Multiple Drug Intolerance Syndrome

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Multiple Drug Intolerance Syndrome

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- Ngoc Ho, PhD
- My other co-authors in the Department of Research and Evaluation
- The San Diego Allergy Department patients, physicians, nurses, and support staff.
Multiple Drug Intolerance Syndrome

- Definition of Multiple Drug Intolerance Syndrome (MDIS)
- Review of recent literature
- New data from Southern California
- How to approach the patient with multiple drug intolerances.

Multiple Drug Intolerance Syndrome

- No uniform definition
- Sullivan (1989)- 437 patients with a history of penicillin allergy
  - 21% had a reaction to a subsequent non-beta-lactam antibiotic
  - 349 inpatients,
    - 17% history of any drug allergy
    - 1% had a history of 2 or more
Multiple Drug Intolerance Syndrome

Nettis (2001) – Reactions to 2 or more classes of antibiotics.
- 362 patients with one antibiotic allergy, 98 with 2 or more
- Risk Factors for MDAS
  - Females
  - NSAID intolerance
- Positive challenges to alternative antibiotics about 3% of the time
- Risk factors for positive challenges
  - Males
  - NSAID intolerance

Multiple Drug Intolerance Syndrome

Asero (2003) – “Allergy” to “several” unrelated anti-bacterial drugs.
- 38 patients with acute urticaria associated with drug use
  - 18 with multiple drug “allergy” syndrome (MDAS)
  - 20 mono-sensitive
  - 20 normal controls
- Autologous serum skin testing
  - 17/18 versus 8/20 versus 0/20 positive
Multiple Drug Intolerance Syndrome

- Gex-Collet (2005) - Any “immune” response against 2 or more different drugs.
  - 7 patients
  - Patch test or lymphocyte transformation test positive to 2 or more chemically unrelated drugs
  - Two sub-types seen
    - Simultaneous sensitization
    - Sequential sensitization

Multiple Drug Intolerance Syndrome

- Schiavino (2007) – Adverse reactions to at least 3 chemically unrelated drugs.
  - 480 patients
  - Negative allergy tests
  - Grouped challenge pretreatment by index reaction severity
  - Challenges with no premedication, cromolyn, or oral H1-antihistamine pretreatment
  - Challenges with medications they had not reacted to
  - Positive challenges in 15.7% versus 11.2% versus 10.8%
  - If positive 56 repeated with another premedication and 44 (79%) became negative

* Very poor quality paper
Multiple Drug Intolerance Syndrome

- Park (2007) – “Allergy” to 2 drugs or more in addition to penicillin.
  - 35% of patients with a history of penicillin allergy had MDAS
  - 10% of patients pending surgery had a history of penicillin allergy
  - Females 2.6 times more likely than males to have MDAS
  - No correlation to being penicillin skin test positive

- Asero (2007) – Reaction to at least 2 drugs or one drug and a positive challenge test to another drug
  - 9 subjects, 74 healthy controls, 13 chronic urticaria controls without MDAS
  - All 9 subjects had positive autologous plasma skin tests
  - Increased histamine releasing activity in plasma
  - Lower plasma D-dimer levels than chronic urticaria patients
Multiple Drug Intolerance Syndrome

- De Pasquale (2012) – Adverse reactions to 3 drugs with negative allergy testing.
  - 30 women with MDIS compared 30 healthy control women at one Italian medical center
    - Higher anxiety (p < 0.01)
    - Higher grade of depression (p < 0.01)
    - Higher grade of alexithymia (p < 0.01)
    - Worse quality of life (p < 0.01)

- Using 3 or more drug class intolerances as the definition for MDIS
  - Positive associations noted with
    - Females
    - Multiple drug use
    - Psychiatric morbidity
    - Lower quality of life
    - Positive challenge tests more common in males

- Negative associations noted with
  - Learning Disability
Multiple Drug Intolerance Syndrome

- IgE-mediated Drug Allergy
  - Antigen-specific IgE-mediated with mast cell degranulation
  - Predicted by skin testing
  - Theoretically predicated by *in vitro* measurement of antigen-specific IgE
  - Gold standard is an acute challenge reaction
  - Requires intact protein antigens (MW>5000), materials that will haptenate proteins, or bifunctional small molecules that can cross link IgE
  - Requires sensitization

Multiple Drug Intolerance Syndrome

- Other Immunologically mediated reactions
  - IgG
    - Complement
    - Cell mediated cytotoxicity
    - Predicted by challenge reactions (<1 day)
  - T Cell
    - Predicted by patch testing
    - Predicted by challenge reactions (2-5 days)
Multiple Drug Intolerance Syndrome

- Non-immunologic adverse drug reactions
  - HIV
    - Slow acetylator phenotype for N-acetyltransferase 2
  - Glutathione deficiency
  - G-6-PDH deficiency
  - X linked recessive
  - Hemolytic anemia with infections or certain drug classes
    - Antimalarial drugs
    - Aspirin
    - Nitrofurantoin
    - Nonsteroidal anti-inflammatory drugs (NSAIDs)
    - Quinidine
    - Quinine
    - Sulfa drugs
  - Chronic urticaria

Multiple Drug Intolerance Syndrome

Antibiotic "Allergy" Incidence per Therapeutic Course Used

<table>
<thead>
<tr>
<th>Antibiotic</th>
<th>Males (95% CI)</th>
<th>Females (95% CI)</th>
<th>p values</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sulfa class</td>
<td>2.23%(a) (1.91, 2.59)</td>
<td>3.42%(a) (3.13, 3.74)</td>
<td>&lt; 0.0001</td>
</tr>
<tr>
<td>Penicillins</td>
<td>1.11%(b) (1.01, 1.24)</td>
<td>1.45%(b) (1.34, 1.57)</td>
<td>&lt; 0.0001</td>
</tr>
<tr>
<td>Tetracyclines</td>
<td>0.47%(d) (0.36, 0.62)</td>
<td>1.27%(d) (1.11, 1.46)</td>
<td>&lt; 0.0001</td>
</tr>
<tr>
<td>Cephalosporins</td>
<td>0.60%(d) (0.49, 0.72)</td>
<td>1.08%(d) (0.96, 1.21)</td>
<td>&lt; 0.0001</td>
</tr>
<tr>
<td>Macrolides</td>
<td>0.52%(d) (0.38, 0.72)</td>
<td>1.34%(c) (1.13, 1.58)</td>
<td>&lt; 0.0001</td>
</tr>
<tr>
<td>Quinolones</td>
<td>0.52%(d) (0.42, 0.65)</td>
<td>1.01%(d) (0.85, 1.14)</td>
<td>&lt; 0.0001</td>
</tr>
</tbody>
</table>
Multiple Drug Intolerance Syndrome

- How big is the problem?

Data from 2,375,424 KPSC healthplan members who had at least one visit during 2009

- If 3 or more drug class "allergies" is the cut off, 2.1% have MDIS

<table>
<thead>
<tr>
<th>Number Of &quot;Allergies&quot; Reported</th>
<th>Total Reporting</th>
<th>Percent Reporting</th>
<th>Population Percent</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>318,873</td>
<td>66.6%</td>
<td>13.4%</td>
</tr>
<tr>
<td>2</td>
<td>109,875</td>
<td>23.0%</td>
<td>4.6%</td>
</tr>
<tr>
<td>3+</td>
<td>49,582</td>
<td>10.4%</td>
<td>2.1%</td>
</tr>
<tr>
<td>Total</td>
<td>478,330</td>
<td>100%</td>
<td>20.1%</td>
</tr>
</tbody>
</table>
Multiple Drug Intolerance Syndrome

- Data from 2,375,424 KPSC healthplan members who had at least one visit during 2009

- Antibiotics are still the most common medication class with reported "allergies"

- Females report more drug "allergy" than males

<table>
<thead>
<tr>
<th>Medication class</th>
<th>Females</th>
<th>Males</th>
</tr>
</thead>
<tbody>
<tr>
<td>Penicillin</td>
<td>122,622</td>
<td>64,008</td>
</tr>
<tr>
<td>Sulfonamide</td>
<td>80,689</td>
<td>21,263</td>
</tr>
<tr>
<td>Macrolide</td>
<td>22,494</td>
<td>5,781</td>
</tr>
<tr>
<td>Cephalosporin</td>
<td>18,757</td>
<td>7,199</td>
</tr>
<tr>
<td>At least one antibiotic</td>
<td>216,192</td>
<td>94,576</td>
</tr>
<tr>
<td>Narcotic</td>
<td>69,996</td>
<td>17,279</td>
</tr>
<tr>
<td>NSAID</td>
<td>34,459</td>
<td>14,441</td>
</tr>
<tr>
<td>ACE inhibitor</td>
<td>19,918</td>
<td>10,669</td>
</tr>
<tr>
<td>At least one non-antibiotic</td>
<td>172,551</td>
<td>73,311</td>
</tr>
<tr>
<td>Any drug &quot;allergy&quot;</td>
<td>325,381</td>
<td>152,902</td>
</tr>
</tbody>
</table>

Multiple Drug Intolerance Syndrome

<table>
<thead>
<tr>
<th></th>
<th>Severe MDIS n = 537 (0.023%)</th>
<th>Moderate MDIS n = 49,045 (2.1%)</th>
<th>Any drug &quot;allergy&quot; n = 478,283 (20.1%)</th>
<th>No drug &quot;allergy&quot; n = 1,897,141 (79.9%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Females (%)</td>
<td>509 (94.8%)</td>
<td>41,603 (84.8%)</td>
<td>325,381 (68.0%)</td>
<td>971,422 (51.2%)</td>
</tr>
<tr>
<td>Age</td>
<td>68.3 ± 13.6</td>
<td>62.3 ± 16.1</td>
<td>52.0 ± 20.6</td>
<td>35.7 ± 22.1</td>
</tr>
<tr>
<td>BMI</td>
<td>29.7 ± 7.5</td>
<td>29.3 ± 7.1</td>
<td>28.3 ± 7.1</td>
<td>26.3 ± 7.2</td>
</tr>
<tr>
<td>Died during 2010</td>
<td>19 (3.5%)</td>
<td>952 (2.3%)</td>
<td>5,103 (1.1%)</td>
<td>6,583 (0.3%)</td>
</tr>
<tr>
<td>Total prescriptions</td>
<td>40.0 ± 27.3</td>
<td>26.3 ± 21.1</td>
<td>16.5 ± 17.3</td>
<td>7.5 ± 10.9</td>
</tr>
<tr>
<td>New antibiotic &quot;allergies&quot;</td>
<td>0.10 ± 0.36</td>
<td>0.06 ± 0.26</td>
<td>0.03 ± 0.18</td>
<td>0.01 ± 0.11</td>
</tr>
<tr>
<td>New non-antibiotic &quot;allergies&quot;</td>
<td>0.52 ± 0.99</td>
<td>0.24 ± 0.58</td>
<td>0.11 ± 0.38</td>
<td>0.02 ± 0.16</td>
</tr>
<tr>
<td>Outpatient visits</td>
<td>26.6 ± 19.5</td>
<td>15.4 ± 14.9</td>
<td>10.2 ± 11.6</td>
<td>6.1 ± 7.7</td>
</tr>
<tr>
<td>ED visits</td>
<td>1.5 ± 2.8</td>
<td>0.7 ± 1.7</td>
<td>0.4 ± 1.1</td>
<td>0.3 ± 0.7</td>
</tr>
<tr>
<td>Hospital days</td>
<td>12.4 ± 46.1</td>
<td>6.3 ± 39.2</td>
<td>3.3 ± 28.2</td>
<td>1.1 ± 14.9</td>
</tr>
</tbody>
</table>
Multiple Drug Intolerance Syndrome

- MDIS is in part iatrogenic.
- MDIS is associated with overweight elderly females who have high rates of healthcare and medication usage, but are “healthier” than age matched controls.
- Urticarial syndromes only explain a small fraction of MDIS cases.
- MDIS is associated with anxiety, depression, an inability to express feelings, and a lower quality of life.
- MDIS is not associated with IgE-mediated allergy or life-threatening illness.
- MDIS can be managed by medication avoidance and judicious re-challenge.

Multiple Drug Intolerance Syndrome

- What can an Allergist do?
Multiple Drug Intolerance Syndrome

- Collect the following data for each medication associated with an adverse reaction
  - Indication
  - Prior exposures without reaction
  - Prior exposures with reaction
  - Date of last exposure
  - Route of administration and dose
  - Type of adverse reaction
  - Duration of reaction
  - Treatment for reaction
  - Permanent sequelae
  - Diagnostic tests obtained (LFTs, CBC, ESR, biopsy)

Multiple Drug Intolerance Syndrome

- Document other potential risk factors
  - AIDS
  - Autoimmunity
  - CHF
  - Chronic urticaria
  - Cystic fibrosis
  - Depression
  - Dermographism
  - G-6-P deficiency
  - GERD
  - Immune deficiency
  - Liver disease
  - Myasthenia gravis
  - Aspirin associated respiratory disease
  - Renal dysfunction
  - Serious mental illness
Multiple Drug Intolerance Syndrome

Other factors to consider
- Inappropriate medication use
  - multiple courses of antibiotics for presumed sinusitis when the patient actually has migraine as the cause of recurrent facial pain.
- Group and ungroup where appropriate.
  - NSAIDs
  - Opiates
  - Cephalosporins
  - Macrolides

Who can you skin test or re-challenge?
- Any potential IgE mediated reaction
  - anaphylaxis
  - respiratory problems
  - hives
  - local swelling at the site of injection
- Other macular papular rashes
- Gastrointestinal symptoms
- Unknown index symptoms
- Mild symptoms not specifically excluded on the next slide.
Multiple Drug Intolerance Syndrome

Who should not be skin tested or re-challenged?

- Stevens-Johnson Syndrome
- Toxic epidermal necrolysis
- Hemolytic anemia
- Nephritis
- Hepatitis
- Oral and/or skin blisters associated with or attributed to previous drug use
- Drug reaction with eosinophilia and systemic symptoms (DRESS)
- Tendon rupture
- Myalgias – particularly associated with statins
- ACE inhibitor associated angioedema

How to deal with “allergy” to one member of various common antibiotic classes

- Penicillins
  - Avoid all penicillins
  - Skin test with native penicillin and Pre-Pen® and oral amoxicillin challenge
- Sulfonamides
  - Consider 5 day oral co-trimoxazole re-challenge
  - Non-antibiotic sulfonamides are not an issue
- Cephalosporins
  - No increased risk with history of penicillin “allergy”, even if penicillin skin test positive
  - Skin testing is not helpful
  - Avoid the specific cephalosporin associated with the reaction
  - OK to use other cephalosporins
  - Try to avoid exactly the same side chains
Multiple Drug Intolerance Syndrome

- How to deal with “allergy” to one member of various antibiotic classes
  - Quinolones
    - Avoid the entire family
    - Skin testing is not helpful
    - In rare cases consider an oral rechallenge
  - Tetracycline
    - OK to rechallenge
    - Expect photo dermatitis, esophagitis, GI upset
  - Macrolides
    - OK to rechallenge
    - No IgE produced against macrolides
    - OK to use other macrolides

Elements of an effective multiple drug allergy treatment plan

- These drugs are OK to use if clinically indicated
- These drugs should be avoided
- These drugs may be used if a challenge is tolerated
Multiple Drug Intolerance Syndrome

- **Elements of an effective treatment plan**
  - These drugs can be used with pretreatment
    - Provide pretreatment plan.
  - These drugs can be used if a challenge is tolerated
    - Provide a challenge plan.
    - Challenges are generally initiated or done in the Allergy Department

- **Challenges**
  - Oral challenges are always preferred over parenteral challenges when ever possible
  - Structure the challenge to fit the expected reaction
    - Possible direct mast cell activation or IgE-mediated: 1-2 hours of observation
    - Possible T-cell mediated: 2-5 days of observation
  - An adequate final dose is typically a full therapeutic dose
Multiple Drug Intolerance Syndrome

- Re-challenge dosing with a history of an acute reaction
  - 1/10 of a therapeutic dose and then a full dose ½ hour later is usually adequate
  - Observe for at least 1 hour after the last dose
  - Be ready to treat anaphylaxis
  - Typically no more risky than a food challenge

- Standard delayed reaction rechallenge method for Co-trimoxazole
  - Materials
    - Trimethoprim-sulfamethoxazole pediatric suspension
      - Dispense 30 mls, 20 mls needed
    - Bactrim SS tablet
      - Dispense 1
  - Self administered at home
    - 12 total doses given over a 6 day period.
    - Cross off dose after taking it.
    - Call the Allergy Department to report any adverse reactions
    - OK to take OTC Benadryl 25 to 50 mg every 6 hours if any itching.
Multiple Drug Intolerance Syndrome

Outpatient sulfonamide antibiotic 6 day oral challenge method

<table>
<thead>
<tr>
<th>Day</th>
<th>Amount</th>
<th>AM dose</th>
<th>Noon dose</th>
<th>PM dose</th>
<th>Total TMP (mg)</th>
<th>Total SMZ (mg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>1.25 ml</td>
<td>X</td>
<td></td>
<td></td>
<td>10</td>
<td>50</td>
</tr>
<tr>
<td>2</td>
<td>1.25 ml</td>
<td>X</td>
<td>X</td>
<td></td>
<td>20</td>
<td>100</td>
</tr>
<tr>
<td>3</td>
<td>1.25 ml</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>30</td>
<td>150</td>
</tr>
<tr>
<td>4</td>
<td>2.5 ml</td>
<td>X</td>
<td></td>
<td>X</td>
<td>40</td>
<td>200</td>
</tr>
<tr>
<td>5</td>
<td>2.5 ml</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>60</td>
<td>300</td>
</tr>
<tr>
<td>6</td>
<td>1 SS tab</td>
<td>X</td>
<td></td>
<td></td>
<td>80</td>
<td>400</td>
</tr>
</tbody>
</table>

Selected References

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