Drug Reaction or Allergy? Diagnosis and Treatment Strategies for Use in Any Medical Practice

Presented by
Susan Andrew, MD
Mainland Allergy Clinic
Dickinson, TX

Objectives:

1) Give overview of general themes of drug reactions and drug allergies
2) Dispel some common myths regarding drug allergy
3) Review reactions to commonly used medications
4) Go over drug reaction “worst case scenarios”
5) Review Penicillin allergy and testing; discuss testing to other drugs
6) Discuss strategies for determining which drug is causing a reaction

Overview

- Clarifying Some Common Myths Regarding Drug Allergy
- General Themes of Drug Allergy
- Scope of Adverse Drug Reactions (ADR)
- Classification of Adverse Drug Reactions
  - Predictable adverse effects (i.e. side effects)
  - Gell-Coombs classifiable reactions
  - Miscellaneous immunologic drug allergy syndromes
- Drug Rash

Click to Edit Title
Overview

- Pseudoallergic/Anaphylactoid Reactions
- Risk Factors for Drug Allergy
- Reactions to Commonly Used Medications
  - Aspirin and other NSAIDs
  - ACE-inhibitors
  - Penicillin including penicillin testing
- Drug Challenge vs Desensitization (Induction of Rapid Tolerance)
- Evaluation of patient with suspected drug reaction

Dispelling Myths Regarding Drug Allergy

- Seafood allergic patients are NOT at increased risk for reactions to radiocontrast media*
- There is no cross-reactivity between sulfonamide antibiotics and non-antibiotic sulfonamides
  - A patient allergic to trimethoprim-sulfamethaxazole does not have an increased risk of being allergic to furosemide, sulfonylureas, celecoxib**
- Drug desensitization does not create permanent tolerance
- A skin testing protocol is available for penicillin; protocols DO NOT exist for most drugs
  - Many antibiotics besides penicillin have established, non-irritating concentrations
  - Other drugs have no standardized non-irritating concentrations
*Drug Allergy: An Updated Practice Parameter. AAAAI, ACAAI, JCAAI. Annals of Allergy, Asthma, and Immunology. 2010 pp 259-273

General Themes of Drug Allergy

- A drug allergy is an unintended, immunologically mediated response to a pharmaceutical agent in a sensitized person
- Underlying mechanisms of drug allergy are poorly understood for many drugs
- Allergic reactions may occur at any point during treatment course
- Patient history, physical and chart review are vital to classifying drug reactions
  - A single drug may cause many types of reactions
  - Distinguishing the type of reaction will tailor work-up & treatment
Scope of Adverse Drug Reactions (ADR)

- ADR are a major health concern in the USA
- ADR occur in 15.1% of all inpatients according to one meta-analysis
- Over a 4 week period, ADR occurred in 25% of outpatients in one study


Scope of Adverse Drug Reactions

- 80% are predictable
  - Known side effects (i.e. renal or hepatic toxicity)
  - Usually dose dependent
- 20% can be classified as “drug allergy”
  - Unpredictable
  - Dose independent
  - Various mechanisms
**Gell-Coombs Classification of Hypersensitivity Drug Reactions**

<table>
<thead>
<tr>
<th>Type</th>
<th>Symptom Onset</th>
<th>Classic Symptoms</th>
<th>Mechanism</th>
<th>Examples</th>
<th>Rapid Desensitization Candidate?</th>
</tr>
</thead>
<tbody>
<tr>
<td>Type I</td>
<td>Few minutes-2hrs</td>
<td>Anaphylaxis, urticaria, rash</td>
<td>IgE-mediated mast cell activation</td>
<td>Beta-lactam antibiotics, anesthetics</td>
<td>Yes</td>
</tr>
<tr>
<td>Type II</td>
<td>7-21 days</td>
<td>Cytopenias</td>
<td>Non-IgE-antibody mediated</td>
<td>PCN, quinine, sulfa abx</td>
<td>No</td>
</tr>
<tr>
<td>Type III</td>
<td>5-21 days</td>
<td>Serum sickness</td>
<td>Immune complex deposition</td>
<td>PCN, infliximab</td>
<td>No</td>
</tr>
<tr>
<td>Type IV</td>
<td>Variable</td>
<td>Maculopapular rash</td>
<td>T-cell-mediated</td>
<td>Various antibiotics</td>
<td>No</td>
</tr>
</tbody>
</table>

**Drug Rash**

- Not all rashes are drug rashes
- Drug rash can be from various underlying mechanisms
- Most drug rashes are Type I and Type IV hypersensitivity reactions
  - Type I: classically occurs within 30 min-1 hr of an exposure in a previously exposed patient
  - May portend a more serious reaction in future
  - Type IV: typically **maculopapular rash** several days after starting medication
    - Not a contraindication to repeat usage

**Pseudoallergic/Anaphylactoid Reactions**

- Immediate systemic reactions that mimic anaphylaxis but are caused by **non-IgE-mediated** release of mediators from mast cells and basophils
- May occur without sensitization/prior exposure
- Common culprits: radiocontrast media, colloid expanders, opiates, vancomycin (“red man” syndrome)
- Premedication protocols exist for their administration
Pre-contrast Medium Study Prophylaxis

- Ensure proper hydration
- Use nonionic, iso-osmolar RCM
- Prednisone 50 mg (1 mg/kg for children) @13, 7 & 1 hour before test
- Diphenhydramine 1.5 mg/kg IM up to 50 mg total dose 1 hour prior to test
- If no CV disease present can consider giving Ephedrine 25 mg (0.5-1.0 mg/kg for children) or albuterol 4 mg @ 1 hour prior to test

Risk Factors for Drug Allergy

- Chemical properties of drug:
  - Large molecular weight agents may be more immunogenic
- Frequency of use:
  - Frequent, repetitive courses of therapy are more likely to sensitize (i.e. cystic fibrosis patients)
- Genetic:
  - HLA B5701 and Abacavir hypersensitivity (4-5% of patients)
  - HLA B1502 allele screening and carbamazepine avoidance decreases risk of SJS/TEN in Southeast Asian countries*
- Infectious: Concomitant viral infections increase risk of drug rash (usually non-IgE mediated)
  - Almost 100% of patients with acute Epstein-Barr virus infection will develop nonpruritic rash with amoxicillin
  - HIV patients have increased risk of rash to trimethoprim-sulfamethoxazole**

Aspirin (ASA)/NSAID Allergy

- Reactions classically of two types:
  - Immediate ASA hypersensitivity
    - Desensitization protocols available which are especially important in patients with coronary artery disease that require aspirin
  - Aspirin Exacerbated Respiratory Disease (AERD)

**Drug Allergy: An Updated Practice Parameter. AAAAI, ACAAI, JCAAI. Annals of Allergy, Asthma, and Immunology. 2010 pp 259-273

Aspirin (ASA)/NSAID Allergy

- Reactions classically of two types:
  - Immediate ASA hypersensitivity
    - Desensitization protocols available which are especially important in patients with coronary artery disease that require aspirin
  - Aspirin Exacerbated Respiratory Disease (AERD)
Aspirin Exacerbated Respiratory Disease (AERD)

- Worsening of asthma with ASA and other NSAIDs
- Patients have Samter’s triad (asthma, nasal polyps, ASA sensitivity) and rhinosinusitis
- Mechanism is shunting of arachidonic acid pathway to leukotrienes in the presence of aspirin (not immunologic)

Treatment:
- Aggressive medical/surgical treatment of asthma/rhinosinusitis
- Avoidance of ASA/NSAIDs
- ASA desensitization can help with AERD and nasal polyp recurrence
- Protocol is different from protocol for Type 1 hypersensitivity patients
- Patients maintain on 325-650mg ASA daily for life

Adverse Reactions to ACE-inhibitors

- Two major reactions are cough and angioedema
- Cough with ACE-inhibitors:
  - Occurs in 20% of patients
  - Generally occurs in first few weeks of treatment
  - Reputed to be more common in women, African Americans, Asians
  - Mechanism unclear thought to be bradykinin-induced formation of proinflammatory mediators
  - Typically resolves after stopping the medication

ACE-Inhibitor Associated Angioedema

- Incidence 0.1-0.7%
- Most common in African Americans
- Time to onset is variable; average time to onset is 1.8 years
- Can be difficult to manage and life-threatening
- Patients can typically tolerate angiotensin receptor blockers (ARBs)
DRESS Syndrome

- Drug Rash with Eosinophilia and Systemic Symptoms
- Systemic symptoms include fever, renal and hepatic abnormalities, lymphadenopathy
- Reactions begin usually 2-8 weeks after initiation of therapy and can persist for several weeks after discontinuing offending agent
- Implicated medications: anticonvulsants, sulfonamides, allopurinol, minocycline, dapsone, sulfasalazine, abacavir, nevirapine, and hydroxychloroquine
- Patients may require hospitalization and intensive care monitoring

Stevens Johnson Syndrome (SJS) and Toxic Epidermal Necrolysis (TEN)

- Severe blistering reaction characterized by epidermal detachment
  - Mechanism unknown
- Degree of detachment determines TEN or SJS
  - <10% is SJS
  - >30% is TEN
  - Between 10%–30% is considered overlapping
- Over 100 drugs have been implicated
  - High relative risk: sulfonamides, cephalosporins, imidazole agents, oxicam derivatives
  - Moderate relative risk: quinolones, carbamazepine, phenytoin, valproic acid


Stevens-Johnson Syndrome

- Features:
  - Confluent purpuric macules on face and trunk
  - Severe, explosive mucosal erosions, usually at more than one mucosal surface
  - high temperature and severe constitutional symptoms
  - Eye, liver, kidney, lung involvement may occur
- Glucocorticoid therapy is controversial
- Patients may require ICU level care
- Patient must avoid drug for life

-Drug Allergy: An Updated Practice Parameter. AAAAI, ACAAI, JCAAI. Annals of Allergy, Asthma, and Immunology. 2010: pp 259-273
Toxic Epidermal Necrolysis

- Manifested by widespread areas of confluent erythema followed by epidermal necrosis and detachment
- Severe mucosal involvement present
- Patients must be managed in a burn unit
  - Mainly supportive care, prevention of infection, etc
  - Mortality rates may approach 50%
- Glucocorticoids contraindicated
- Conflicting evidence on IVIG benefit
- Patient must avoid drug for life

Case Study

42yo female presented to the hospital with several weeks of worsening delirium and dementia. CT head was normal. CSF analysis was consistent with neurosyphilis.

Patient’s physician prescribed IV penicillin G. However, he was informed that the patient has a “penicillin allergy” by the pharmacist. Further investigation revealed “whole body swelling and rash” (per patient’s mother) when the patient was 10 years old after she had received PCN for a tooth abscess. Patient was not hospitalized at that time for the reaction and further details have been forgotten.

How should the physician proceed?
Penicillin (PCN) Allergy

- About 10% of patients report penicillin “allergy”
  - Upon evaluation, 90% of these patients are not really allergic to penicillin
    - Anti-PCN antibodies tend to wane over time
    - Many patients were not allergic at all
- PCN reactions can be Type I, II, III, IV hypersensitivity reactions
  - Skin testing indicated for Type I reactions only

Drug Allergy: An Updated Practice Parameter. AAAAI, ACAAI, JCAA, Annals of Allergy, Asthma, and Immunology. 2010; pp 263-273

Penicillin Skin Testing

- Gold standard for evaluation of IgE-mediated (Type I) PCN allergy
- PCN itself is immunologically inert and is metabolized to reactive intermediates
- Major determinant
  - Penicilloyl (commercially available as PrePen®)
- Minor determinants
  - Penicillin G (only commercially available minor determinant)
  - Penicilloate
  - Penilloate
  - “Aged” PCN G does not create minor determinants

Penicillin and Select Immunogenic Determinants

Penicillin Skin Testing

- Testing should be done by someone comfortable with application/interpretation of skin tests (i.e. allergist)
  - No antihistamines for five days prior
  - Can be done electively or when PCN is needed
  - Entire testing process takes <90 minutes
  - Negative tests are usually confirmed with a drug challenge with a full dose if alleged reaction was minimal, start at 1/100 full dose if reaction was anaphylaxis

Penicillin Skin Test & Challenge Forms

<table>
<thead>
<tr>
<th>Antigens</th>
<th>Prick Test</th>
<th>Intradermal Test</th>
<th>Reaction</th>
</tr>
</thead>
<tbody>
<tr>
<td>Histamine</td>
<td>0</td>
<td>0</td>
<td>0 mm larger</td>
</tr>
<tr>
<td>PCN 10,000 U/ml</td>
<td>0</td>
<td>0</td>
<td>0 mm larger</td>
</tr>
<tr>
<td>Pre Pen</td>
<td>0</td>
<td>0</td>
<td>0 mm larger</td>
</tr>
</tbody>
</table>

If negative test, then alternative Amoxil Challenge: 250mg, observe for 45 minutes to 1 hour, then increase dose to 500mg and observe for another hour (CPT 95075).

Testing involves prick and intradermal testing with PrePen®, Pen G (concentration of 10,000 U/mL), saline negative control, and positive histamine control.

Combination of PrePen® & Pen G has negative predictive value (NPV) approaching 100% & positive predictive value (PPV) of 40-100%

In Vitro Tests for Penicillin Allergy

- Few studies with small numbers of patients exist evaluating third-generation assays for detection of penicillin specific IgE in vitro.
  - High specificity (97%–100%)
  - Lower sensitivity (29%-68%)
  - "Therefore, although a positive in vitro test result for penicillin specific IgE is highly predictive of penicillin allergy, a negative in vitro test result does not adequately exclude penicillin allergy."

Drug Allergy: An Updated Practice Parameter. AAAAI, ACAAI, JCAAI, Annals of Allergy, Asthma, and Immunology. 2010: pp 259-273
Administration of Other Beta-Lactam Antibiotics in PCN-Allergic Patients

- **Cephalosporins:**
  - Cross-reactivity is estimated at 2%
  - If PCN reaction was mild, can consider graded challenge to cephalosporin instead of skin testing to PCN

- **Aztreonam:**
  - No cross-reactivity demonstrated
  - PCN allergic patients may safely receive aztreonam

- **Carbapenems (Imipenem/Meropenem):**
  - Cross-reactivity unknown
  - PCN allergic patients who are PCN skin test negative may safely receive carbapenems
  - PCN allergic patients who are skin test positive and those who did not undergo skin testing may receive carbapenems via graded challenge

Drug Allergy: An Updated Practice Parameter. AAAAI, ACAAI, JCAAI. Annals of Allergy, Asthma, and Immunology. 2010: pp 259-273
Back to Our Case…

Summary: 42yo patient has neurosyphilis. Physician ordered IV Pen G, but told that patient had “swelling and rash” 30+ years ago to penicillin and has been avoiding since.

Since Pen G is treatment of choice, how should the treating physician proceed?

Case Study

Patient underwent Penicillin skin testing. Results of the skin tests were negative.
Case Study

Patient underwent graded challenge to Pen G. After successfully passing the challenge, she underwent a full treatment course without any allergic reactions.
Prior to Performing Drug Challenge or Desensitization

- Need for drug should be re-examined
  - Avoid empiric treatment of mild infections with antibiotics
  - Follow established treatment guidelines
- Attempt to find alternative drug
- Risk stratification of patient
  - Severity of reaction
  - Cardiac history
  - FEV1 in patients with asthma/COPD

Drug Challenge vs Desensitization

- Goal of a graded drug challenge is to cautiously administer a drug in escalating doses to assess whether a patient will have a rapid adverse reaction to drug
  - Indicated for patients who are unlikely to be allergic to the drug in question
  - Patient’s underlying biological response to drug is not altered
- Goal of rapid induction of drug tolerance (drug desensitization) is to alter the patient’s biologic response to drug so that it may be given safely
  - Indicated for patients who are likely allergic to the drug
  - Most common scenario: desensitization for serious IgE-mediated reaction; patient MUST have specific drug

Drug Challenges

- Common indications for drug challenges:
  - Reaction mild/unconvincing
  - Exclude cross-reactivity of structurally related drugs
  - Convince nervous/skeptical patients who are not likely to have serious reactions (i.e. multiple drug allergic patients)
- Drug challenges are not indicated for severe drug reactions
- Drug challenges should not be done in pregnant patients
- Usually 1-4 steps: can start at 1/1000th or 1/100th of full dose and increase by factor of 10 every 20-30 minutes
- Ideally done by an allergist
  - Can be done by PCP if patient very, very unlikely to react
Drug Desensitization

- Desensitization is indicated when specific drug is necessary and patient has history of severe IgE-mediated reaction to that drug.
- 10-15 step process of escalating doses done in hospital (usually ICU) by an allergist over 4-12 hours.
- Renders immune cells unreactive (alters biologic response) to offending drug.
- Desensitization is a temporary phenomenon.
  - Re-desensitization must be performed if 2 half lives of drug have elapsed to taper risk of original reaction.
- SJS/TEN and Type III/IV hypersensitivity reaction patients are not candidates for rapid desensitization.

Drug Challenge vs Desensitization

<table>
<thead>
<tr>
<th></th>
<th>Drug Challenge</th>
<th>Drug Desensitization</th>
</tr>
</thead>
<tbody>
<tr>
<td>Indicated for serious IgE-mediated reactions</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>Indicated for non-IgE-mediated reactions</td>
<td>Yes (for non-serious reactions)</td>
<td>Sometimes (i.e. allopurinol, Bactrim, aspirin for AERD)</td>
</tr>
<tr>
<td>Suggests or establishes permanent tolerance</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Modifies immune response to drug</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>Number of steps</td>
<td>1-4</td>
<td>10-15</td>
</tr>
<tr>
<td>Starting dose</td>
<td>1/1,000-1/100 of final dose</td>
<td>Usually 1/10,000 of final dose</td>
</tr>
<tr>
<td>Should be performed by an allergist</td>
<td>In most cases</td>
<td>Yes</td>
</tr>
</tbody>
</table>

Oral Penicillin Tolerance (Desensitization) Protocol

<table>
<thead>
<tr>
<th>Step</th>
<th>PCN mg/mL</th>
<th>Amount ml</th>
<th>Dose given, mg</th>
<th>Cumulative Dose, mg</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>0.5</td>
<td>0.1</td>
<td>0.05</td>
<td>0.05</td>
</tr>
<tr>
<td>2</td>
<td>0.5</td>
<td>0.2</td>
<td>0.1</td>
<td>0.15</td>
</tr>
<tr>
<td>3</td>
<td>0.5</td>
<td>0.4</td>
<td>0.2</td>
<td>0.35</td>
</tr>
<tr>
<td>4</td>
<td>0.5</td>
<td>0.8</td>
<td>0.4</td>
<td>0.75</td>
</tr>
<tr>
<td>5</td>
<td>0.5</td>
<td>1.6</td>
<td>0.8</td>
<td>1.55</td>
</tr>
<tr>
<td>6</td>
<td>0.5</td>
<td>3.2</td>
<td>1.6</td>
<td>3.15</td>
</tr>
<tr>
<td>7</td>
<td>0.5</td>
<td>6.4</td>
<td>3.2</td>
<td>6.35</td>
</tr>
</tbody>
</table>
Oral Penicillin Tolerance (Desensitization) Protocol

<table>
<thead>
<tr>
<th>Step</th>
<th>PCN mg/mL</th>
<th>Amount ml</th>
<th>Dose given, mg</th>
<th>Cumulative Dose, mg</th>
</tr>
</thead>
<tbody>
<tr>
<td>8</td>
<td>5</td>
<td>1.2</td>
<td>16</td>
<td>12.35</td>
</tr>
<tr>
<td>9</td>
<td>5</td>
<td>2.4</td>
<td>12</td>
<td>24.35</td>
</tr>
<tr>
<td>10</td>
<td>5</td>
<td>5</td>
<td>25</td>
<td>49.35</td>
</tr>
<tr>
<td>11</td>
<td>50</td>
<td>1</td>
<td>50</td>
<td>100</td>
</tr>
<tr>
<td>12</td>
<td>50</td>
<td>2</td>
<td>100</td>
<td>200</td>
</tr>
<tr>
<td>13</td>
<td>50</td>
<td>4</td>
<td>200</td>
<td>400</td>
</tr>
<tr>
<td>14</td>
<td>50</td>
<td>8</td>
<td>400</td>
<td>800</td>
</tr>
</tbody>
</table>

Skin Testing for Non-PCN Antibiotics

- **There are no validated diagnostic tests** for IgE mediated allergy to non-penicillin antibiotics.
- Skin testing with non-irritating concentrations established for 15 commonly used antibiotics.
- A negative skin test result does not rule out the possibility of an immediate-type allergy.
- Positive skin test results to a drug concentration known to be nonirritating suggests the presence of drug-specific IgE.
  - Empedrad R et al. J Allergy Clin Immunology 2003;112:629

<table>
<thead>
<tr>
<th>Antimicrobial drug</th>
<th>Nonirritating concentration</th>
<th>Full-strength concentration</th>
<th>Dilution from full strength</th>
</tr>
</thead>
<tbody>
<tr>
<td>azithromycin</td>
<td>10 µg/ml</td>
<td>100 mg/ml</td>
<td>1:10,000</td>
</tr>
<tr>
<td>cefotaxime</td>
<td>10 mg/ml</td>
<td>100 mg/ml</td>
<td>1:10</td>
</tr>
<tr>
<td>cefuroxime</td>
<td>10 mg/ml</td>
<td>100 mg/ml</td>
<td>1:10</td>
</tr>
<tr>
<td>cefazolin</td>
<td>33 mg/ml</td>
<td>330 mg/ml</td>
<td>1:10</td>
</tr>
<tr>
<td>ceftriaxone</td>
<td>10 mg/ml</td>
<td>100 mg/ml</td>
<td>1:10</td>
</tr>
<tr>
<td>clindamycin</td>
<td>15 mg/ml</td>
<td>150 mg/ml</td>
<td>1:10</td>
</tr>
<tr>
<td>cotrimoxazole</td>
<td>800 µg/ml</td>
<td>80 mg/ml</td>
<td>1:100</td>
</tr>
<tr>
<td>erythromycin</td>
<td>50 µg/ml</td>
<td>50 mg/ml</td>
<td>1:1000</td>
</tr>
<tr>
<td>gentamicin</td>
<td>4 mg/ml</td>
<td>40 mg/ml</td>
<td>1:10</td>
</tr>
<tr>
<td>levofloxacin</td>
<td>25 µg/ml</td>
<td>25 mg/ml</td>
<td>1:1000</td>
</tr>
<tr>
<td>imipenemcilastatin</td>
<td>0.5 mg/ml</td>
<td>500 mg/100 ml</td>
<td>1:10</td>
</tr>
<tr>
<td>meropenem</td>
<td>1 mg/ml</td>
<td>50 mg/ml</td>
<td>1:50</td>
</tr>
<tr>
<td>nalidixic</td>
<td>25 µg/ml</td>
<td>250 mg/ml</td>
<td>1:10,000</td>
</tr>
<tr>
<td>ticarcillin</td>
<td>20 mg/ml</td>
<td>200 mg/ml</td>
<td>1:10</td>
</tr>
<tr>
<td>tobramycin</td>
<td>4 mg/ml</td>
<td>80 mg/2 ml</td>
<td>1:10</td>
</tr>
<tr>
<td>vancomycin</td>
<td>5 µg/ml</td>
<td>50 mg/ml</td>
<td>1:10,000</td>
</tr>
</tbody>
</table>

Khan UA. Drug Allergy, in Manual of Allergy & Immunology 5th Ed. 2012
Cephalosporin Skin Tests

- Cefuroxime is often implicated in perioperative hypersensitivity reactions to IV antibiotics
- 89 patients tested (skin tests, in vitro and IV provocation)
- All patients who tested positive (22/22) reacted to IV provocation.
- BUT a third of patients who were negative on skin and in vitro testing reacted to cefuroxime on IV provocation
- Cephalosporin skin tests helpful if positive but beware false negatives

Other Tests for Drug Allergy

- Measuring drug-specific IgE in blood
  - Poor sensitivity (studied in PCN allergy)
- Basophil Activation Assay
  - Evaluates expression of CD63 on basophils after stimulation with an allergen
  - Minimal data, appears to lack specificity
- Patch testing
  - Useful for topically applied drugs
  - Questionable benefit in Type IV hypersensitivity drug reactions
- Skin biopsy
  - No specific histological criteria to distinguish drug reactions from alternative causes of rash

Take Home Pearls

- Drug reactions can occur at any point during treatment course
- It is important to clarify whether or not a reaction is IgE-mediated to dictate work-up and treatment
- With proper evaluation and execution, drug challenges can remove medications from a patient’s drug allergy list
- Skin testing is the gold standard for evaluation of suspected IgE-mediated penicillin allergy
- When in doubt, always consult with an allergist
Excellent References for Drug Allergy

Drug Allergy: An Updated Practice Parameter