Multiple Antibiotic Allergies

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Conflict of Interest

- Financial: None
- Research: Merck, AllerQuest
- Legal Consult/Expert Witness: Antibiotic allergies
- Organizational: None
- Gifts: None
Definition

- **Multiple Drug Allergy Syndrome (MDAS)**
  - hypersensitivity to 2 or more structurally unrelated medications
  - “propensity to make immune responses to haptens and then express a broad range of immunopathologic responses, rather than a propensity to react in specific ways to specific classes of drugs”*

### Table 2

Number of Patients Reporting One or More Drug Allergy in 2007

<table>
<thead>
<tr>
<th>Number of “Allergies”</th>
<th>Individuals</th>
<th>Percent Reporting</th>
<th>Population Percent</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>57,310</td>
<td>62.2%</td>
<td>13.9%</td>
</tr>
<tr>
<td>2</td>
<td>19,997</td>
<td>21.7%</td>
<td>4.9%</td>
</tr>
<tr>
<td>3</td>
<td>7994</td>
<td>8.7%</td>
<td>1.9%</td>
</tr>
<tr>
<td>4</td>
<td>3467</td>
<td>3.8%</td>
<td>0.8%</td>
</tr>
<tr>
<td>5</td>
<td>1552</td>
<td>1.7%</td>
<td>0.4%</td>
</tr>
<tr>
<td>6</td>
<td>786</td>
<td>0.9%</td>
<td>0.2%</td>
</tr>
<tr>
<td>7</td>
<td>447</td>
<td>0.5%</td>
<td>0.1%</td>
</tr>
<tr>
<td>8</td>
<td>240</td>
<td>0.3%</td>
<td>0.06%</td>
</tr>
<tr>
<td>9</td>
<td>127</td>
<td>0.1%</td>
<td>0.03%</td>
</tr>
<tr>
<td>10+</td>
<td>275</td>
<td>0.3%</td>
<td>0.07%</td>
</tr>
<tr>
<td>Totals</td>
<td>92,195</td>
<td>100%</td>
<td>22.4%</td>
</tr>
</tbody>
</table>
MDAS: Evidence From Challenge Studies

- Patients with recent, convincing reactions to ≥ 1 antibiotic(s)
- Elective challenges with alternate antibiotics

<table>
<thead>
<tr>
<th>Study</th>
<th>Positive Challenges in Patients with History of Allergy to &gt; 1 Antibiotic</th>
<th>Positive Challenges in Patients with History of Allergy to 1 Antibiotic</th>
<th>RR</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Asero R (1998)</td>
<td>7/20 (35%)</td>
<td>16/100 (16%)</td>
<td>2.8</td>
<td>&gt; 0.05</td>
</tr>
<tr>
<td>Nettis E (2001)</td>
<td>5/98 (5.1%)</td>
<td>8/362 (2.2%)</td>
<td>2.4</td>
<td>&gt; 0.1</td>
</tr>
</tbody>
</table>
Case History

- 61 Y/O female:
  - Age 21: anaphylaxis to IM penicillin
  - Age 28: “rash” on PO cephalexin
  - Age 30: “rash” on PO TMP/SMX
  - Age 51: urticaria on PO ciprofloxacin
  - Age 58: pruritic M-P rash, day 2 of PO azithromycin
  - Age 59: cutaneous pruritus, nausea, day 1 of PO doxycycline
MDAS: Evaluation and Management

• Evaluation
  – History
  – Skin testing
  – Challenges

• Management
  – Goal = open ≥2 classes of antibiotics for future use
  – Plan for each antibiotic
    • Avoid
    • Give via graded challenge
    • Give via induction of drug tolerance (desensitization)
• Start with penicillin
• Evaluate other antibiotic classes depending on clinical usefulness
  – Cephalosporins
  – Quinolones
  – Macrolides
• Skin testing with non-irritating concentration of native antibiotics
  – Positive result suggests presence of drug-specific IgE antibodies
  – Negative result does not rule out IgE-mediated allergy
<table>
<thead>
<tr>
<th>Rapid Desensitization</th>
<th>Graded Challenge</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patient probably allergic</td>
<td>Patient probably not allergic</td>
</tr>
<tr>
<td>Modifies immune response</td>
<td>No Δ in immune response</td>
</tr>
<tr>
<td>PO, IV or IM</td>
<td>PO, IV or IM</td>
</tr>
<tr>
<td>Starting dose $\leq 1/10,000$</td>
<td>Starting dose $\geq 1/100$</td>
</tr>
<tr>
<td>10 or more steps</td>
<td>2-5 steps</td>
</tr>
<tr>
<td>15-20 min between doses</td>
<td>$\geq 1$ hour between doses</td>
</tr>
<tr>
<td>IV, continual monitoring</td>
<td>No IV, ‘frequent’ monitoring</td>
</tr>
<tr>
<td>Inpatient or outpatient</td>
<td>Outpatient</td>
</tr>
<tr>
<td>At end, requires continued administration of drug</td>
<td>No need to continue treatment with drug</td>
</tr>
<tr>
<td>Future treatment again via desensitization</td>
<td>No special precautions regarding future treatment</td>
</tr>
<tr>
<td>Step*</td>
<td>Penicillin (mg/ml)</td>
</tr>
<tr>
<td>-------</td>
<td>--------------------</td>
</tr>
<tr>
<td>1</td>
<td>0.5</td>
</tr>
<tr>
<td>2</td>
<td>0.5</td>
</tr>
<tr>
<td>3</td>
<td>0.5</td>
</tr>
<tr>
<td>4</td>
<td>0.5</td>
</tr>
<tr>
<td>5</td>
<td>0.5</td>
</tr>
<tr>
<td>6</td>
<td>0.5</td>
</tr>
<tr>
<td>7</td>
<td>0.5</td>
</tr>
<tr>
<td>8</td>
<td>5</td>
</tr>
<tr>
<td>9</td>
<td>5</td>
</tr>
<tr>
<td>10</td>
<td>5</td>
</tr>
<tr>
<td>11</td>
<td>50</td>
</tr>
<tr>
<td>12</td>
<td>50</td>
</tr>
<tr>
<td>13</td>
<td>50</td>
</tr>
<tr>
<td>14</td>
<td>50</td>
</tr>
</tbody>
</table>

* Time interval between steps = 15 min
### Levofloxacin Oral Graded Challenge

<table>
<thead>
<tr>
<th>Step</th>
<th>Conc (mg/ml)</th>
<th>Amount (ml)</th>
<th>Dose (mg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>5</td>
<td>0.5</td>
<td>2.5</td>
</tr>
<tr>
<td>2</td>
<td>50</td>
<td>0.5</td>
<td>25</td>
</tr>
<tr>
<td>3</td>
<td>N/A</td>
<td>1 tablet</td>
<td>250</td>
</tr>
</tbody>
</table>

- Oral suspension prepared by compounding pharmacist
- Interval between doses = 60 min
- If allergic reaction occurs, D/C procedure and consider desensitization
Antibiotic Allergy History

- **Name** of the antibiotic
- **When** during course did reaction occur
- **Characteristics** of reaction
- **Previous exposure** to same or similar antibiotic
- **Reason** for administration
- **Concurrent medications** at time of reaction
- **Management** required for reaction
- **Time elapsed** since the reaction
- **Subsequent exposure** to same or similar antibiotic
- **Similar symptoms** in absence of antibiotic treatment

## Cephalosporin Non-irritating Skin Test Concentrations in Non-allergic Control Subjects

<table>
<thead>
<tr>
<th>IV Cephalosporin</th>
<th>Full Strength Concentration (mg/ml)</th>
<th>Highest Non-irritating Concentration</th>
<th>Dilution from Full Strength</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cefazolin</td>
<td>330</td>
<td>33 mg/ml</td>
<td>1:10</td>
</tr>
<tr>
<td>Cefuroxime</td>
<td>100</td>
<td>10 mg/ml</td>
<td>1:10</td>
</tr>
<tr>
<td>Cefotaxime</td>
<td>100</td>
<td>10 mg/ml</td>
<td>1:10</td>
</tr>
<tr>
<td>Ceftriaxone</td>
<td>100</td>
<td>10 mg/ml</td>
<td>1:10</td>
</tr>
<tr>
<td>Ceftazidime</td>
<td>100</td>
<td>10 mg/ml</td>
<td>1:10</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>IV Antibiotic</th>
<th>Full Strength Conc (mg/ml)</th>
<th>Highest Non-irritating Conc</th>
<th>Dilution from Full Strength</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tobramycin</td>
<td>40</td>
<td>4 mg/ml</td>
<td>1:10</td>
</tr>
<tr>
<td>Ticarcillin</td>
<td>200</td>
<td>20 mg/ml</td>
<td>1:10</td>
</tr>
<tr>
<td>Clindamycin</td>
<td>150</td>
<td>15 mg/ml</td>
<td>1:10</td>
</tr>
<tr>
<td>Gentamycin</td>
<td>40</td>
<td>4 mg/ml</td>
<td>1:10</td>
</tr>
<tr>
<td>Trimethoprim-sulfa</td>
<td>80 (sulfa)</td>
<td>0.8 mg/ml</td>
<td>1:100</td>
</tr>
<tr>
<td>Levofloxacin</td>
<td>25</td>
<td>0.025 mg/ml</td>
<td>1:1,000</td>
</tr>
<tr>
<td>Erythromycin</td>
<td>50</td>
<td>0.05 mg/ml</td>
<td>1:1,000</td>
</tr>
<tr>
<td>Nafcillin</td>
<td>250</td>
<td>0.025 mg/ml</td>
<td>1:10,000</td>
</tr>
<tr>
<td>Vancomycin</td>
<td>50</td>
<td>0.005 mg/ml</td>
<td>1:10,000</td>
</tr>
<tr>
<td>Azithromycin</td>
<td>100</td>
<td>0.01 mg/ml</td>
<td>1:10,000</td>
</tr>
</tbody>
</table>

Macrolides (I)

- 73 consecutive pediatric patients referred for suspected clarithromycin allergy (Florence, Italy)
  - Urticaria (62%), angioedema (18%), M-P rash (19%)
  - Immediate (27%), delayed (67%), undetermined (6%)
- All patients underwent skin testing with IV clarithromycin
- 64/73 patients underwent clarithromycin challenges, irrespective of skin test results (9 refused)
  - 5 days (7.5 mg/kg bid)
  - Initial dose single blinded
  - Initial dose given via 4 step graded challenge (1/100, 1/10, 2/10, 7/10)

Macrolides (I)

4 reactions:
- 2 immediate (urticaria, urticaria/AE)
- 2 delayed (M-P rashes on days 3 & 4)

### Macrolides (I)

<table>
<thead>
<tr>
<th></th>
<th>Challenge Positive</th>
<th>Challenge Negative</th>
</tr>
</thead>
<tbody>
<tr>
<td>Skin Test Positive</td>
<td>3</td>
<td>6</td>
</tr>
<tr>
<td>Skin Test Negative</td>
<td>1</td>
<td>54</td>
</tr>
</tbody>
</table>

- Sensitivity = 75%
- Specificity = 90%
- PPV = 33%
- NPV = 98%

Macrolides (II)

- 107 patients (24/83 M/F) referred to academic allergy clinic for suspected macrolide allergy (Montpellier, France)
- Skin testing with macrolide in 33/107 patients (up to 10mg/cc ID)
- All patients underwent challenges:
  - Same macrolide associated with historical reaction
  - Single blinded (? placebo)
  - Dosing: Starting with 1 mg, 6 total doses up to full dose
  - Doses given Q 30 min

| Positive macrolide skin test | 4/8 | 7/25 |

**Table 1. Clinical characteristics of the macrolide hypersensitive (DPT+) and macrolide non-hypersensitive (DPT-) subjects**

<table>
<thead>
<tr>
<th></th>
<th>DPT +</th>
<th>DPT -</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Number</strong></td>
<td>8 (7.5%)</td>
<td>99 (92.5%)</td>
<td>107 (100%)</td>
</tr>
<tr>
<td><strong>Sex (M/F)</strong></td>
<td>2/6</td>
<td>22/77</td>
<td>24/83</td>
</tr>
<tr>
<td><strong>Time elapsed since the reaction</strong> (months)</td>
<td>84 [33–126]</td>
<td>36 [6–81]</td>
<td>36 [6–93]</td>
</tr>
<tr>
<td><strong>Chronology of the reaction</strong>&lt;sup&gt;↑&lt;/sup&gt;</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≤ 1 h</td>
<td>1 (12.5%)</td>
<td>11 (11.1%)</td>
<td>12 (11.2%)</td>
</tr>
<tr>
<td>1 &lt; ≤ 24 h</td>
<td>5 (62.5%)</td>
<td>22 (22.2%)</td>
<td>27 (25.2%)</td>
</tr>
<tr>
<td>&gt; 24 h</td>
<td>2 (25%)</td>
<td>42 (42.4%)</td>
<td>44 (41.1%)</td>
</tr>
<tr>
<td>Unknown</td>
<td>0 (0%)</td>
<td>24 (24.3%)</td>
<td>24 (22.5%)</td>
</tr>
<tr>
<td><strong>Clinical symptoms</strong> (≤ 24 h)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Anaphylactic shock</td>
<td>0</td>
<td>1</td>
<td>1 (0.9%)</td>
</tr>
<tr>
<td>Anaphylaxis&lt;sup&gt;‡&lt;/sup&gt;</td>
<td>0</td>
<td>4</td>
<td>4 (3.7%)</td>
</tr>
<tr>
<td>Urticaria (only)</td>
<td>3</td>
<td>38</td>
<td>41 (38.3%)</td>
</tr>
<tr>
<td>Angioedema/urticaria</td>
<td>3</td>
<td>6</td>
<td>9 (8.4%)</td>
</tr>
<tr>
<td>Angioedema (only)</td>
<td>0</td>
<td>7</td>
<td>7 (6.5%)</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td>6/8 (75%)</td>
<td>56/99 (56.5%)</td>
<td>62/107 (57.9%)</td>
</tr>
<tr>
<td><strong>Clinical symptoms</strong> (&gt; 24 h or unknown)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MPE&lt;sup&gt;§&lt;/sup&gt;</td>
<td>1</td>
<td>25</td>
<td>26 (24.3%)</td>
</tr>
<tr>
<td>Other skin eruptions&lt;sup&gt;¶&lt;/sup&gt;</td>
<td>0</td>
<td>8</td>
<td>8 (7.5%)</td>
</tr>
<tr>
<td>Others&lt;sup&gt;**&lt;/sup&gt;</td>
<td>1</td>
<td>2</td>
<td>3 (2.8%)</td>
</tr>
<tr>
<td>Unknown</td>
<td>0</td>
<td>8</td>
<td>8 (7.5%)</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td>2/8 (25%)</td>
<td>43/99 (43.5%)</td>
<td>45/107 (42.1%)</td>
</tr>
<tr>
<td><strong>Atopy</strong>&lt;sup&gt;††&lt;/sup&gt;</td>
<td>5 (62.5%)</td>
<td>35 (35.4%)</td>
<td>40 (37.4%)</td>
</tr>
</tbody>
</table>

**PPV = 36%**
**NPV = 82%**
**Sens = 50%**
**Spec = 72%**
Macrolides (III)

- 125 consecutive patients (33/92 M/F) referred to allergy clinic for suspected macrolide allergy (Germany)
  - 53 Immediate reactors (≤ 1 hour)
  - 72 Delayed reactors (> 1 hour to 12 days)
- Prick and ID skin testing (0.01 mg/ml) – immediate reactors
- Patch testing – delayed reactors
- 113/125 patients underwent macrolide challenges
  - Same macrolide associated with historical reaction
  - 3-4 step graded challenge starting with 10-20% of the full dose

Quinolones

- 101 patients (20/81 M/F) referred for history of allergic reactions to quinolones (Germany)
  - 64 immediate reactors
  - 37 delayed reactors
- Prick skin testing (no ID testing) in immediate reactors (2-5 mg/ml)
- Patch testing in delayed reactors
- Irritant potential of skin test not evaluated in negative controls
- Most patients underwent graded oral challenges

37 patients with suspected delayed hypersensitivity

Skin test

- neg.
- pos.

37 patients

2× contraindicated
7× FDE

28× challenge test

- 2× pos.
- 26× neg.

Two patients with hypersensitivity

26 patients without hypersensitivity

Quinolone Allergy – Natural History of IgE-mediated Reactions

• 55 patients with history of immediate reactions to quinolones (1-48 months before evaluation)
• 30/55 patients (54.5%) positive serum IgE (RIA) to culprit quinolone
• Among 30 IgE-positive patients
  – Recent rx’s (< 8 months): average % bound radioactivity = 14.4%
  – Distant rx’s (> 8 months): average % bound radioactivity = 8.1%
• Average time lapse between reaction and evaluation
  – 9.7 months (IgE-positive group)
  – 15.6 months (IgE-negative group)

Quinolone Allergy – Cross-reactivity for IgE-mediated Reactions

- 24/30 patients (80%) showed positive serum IgE (RIA) to culprit quinolone and ≥1 other quinolone\(^1\)
- 21/28 patients (71%) showed positive serum IgE (RIA) or positive BAT to culprit quinolone and ≥1 other quinolone\(^2\)
- Most smaller case series confirm high degree of allergic cross-reactivity among quinolones – via *in vitro* testing or challenges\(^3-6\)

Case History

• 61 Y/O female:
  – Age 21: anaphylaxis to IM penicillin
  – Age 28: “rash” on PO cephalexin
  – Age 30: “rash” on PO TMP/SMX
  – Age 51: urticaria on PO ciprofloxacin
  – Age 58: pruritic M-P rash, day 2 of PO azithromycin
  – Age 59: cutaneous pruritus, nausea, day 1 of PO doxycycline
Case History (cont)

1) Penicillin skin test negative → oral challenge negative
2) Cefazolin skin test negative → cephalaxin oral graded challenge negative
3) Levofloxacin skin test negative → oral graded challenge negative
4) Azithromycin skin test negative → oral graded challenge ? positive (pruritus) → single-blinded challenge negative
5) Defer evaluation of sulfonamide and doxycycline allergies
Summary

• If allergists don’t help patients with MDAS, who will?

• Focus evaluation on the most clinically useful antibiotics
  – Penicillins, cephalosporins, quinolones, macrolides

• Most patients are candidates for graded challenge and do not need desensitization

• ~ 90% of patients presenting with history of allergy to quinolones and macrolides are able to tolerate them