin, allopurinol
- Type IV: Antibiotics, Antimalarials, Calcium channel blockers, Azathioprine, sulfasalazine, Minocycline, Trimethoprim-sulfamethoxazole, Sirolimus, tacrolimus

Ig = immunoglobulin; SJS = Stevens Johnson Syndrome; TEN = Toxic Epidermal Necrolysis; DIHS = drug-induced hypersensitivity symptoms

Patient Reported Antibiotic Allergy Prevalence

<table>
<thead>
<tr>
<th></th>
<th>Inpatient n=1893</th>
<th>Outpatient n=411,543</th>
</tr>
</thead>
<tbody>
<tr>
<td>Penicillin</td>
<td>15.6%</td>
<td>11%</td>
</tr>
<tr>
<td>Sulfonamide</td>
<td>7.3%</td>
<td>7.9%</td>
</tr>
<tr>
<td>Macrolide</td>
<td>2.0%</td>
<td>1.9%</td>
</tr>
<tr>
<td>Cephalosporin</td>
<td>1.7%</td>
<td>1.7%</td>
</tr>
<tr>
<td>Quinolone</td>
<td>1.2%</td>
<td>0.8%</td>
</tr>
</tbody>
</table>

Incidence increases with age and female sex


Validity of Allergy History

A. 37 yo female
   • Allergy: penicillin – rash

B. 45 yo female
   • Allergy: penicillin – hives, shortness of breath

C. 39 yo female
   • Allergy: penicillin – unknown reaction

Which patient is most likely to experience an allergic reaction if exposed to penicillin?
Correlation between history and reaction

<table>
<thead>
<tr>
<th></th>
<th>Immediate reaction (&lt; 1 hours)</th>
<th>Immediate reaction (1-2 hours)</th>
<th>Delayed reaction (&gt;24 hours)</th>
</tr>
</thead>
<tbody>
<tr>
<td>History of immediate reaction, n=36</td>
<td>0</td>
<td>8 (22%)</td>
<td>1 (3%)</td>
</tr>
<tr>
<td>History of delayed reaction, n=235</td>
<td>6 (3%)</td>
<td>1 (0.5%)</td>
<td>9 (4%)</td>
</tr>
<tr>
<td>Unknown history, n=71</td>
<td>0</td>
<td>0</td>
<td>1 (1%)</td>
</tr>
</tbody>
</table>


Paul 55 yo male with CAP

- **CC**: shortness of breath, cough, and fever x 3 days
- **PMH**: DM II
- **Vitals**: 38.5, 135/90, 98, 22, 91% RA
- **Imaging**: CXR left lower lobe consolidation
- **Allergy**: Penicillin – tongue swelling

CAP = community acquired pneumonia, CC = chief complaint, PMH = past medical history, DM = diabetes mellitus, RA = room air, CXR = chest xray
Treatment Options for CAP

A. Ceftriaxone + azithromycin
B. Doxycycline
C. Moxifloxacin or levofloxacin

What is the best treatment option for Paul?

Cross-reactivity between beta-lactams

- Allergic components: base structure, side chain
- Penicillins, carbapenems, carbapenems, monobactams, beta-lactamase inhibitors
- Historical data
  - Penicillin-cephalosporin 10%
  - Penicillin-carbapenem 5%
  - Cephalosporin-carbapenem 25%

Clinical Evidence

- Outpatient clinic, Italy
- N=214 – documented delayed hypersensitivity to penicillins
- Skin and patch testing
  - No reaction to cefuroxime, ceftriaxone, or aztreonam
  - N=40 (19%) reaction to:
    - Cephalexin (n=31)
    - Cefaclor (n=39)
    - Cefadroxil (n=17)
Crib notes

• Risk of cross-reactivity:
  • With similar side-chains ≈ 20%
  • Without similar side-chains – same as without penicillin allergy status
• Cross-reactive – base and/or side-chain
  • Penicillin, ampicillin, amoxicillin, cephalexin
  • Ceftriaxone and cefepime
  • Ceftazidime and aztreonam
  • Ceftaroline and ceftobiprole
*Cefazolin – no side chain similarities


Paul 55 yo male with CAP

• Allergy: Penicillin – tongue swelling

• Antibiotic options
  A. Ceftriaxone + azithromycin
  B. Moxifloxacin or levofloxacin
  C. Doxycycline

CAP = community acquired pneumonia
Jim 55 yo male with prostatitis

• PMH
  • DM II, A1c 7.9
  • HFREF, EF 40%
• Allergy: sulfa - rash
• Home medications
  • Metformin 1 g BID
  • Lisinopril 20 mg daily
  • Metoprolol 100 mg BID

• New medications
  • TMP/SMX 1 DS BID
  • Glipizide 5 mg daily
  • Furosemide 20 mg daily

Safe or Not Safe?

PMH = past medical history, DM = diabetes mellitus, HFREF = heart failure with reduced ejection fraction, EF = ejection fraction, BID = twice daily, TMP/SMX = trimethoprim/sulfamethoxazole, DS = double strength

Changes to Practice

• Don’t accept penicillin as an allergy – get a specific medication
• Remove penicillin allergy label if there is a remote history (> 10 years) or if reaction is predictable
• Use cephalosporins, other than cephalaxin, in case of true penicillin, amoxicillin, or ampicillin allergy
Investigate Sulfonamide Source

**Antibiotic**
- Sulfamethoxazole
- Sulfazalazine
- Sulfadiazine
- Sulfacetamide
- Sulfanilamide
- Sulfisoxazole

**Non-antibiotics**
- Antivirals (protease inhibitors)
- COX-2 inhibitors
- Diuretics
  - Carbonic anhydrase inhibitors, loop, thiazide
- Sulfonylureas
- Triptans (5-HT3 RA)

COX = cyclooxygenase, RA = receptor antagonist

Sulfa Allergy – Medicinal Chemistry Flashback

Sulfa = sulfonamide

Furosemide

Sulfamethoxazole
Clinical Evidence

- General Practice Research Database in the United Kingdom
  - Outpatient medical records, > 700 general practitioners
  - 8 million patients
  - 1987-1999
- Inclusion: systemic sulfonamide antibiotic and sulfonamide non-antibiotic at least 60 days later
- Case (n=969) allergic reaction to sulfonamide antibiotic
- Controls (n=19,257) no allergic reaction


Cross-Reactivity between Sulfonamide Antibiotics and Sulfonamide Nonantibiotics

<table>
<thead>
<tr>
<th></th>
<th>Case</th>
<th>Control</th>
<th>Unadjusted OR (95% CI)</th>
<th>Adjusted OR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Allergic reaction to sulfa nonantibiotic</td>
<td>9.9%</td>
<td>1.6%</td>
<td>6.6 (5.2–8.4)</td>
<td>2.8 (2.1–3.7)</td>
</tr>
<tr>
<td>Allergic reaction to penicillin</td>
<td>14.0%</td>
<td>2.0%</td>
<td>7.8 (7.1–8.5)</td>
<td>3.9 (3.5–4.3)</td>
</tr>
</tbody>
</table>

Odds ratios adjusted for:
- Sex, age at outcome, asthma, use of drugs for asthma, use of corticosteroids
- History of eczema, hay fever, allergic rhinitis, urticaria, sinusitis, cellulitis, adverse drug reactions, urinary tract infection, systemic lupus erythematosus, rheumatoid arthritis, other connective-tissue diseases, use of antihistamines, and use of anticonvulsants

Cross-reactivity among sulfonamide antibiotics

- 24 patients with sulfamethoxazole fixed drug eruption, verified with oral challenge
- Oral challenge
  - 7/22 (32%) sulfadiazine
  - 6/14 (43%) sulfamethizole
- Poor sulfamethoxazole patch test reliability
  - 5/28 (18%)

Jim 55 yo male with prostatitis

- Allergy investigation → rash from sulfonamide antibiotic
- New medications
  - TMP/SMX 1 DS BID
  - Glipizide 5 mg daily
  - Furosemide 20 mg daily

Safe or Not Safe?

PMH = past medical history, DM = diabetes mellitus, HFREF = heart failure with reduced ejection fraction, BID = twice daily, TMP/SMX = trimethoprim/sulfamethoxazole, DS = double strength
Sulfonamide and sulfone cross-reactivity

- Delayed allergic reaction to TMP/SMX and switched to dapsone for PCP prophylaxis
- Dapsone reaction 13/60 (22%)
  - All delayed
  - Different reaction symptoms from TMP/SMX
- Debate: cross-reaction vs. multiple allergies
- No data in HIV negative population

Changes to Practice

- Don’t accept sulfa as an allergy – get a specific medication
- Use non-antibiotic sulfonamides in cases of sulfonamide antibiotic allergy regardless of reaction
- Avoid use of sulfonamide antibiotics in patients with allergy history
Fluoroquinolone hypersensitivity per 100,000 prescriptions, 2004–2010

National Electronic Injury Surveillance System-Cooperative Adverse Drug Event Surveillance (NEISS-CADES) system

<table>
<thead>
<tr>
<th></th>
<th>Ciprofloxacin</th>
<th>Levofloxacin</th>
<th>Moxifloxacin</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prescriptions</td>
<td>122,466,455</td>
<td>88,144,080</td>
<td>24,395,259</td>
</tr>
<tr>
<td>ED visits</td>
<td>469</td>
<td>505</td>
<td>448</td>
</tr>
<tr>
<td>Mild reaction rate</td>
<td>18.4 (13.9-22.9)</td>
<td>25.0 (18.8-31.1)</td>
<td>82.4 (53.9-110.9)</td>
</tr>
<tr>
<td>Moderate to severe reaction rate</td>
<td>8.0 (6.0-10.0)</td>
<td>15.8 (11.6-20.0)</td>
<td>58.9 (40.5-77.3)</td>
</tr>
</tbody>
</table>

Mild = self-limiting, non-anaphylactic adverse event (rash), no hospital admission
Moderate = signs and symptoms consistent with anaphylaxis without hospitalization
Severe = anaphylaxis, or extensive or desquamating skin reactions requiring hospitalization

Gina 36 yo female with pyelonephritis

- Urine culture and susceptibilities for *Pseudomonas aeruginosa*
- Allergy: levofloxacin

<table>
<thead>
<tr>
<th>Antibiotic</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cefepime</td>
<td>S</td>
</tr>
<tr>
<td>Ciprofloxacin</td>
<td>S</td>
</tr>
<tr>
<td>Gentamicin</td>
<td>S</td>
</tr>
<tr>
<td>Meropenem</td>
<td>S</td>
</tr>
<tr>
<td>Pip/tazo</td>
<td>S</td>
</tr>
</tbody>
</table>

Can ciprofloxacin be used safely or are IV antibiotics necessary?

Pip/tazo = piperacillin/tazobactam
### Case series cross-reactivity of fluoroquinolones

<table>
<thead>
<tr>
<th>N=3 immediate ciprofloxacin allergy</th>
<th>N=3 immediate moxifloxacin allergy</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Skin test</strong></td>
<td><strong>Oral challenge</strong></td>
</tr>
<tr>
<td>Ciprofloxacin</td>
<td>2/3</td>
</tr>
<tr>
<td>Levofloxacin</td>
<td>3/3</td>
</tr>
<tr>
<td>Moxifloxacin</td>
<td>3/3</td>
</tr>
</tbody>
</table>


### Case series cross-reactivity of fluoroquinolones

<table>
<thead>
<tr>
<th>N=12 immediate reaction to a fluoroquinolone</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Ciprofloxacin oral challenge</strong></td>
</tr>
<tr>
<td>Ciprofloxacin allergy</td>
</tr>
<tr>
<td>Levofloxacin allergy</td>
</tr>
<tr>
<td>Moxifloxacin allergy</td>
</tr>
<tr>
<td><strong>Total</strong></td>
</tr>
</tbody>
</table>

Calculating Rates of Cross-reactivity

• Immediate levofloxacin allergy
  • Ciprofloxacin 25%
  • Moxifloxacin 100%
• Immediate ciprofloxacin allergy
  • Levofloxacin 20%
  • Moxifloxacin 25%
• Immediate moxifloxacin allergy
  • Ciprofloxacin 0%
  • Levofloxacin 0%

Cross-reactivity for delayed allergic reactions unknown


Gina 36 yo female with pyelonephritis

• Urine culture *P. aeruginosa*
• Allergy: levofloxacin

Can ciprofloxacin be used safely or are IV antibiotics necessary?

Extra credit: Alternative PO antibiotic?
Cross-reaction vs. multiple allergies

- Multiple hypersensitivity syndrome
- Allergy to ≥ 2 chemically different medications
- 2 subtypes
  - Development of hypersensitivity to multiple medications simultaneously
  - Development of hypersensitivity sequentially sometimes years apart


Antibiotic Predictors Multiple Hypersensitivity Syndrome, n=25,695

Odds ratio

Penicillin
Glycopeptides
TMP/SMX
Macrolides
Tetracyclines
Quinolones
Cephalosporins

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