Update: Drug Allergy

CAOM Winter Conference
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Outline

• History
• Introduction
• Epidemiology
• Burden of Drug Allergy
• Diagnosis
• Prognosis
• Management
• Summary

Penicillin V (1)
History...

- **Alexander Fleming** discovered **penicillin**:
  - “When I woke up just after dawn on September 28, **1928**, I certainly didn't plan to revolutionize all medicine by discovering the world's first antibiotic... But I suppose that was exactly what I did.”

- Saved millions of lives since it came into use during WWII

- **Allergic reactions** to penicillin were described soon after its debut; today it remains the most commonly self-reported medication allergy, with a prevalence of ~**10%**
Introduction to Adverse Drug Reactions

- **Adverse drug reactions:**
  - Type A (85-90%): Predictable, from known drug properties (i.e. side effects)
  - Type B (10-15%): Unpredictable or unexpected (i.e. DRUG ALLERGY)

- Most common drug groups causing hypersensitivity are β-lactam antibiotics and NSAIDs
Epidemiology

Most Common

• Cutaneous reactions – maculopapular eruptions and urticaria
• Acute angioedema, anaphylaxis, dyspnea, rhinitis

Most severe

• Toxic epidermal necrolysis (TEN), Stevens-Johnson Syndrome (SJS), immune hepatitis, drug-induced hypersensitivity syndrome (DiHS) one of which is drug reaction with eosinophilia and systemic symptoms (DRESS)
Burden of Drug Hypersensitivity

- A study of hospital practice showed that penicillin-allergic patients had higher medical costs related to the use of alternative antibiotics
  - Alternative treatment is more expensive & more toxic than 1st-line
- Fleming’s 1945 Nobel Peace Prize lecture cautioned against antibiotic resistance
  - Drug allergy contributes to resistance by use of broad spectrum antibiotics when penicillin alone could be used
Prognosis

• Hypersensitivity decreases with time.
  – IgE antibodies present in 90% of patients 1 year after allergic reaction, but only in 20-30% after 10 years

• Patients who have anaphylactic reactions are \textbf{more likely} to retain antibodies to the drug longer.
Diagnosis of Drug Allergy

• **History is paramount**
  – Consider TIMING, Immunogenicity of drugs
    • Immediate reactions (within 1 hour) usually indicate IgE-mediated
    • Delayed reactions usually indicate T-cell mediated

• **Skin Testing**
• **In Vitro Testing**
• **Provocative Drug Testing (drug challenge)**
Diagnosis: Skin Testing

• **Skin prick & Intradermal**
  – Skin prick first
  – ID if skin prick negative

• **ONLY validated for penicillin**
  – Safe & effective for children/adults with history of penicillin allergy
  – Often extrapolated for other drugs

• **90% of patients “penicillin allergic” are not.**
  – Could safely receive β-lactam antibiotics
## Predictive Value of Penicillin Skin Testing

<table>
<thead>
<tr>
<th>Prior Reaction</th>
<th>PCN Skin Tests</th>
<th>IgE–Dependent Reaction (%)</th>
<th>Any Immunologic Rxn (%)</th>
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<tbody>
<tr>
<td>Any</td>
<td>Pos</td>
<td>50-80*</td>
<td>—</td>
</tr>
<tr>
<td>All histories</td>
<td>Neg</td>
<td>2.6†</td>
<td>5.4</td>
</tr>
<tr>
<td>Anaphylaxis</td>
<td></td>
<td>3.6</td>
<td>7.1</td>
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<tr>
<td>Urticaria</td>
<td></td>
<td>4.7</td>
<td>7.1</td>
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<tr>
<td>Exanthem</td>
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<td>2.0</td>
<td>6.8</td>
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<tr>
<td>Other/unknown</td>
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<tr>
<td>None</td>
<td>Pos</td>
<td>&lt;50‡</td>
<td>—</td>
</tr>
<tr>
<td></td>
<td>Neg</td>
<td>0.4†</td>
<td>1.0</td>
</tr>
</tbody>
</table>
Diagnosis: Provocative Drug Testing, i.e. Drug Challenge

- Provides definitive diagnosis
- Few subjects with + history have positive challenge
- Consider risk-benefit ratio (still risky)
- Graded challenge, completed within 1 day
  - Starting dose between 1:10,000 & 1:10 of therapeutic dose
  - Sequential doses q30-60 minutes
  - 4-5 incremental doses to reach max.

- Re-challenge is contraindicated for history of severe reactions (SJS, DRESS, TEN, DiHS, AGEP)
Management of Drug Allergy

- Supportive treatment for acute reactions
  - O2, epinephrine, H1 & H2 antihistamines, steroids
- Stop offending agent
- Alternatives for Drug-Allergic patients
  - Unrelated med
  - Potentially Cross-reactive med
  - Re-administer Offending drug
    - (desensitization)
Risks

• Risks of second line therapy
  – Treatment failure with antibiotics
  – Toxicity of alternative medication
  – Cost of alternative medication
Drug Desensitization

• Graduated exposure of the allergen can create a temporary state of tolerance to the agent → this is desensitization
  – Incremental doses given, side effects controlled with steroids, epi and H blockers in a controlled setting
  – Patients who undergo desensitization tend to tolerate the offending drug without major adverse events
  – Desensitization is an underutilized process
Drug Desensitization Protocol

• Obtain skin test to determine degree of sensitivity
• Establish baseline monitoring in medical setting with IV
• Prepare drug in 10 fold dilutions from full therapeutic dose (1/10, 1/100, 1/1000)
• If skin test negative, begin with 0.1 mL of 1/100 dilution (1/1000 in severe reactions)
• If skin test positive, begin 100-fold below dose that produces midpoint reaction (5-8 mm wheal)
• Dosing interval every 20 min
• Repeat dose for mild to moderate systemic reactions; drop back 2 doses for reactions producing HD change
• Dose escalation by 2-fold increments until target dose achieved
• Proceed with standard therapy – avoid lapses in therapeutic doses
• Repeat above for every new administration of offending agent
Summary

• Drug Allergy to Penicillin is common

• Drug allergy is a burden to the healthcare system
  • High cost, morbidity & mortality
  • Toxic effects of alternative meds, antibiotic resistance, treatment failure

• 90% of patients are not truly allergic and could safely receive β-lactam antibiotics

• Penicillin skin testing is safe and effective for children & adults with a history of penicillin allergy

• Provocative Drug Challenge can be done safely the same day

• Even if patient is allergic, drug desensitization is always possible
Thank you!