Top 10+ Facts About Drug Allergy

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Overview
- Classification
- Spectrum of Drug Allergic Reactions
- Specific Drug Reactions
- Approach to the Patient with Drug Allergy
- 13 Key Important Points

Classification of Drug Reactions
- Type A Reactions (Most common)
  - Features
    - Predictable
    - Related to pharmacologic actions of the drug
    - No specific host factors

Classification of Drug Reactions
- Type B Reactions
  - Unpredictable
  - Less Common
  - Occur in susceptible individuals

Adverse Drug Reactions ≠ Drug Allergy

Key Point 1

Classification of Drug Reactions
- Type A Reactions
  - Toxicity
    - Renal failure from aminoglycosides
  - Side effect
    - Sedation from antihistamines
  - Secondary effect
    - Diarrhea from antibiotics
  - Drug Interaction
    - Theophylline toxicity from concomitant erythromycin
Classification of Drug Reactions

- Type B Reactions
  - Idiosyncratic reaction
  - Hemolysis with dapsone in G6PD deficiency
  - Hypersensitivity (Specific immunologic)
    - Anaphylaxis after penicillin
  - Pseudoallergic (non-immunologic)
    - Anaphylactoid reaction to radiocontrast media

Sub classification of Type IV Reactions

<table>
<thead>
<tr>
<th>Classification</th>
<th>Immune Response</th>
<th>Pathology</th>
<th>Reaction</th>
</tr>
</thead>
<tbody>
<tr>
<td>Type IVa</td>
<td>Th1 IFN-γ</td>
<td>Monocyte</td>
<td>Eczema</td>
</tr>
<tr>
<td>Type IVb</td>
<td>Th2 IL-4, IL-5</td>
<td>Eosinophil</td>
<td>Maculopapular, bullous</td>
</tr>
<tr>
<td>Type IVc</td>
<td>CTL Perforin, granzyme</td>
<td>CD4, CD8</td>
<td>Maculopapular, Bullous (↑ CD8) Pustular</td>
</tr>
<tr>
<td>Type IVd</td>
<td>T cells IL-8</td>
<td>Neutrophils</td>
<td>Pustular</td>
</tr>
</tbody>
</table>


Hapten Hypothesis

- Haptens are chemically reactive small molecules
- Undergo stable covalent binding to a larger protein or peptide
- Covalent binding of small hapten drugs to self-proteins leads to immunogenic compounds
- Penicillin classic example

Prohapten Hypothesis

- Drug that is not chemically reactive becomes reactive after metabolism
- Chemically reactive drug metabolite can then bind covalently to proteins/peptides and become immunogenic
- Sulfamethoxazole example
  - Metabolized to sulfamethoxazole-nitroso (highly reactive)

p-i Concept

- Pharmacologic interaction with immune receptors (p-i concept)
- Drug binds directly to T-cell receptor
- Interaction with MHC molecules results in T cell stimulation
- Examples
  - Sulfamethoxazole
  - Ciprofloxacin
  - Lidocaine
  - Carbamazepine
  - Lamotrigine
  - P-phenylenediamine

There are Many Types of Drug Allergies!

Key Point #2

Organ Specific Drug Allergic Reactions

<table>
<thead>
<tr>
<th>Clinical Features</th>
<th>Examples of causative agents</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cutaneous</td>
<td>exanthem, urticaria, angioedema, fixed drug eruption, pustules, bullous, cutaneous lupus, Stevens-Johnson syndrome, toxic epidermal necrolysis</td>
</tr>
<tr>
<td>Hematologic</td>
<td>hemolytic anemia, thrombocytopenia</td>
</tr>
<tr>
<td>Hepatic</td>
<td>hepatitis, cholestatic jaundice</td>
</tr>
<tr>
<td>Pulmonary</td>
<td>pneumonitis, fibrosis</td>
</tr>
<tr>
<td>Renal</td>
<td>interstitial nephritis, membranous glomerulonephritis</td>
</tr>
</tbody>
</table>

Key Point #3

Multi-Organ Drug Allergic Reactions

<table>
<thead>
<tr>
<th>Clinical Features</th>
<th>Examples of causative agents</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anaphylaxis</td>
<td>urticaria, angioedema, bronchospasm, gastrointestinal symptoms, hypotension</td>
</tr>
<tr>
<td>Drug rash with eosinophilia and systemic symptoms (DRESS)</td>
<td>urticaria, angioedema, eosinophilia, lymphadenopathy</td>
</tr>
<tr>
<td>Serum sickness</td>
<td>urticaria, arthralgia, fever</td>
</tr>
<tr>
<td>Systemic Lupus</td>
<td>arthralgia, myalgia, fever, malaise</td>
</tr>
<tr>
<td>Vasculitis</td>
<td>cutaneous or visceral vasculitis</td>
</tr>
</tbody>
</table>

Key Point #4

Different Types of Drug Rashes Mean Different Things

Patterns of Drug-Induced Cutaneous Reactions

- Acanthosis nigricans
- Acneiform lesions
- Acute generalized exanthematous pustulosis
- Alopecia
- Angioedema
- Aphthous stomatitis
- Black hairy tongue
- Bullous eruptions
- Erythema multiforme and Stevens-Johnson syndrome
- Erythema nodosum
- Exanthems
- Exfoliative dermatitis
- Fixed drug eruption
- Gingival hyperplasia
- Lichenoid (lichen planus-like) eruptions
- Lupus erythematosus
- Onycholysis
- Pemphigus vulgaris
- Photosensitivity
- Pigmentation
- Pythagoras rosea-like eruptions
- Pruritus
- Psoriasis
- Purpura
- Raynaud’s phenomenon
- Toxic epidermal necrolysis
- Urticaria
- Vasculitis
- Xerostomia

Urticaria from Aspirin
ACE-I Angioedema

Drug-Induced Urticaria and Angioedema
- IgE Mediated
- Pseudoallergic Reactions
- Serum Sickness
- Other

IgE Mediated Reactions
- Onset
  - Usually minutes to hour after drug exposure
  - Requires prior exposure to drug or cross-reacting drug (sensitization)
- Symptoms
  - Urticaria, flushing, pruritus, angioedema, anaphylaxis
- Rash resolves without peeling, or changes in pigmentation

Pseudoallergic Reactions
- Resemble true IgE allergic reactions but IgE not involved
- Pathophysiology
  - Non-specific mast cell degranulation
- Onset usually minutes to hour after exposure (like IgE)
  - May occur with 1st exposure
- Urticaria, flushing, pruritus, rarely hypotension
- Examples
  - Opiates, vancomycin

Drug Exanthem

Drug Exanthems
(Maculopapular Eruptions)
- Most common drug allergic reaction
- Pathophysiology mixed
  - Often T-cell mediated
- Onset variable often within days or longer
- Erythema, fine papules, typically widespread, usually spares palms and soles
- Often resolves with scaling/peeling
- Do not evolve into anaphylaxis
Life-Threatening Cutaneous Drug Reactions

Stevens Johnson Syndrome (SJS)
Toxic Epidermal Necrolysis (TEN)
Drug Rash with Eosinophilia and Systemic Symptoms (DRESS)
Exfoliative Dermatitis

SJS & TEN
- Stevens Johnson Syndrome (SJS) & Toxic Epidermal Necrolysis (TEN)
  - Most-likely spectrum of the same disease
  - Epidermal detachment more extensive in TEN
  - Skin and mucosal involvement
    - conjunctiva, oral and genital mucosa
  - Mortality 5-40%

SJS & TEN
- Higher Risk Patients
  - HIV
  - SLE
  - Bone marrow transplant
- High risk agents
  - sulfonamides, cephalosporins, anticonvulsants (imidazole), NSAID's, allopurinol

Toxic Epidermal Necrolysis
Nikolsky's sign in TEN

DRESS
- Drug Rash Eosinophilia Systemic Symptoms
- Rash, fever, eosinophilia, hepatic dysfunction, lymphadenopathy
- Symptoms may persist months after drug is discontinued
- Most Common Causes
  - anticonvulsants, sulfonamides, minocycline, allopurinol
Most patients who think they are allergic to penicillin are not allergic to penicillin.

Key Point #4

Most patients who really were allergic to penicillin in the past, lose their allergy over time.

Key Point #5

Penicillin (PCN) Allergy
- 90% patients with a history of PCN allergy will tolerate PCN
- ~ 80% PCN allergic patients lose PCN-IgE after 10 years
- 1/3 patients with vague history of PCN allergy are PCN skin test positive

PCN Skin Tests
- Negative penicillin skin tests (using the proper reagents) equate with no risk for anaphylaxis
Ampicillin/Amoxicillin

- Amoxicillin and ampicillin are associated with the development of a delayed maculopapular rash in about 5-10% of patients
  - not IgE-mediated
- If amoxicillin taken during infectious mononucleosis ~100% develop rash

Risk of reacting to cephalosporins in a patient with a history of a non-severe penicillin allergy is ~ 0.1%

Key Point #6

Penicillin and Cephalosporins

- Share a common beta-lactam ring

Cephalosporin & PCN Allergy

- Only 2% of penicillin skin test-positive patients react to treatment with cephalosporins
  - Rare reports of fatal reactions
- Penicillin skin test-negative patients may receive cephalosporins safely

Cephalosporin & PCN Allergy

- 606 patients with history of PCN allergy received 685 cephalosporin courses
  - 42% 1st gen, 21% 2nd gen, 37% 3rd/4th gen
- 1/606 pts (0.07%) had adverse reaction
  - Mild worsening of eczema
- Patients with a severe PCN allergy history (e.g. anaphylaxis) were denied cephalosporins by pharmacy service
- Patients with histories of non-severe reactions to penicillin typically tolerate cephalosporins

Lack of Cross-Reactivity with Cephalosporins and Penicillin

- Data from large EMR in United Kingdom was analyzed evaluating > 500,000 patients prescribed penicillin followed by a cephalosporin
- Similar increased risk for patients with “allergic like events” after penicillin after receiving cephalosporins (RR 10.0) and sulfonamide antibiotics (RR 7.2)
- Data do not support immunologic cross-reactivity


Risk of reacting to carbapenems in a patient with a history of penicillin allergy is 0-11%  

Key Point #7

People who are allergic to “sulfa” usually do fine with other “sulfa” medications  

Key Point #8

Absence of Cross-Reactivity between Sulfonamide Antibiotics and Sulfonamide Nonantibiotics

- Study that analyzed pharmacy database from England
- Patients with sulfonamide antibiotic allergy (e.g., Bactrim allergy) were more likely to react to penicillin than a sulfonamide nonantibiotic (e.g., hydrochlorothiazide)
- Penicillin allergic patients were more likely to react to sulfonamide nonantibiotics than Bactrim allergic patients!
- Patients who are allergic to any antibiotic are more likely than those with no drug allergy to react to other medicines….common sense!  
  Sisom HL et al. NEJM 2003;349:1628-35.

Allergy to Local Anesthetics is More Myth than Reality

Key Point #9

PCN Allergy and Carbapenems

- Carbapenems
  - 50% allergic cross-reactivity between penicillin and carbapenems based on skin tests
  - Clinical cross-reactivity variable
    - Recent studies suggest 0-11% react
    - Negative carbapenem skin test appears to predict tolerance (Romano 2006,2007)

Sulfonamide Allergy

“I’m allergic to sulfa”

- A sulfonamide is any compound that contains a sulfonamide (SO₂NH₂) moiety
- Sulfonamide antimicrobial drugs
  - trimethoprim/sulfamethoxazole (Bactrim)
- Sulfonamide nonantimicrobials
  - thiazide diuretics, glyburide, dapsone, etc.
- Sulfonamide antimicrobials have a different aromatic ring structure
Local Anesthetic Allergy

- Most adverse reactions to local anesthetics are due to nonallergic factors
  - Vasovagal, anxiety
  - Toxic or idiosyncratic reactions due to inadvertent intravenous epinephrine
  - True IgE-mediated reactions are exceedingly rare
- Graded challenge test of choice for disproving local anesthetic allergy

There are many types of aspirin “allergy”

Key Point #10

Aspirin-Exacerbated Respiratory Disease (AERD)

- Associated with asthma, rhinitis, sinusitis, nasal polyposis
- Symptoms with NSAID’s
  - Rhinorrhea, conjunctivitis, bronchospasm
- Dependent on cyclooxygenase (COX)-1 inhibition
- COX-2 inhibitors generally safe (Celebrex)
- Diagnosis with oral ASA challenge

NSAID Allergic Reactions

<table>
<thead>
<tr>
<th>Reaction</th>
<th>Underlying Disease</th>
<th>Cross Reaction with other NSAID’s</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rhinitis/Asthma</td>
<td>Asthma (AERD)</td>
<td>Yes</td>
</tr>
<tr>
<td>Urticaria/AE</td>
<td>Chronic urticaria</td>
<td>Yes</td>
</tr>
<tr>
<td>Anaphylaxis</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>Urticaria/AE</td>
<td>No</td>
<td>Yes or No</td>
</tr>
</tbody>
</table>

Aspirin Desensitization

- Many patients with reactions to aspirin may be desensitized
- Patients with respiratory reactions to aspirin (AERD) have improvement in asthma and sinus disease/nasal polyposis after desensitization and treatment with aspirin
- Patients in need of low-dose aspirin for cardiac disease may also be “desensitized/challenged” to aspirin

Angiotensin Converting Enzyme (ACE) Inhibitors

- Cough
  - Incidence up to 20%
  - Mechanism unknown
  - Angiotensin II receptor blockers (ARBs) tolerated
- Angioedema
  - 0.1-0.7%, more common in African-Americans
  - Usually delayed in onset
    - Mean 1.8 yrs (Malde 2007)
  - Occurs sporadically despite daily ingestion
  - Likely bradykinin induced
  - Usually tolerate ARBs but case reports of AE with ARBs too
Radiocontrast Media (RCM) Reactions

- Mechanisms
  - Anaphylactoid
    - Direct mast cell activation
    - Complement activation
    - Not IgE mediated
    - Delayed reactions due to type IV hypersensitivity
  - Reaction rate from ionic contrast > non-ionic contrast
  - No evidence that sensitivity to seafood or iodine specifically predisposes or is cross-reactive with RCM reactions

Radiocontrast Anaphylactoid Reactions

- Risk Factors
  - Female
  - Asthma
  - Cardiovascular disease
  - Prior reaction to RCM

Radiocontrast Media (RCM) Reactions

- Management
  - Non-ionic RCM
  - Pre-treatment
    - Prednisone 50 mg
      - 13, 7, 1 hr prior
    - Diphenhydramine 50 mg
      - 1 hr prior
    - Ephedrine/albuterol
    - H2-antagonists controversial

Approach to the patient with Drug Allergy

Evaluation of the Drug-allergic Patient

- Identify all medication usage and dosages
- Determine when a medication was initiated and establish a temporal relationship
- Determine if there was a prior history of drug exposure
- Characterize the reaction type
  - IgE vs. other
- Determine the propensity for a given drug to cause certain reactions

You can skin test to most any drug...interpreting the results is a different story

Take Home Point #11

PCN Skin Tests
- Only helpful for suspected IgE drug reactions (urticaria, angioedema, anaphylaxis)
- When Pre Pen and minor determinants used for skin testing, if penicillin skin test was negative, no risk for anaphylaxis
- Penicillin skin testing is no longer available due to lack of proper skin testing reagents (Pre Pen)

Caveats of In Vitro PCN Data
- Limited number of studies
  - especially with 3rd generation assays
- Small number of patients in comparison to PCN skin test studies
- Include groups with negative skin tests and positive challenges (rare in US reports)
- No recent data from US, where data on PCN skin test differs from European data
- Overall, high specificity may be useful for initial screening test
- A negative in vitro PCN test does not exclude PCN allergy

Skin testing for Other Antibiotics
- There are no validated diagnostic tests for evaluation of IgE-mediated allergy to non-penicillin antibiotics
- Skin testing with non-irritating concentrations of non-penicillin antibiotics is not standardized
- 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

Management of the Drug Allergic Patient
- For most drugs no validated in vivo or in vitro diagnostic tests are available
- If a patient requires a medication they are allergic to options include:
  1) finding an alternative medication
  2) performing a graded challenge
  3) performing a an induction of drug tolerance procedure (e.g. desensitization)

Non-Irritating Skin Test Concentrations

<table>
<thead>
<tr>
<th>Medication</th>
<th>Full-strength concentration</th>
<th>Dilution from full-strength concentration</th>
</tr>
</thead>
<tbody>
<tr>
<td>cefotaxime</td>
<td>100 mg/ml</td>
<td>10^-1</td>
</tr>
<tr>
<td>cefuroxime</td>
<td>100 mg/ml</td>
<td>10^-1</td>
</tr>
<tr>
<td>cefazolin</td>
<td>130 mg/ml</td>
<td>10^-1</td>
</tr>
<tr>
<td>ceftriaxone</td>
<td>100 mg/ml</td>
<td>10^-1</td>
</tr>
<tr>
<td>tobramycin</td>
<td>80 mg/2 ml</td>
<td>10^-1</td>
</tr>
<tr>
<td>ticarcillin</td>
<td>200 mg/ml</td>
<td>10^-1</td>
</tr>
<tr>
<td>clindamycin</td>
<td>150 mg/ml</td>
<td>10^-1</td>
</tr>
<tr>
<td>gentamicin</td>
<td>40 mg/ml</td>
<td>10^-1</td>
</tr>
<tr>
<td>netilmicin</td>
<td>80 mg/ml</td>
<td>10^-1</td>
</tr>
<tr>
<td>teicoplanin</td>
<td>25 mg/ml</td>
<td>10^-1</td>
</tr>
<tr>
<td>erythromycin</td>
<td>50 mg/ml</td>
<td>10^-1</td>
</tr>
<tr>
<td>azithromycin</td>
<td>100 mg/ml</td>
<td>10^-1</td>
</tr>
<tr>
<td>nafcillin</td>
<td>250 mg/ml</td>
<td>10^-1</td>
</tr>
<tr>
<td>vancomycin</td>
<td>50 mg/ml</td>
<td>10^-1</td>
</tr>
</tbody>
</table>

There are many types of procedures to Induce Drug Tolerance a.k.a. Drug Desensitization

Key Point #12

## Induction of Drug Tolerance (IDT)

- **Benefit**
  - Established protocols for many drugs
  - Relatively safe
    - May be done in an office setting
    - Reactions during procedure variable depending on drug but rarely severe
- **Disadvantages**
  - **Temporary effect**
    - Need to take medicine continuously to maintain tolerant state
  - **Does not determine if allergic to drug**
    - Need to repeat for every subsequent courses

### Immunologic IgE IDT

<table>
<thead>
<tr>
<th>Type of tolerance</th>
<th>Time/Duration</th>
<th>Initial Dose</th>
<th>Possible outcomes</th>
<th>Example</th>
</tr>
</thead>
<tbody>
<tr>
<td>Immunologic IgE</td>
<td>Hours</td>
<td>mcg</td>
<td>Reduction of antigen-specific mast cell degranulation, desensitization of</td>
<td>Penicillin</td>
</tr>
<tr>
<td>Drain desensitization</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Immunologic non-IgE</td>
<td>Hours to Days</td>
<td>mg</td>
<td>Unknown</td>
<td>TMP/SMX</td>
</tr>
<tr>
<td>Pharmacologic</td>
<td>Hours to Days</td>
<td>mg</td>
<td>Unknown</td>
<td>Aspirin</td>
</tr>
<tr>
<td>Undefined</td>
<td>Days to Weeks</td>
<td>mg</td>
<td>Unknown</td>
<td>AllUnpaired</td>
</tr>
</tbody>
</table>

### Pharmacologic IDT Aspirin Desensitization

<table>
<thead>
<tr>
<th>Time</th>
<th>Aspirin Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>0 min</td>
<td>20.25 mg</td>
</tr>
<tr>
<td>90 min</td>
<td>40.5 mg</td>
</tr>
<tr>
<td>180 min</td>
<td>81 mg</td>
</tr>
<tr>
<td>270 min</td>
<td>162.5 mg</td>
</tr>
<tr>
<td>360 min</td>
<td>325 mg</td>
</tr>
</tbody>
</table>

### TMP/SMX Induction of Drug Tolerance (10 day)

<table>
<thead>
<tr>
<th>Day</th>
<th>Dosage TMP/SMX</th>
<th>Concentration/Tablet</th>
<th>Amount</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>0.3/2 mg</td>
<td>0.6/2 mg/ml</td>
<td>1 ml</td>
</tr>
<tr>
<td>2</td>
<td>0.8/4 mg</td>
<td>0.4/2 mg/ml</td>
<td>2 ml</td>
</tr>
<tr>
<td>3</td>
<td>1.6/8 mg</td>
<td>0.5/2 mg/ml</td>
<td>4 ml</td>
</tr>
<tr>
<td>4</td>
<td>3.2/16 mg</td>
<td>0.4/2 mg/ml</td>
<td>8 ml</td>
</tr>
<tr>
<td>5</td>
<td>6.5/30 mg</td>
<td>0.8/5 mg/ml</td>
<td>1 ml</td>
</tr>
<tr>
<td>6</td>
<td>14.0/60 mg</td>
<td>1.6/10 mg/ml</td>
<td>2 ml</td>
</tr>
<tr>
<td>7</td>
<td>32/150 mg</td>
<td>0.8/10 mg/ml</td>
<td>5 ml</td>
</tr>
<tr>
<td>8</td>
<td>64/220 mg</td>
<td>0.8/20 mg/ml</td>
<td>10 ml</td>
</tr>
<tr>
<td>9</td>
<td>96/400 mg</td>
<td>1.6/40 mg/ml</td>
<td>1 tablet</td>
</tr>
<tr>
<td>10</td>
<td>140/800 mg</td>
<td>1.6/80 mg/ml</td>
<td>1 tablet</td>
</tr>
</tbody>
</table>


Drug Desensitization

- Not every drug (or reaction to a drug) can be desensitized
  - Patients with severe skin reactions (TEN, DRESS, SJS) should not be desensitized
  - Patients with ACE-I reactions cannot be desensitized

Drug Challenges are more useful than skin tests and can be done safely in the office

Take Home Point #13

Graded Challenge (Test Dose)

- A graded challenge is a procedure to determine if a drug is safe to administer
- Intended for patients who are unlikely to be allergic to the given drug
- In contrast to a desensitization, a graded challenge does not modify the patient's response to a drug
- Benefit
  - Easy to perform
  - Typically start with 1/100th of final dose, then 1/10th and full dose usually given every 30-60 minutes
  - Confirms or negates drug allergy history
- Disadvantages
  - Potentially higher risk

To Challenge or Desensitize?

- A healthy patient with a childhood history of a “measles” like eruption to penicillin 30 years prior and needs penicillin
  - a graded challenge should be considered
- A patient with a history of anaphylaxis to penicillin two years ago who needs penicillin
  - an empiric penicillin desensitization should be performed

Multiple Drug Allergic Patients

- Most often due to intolerances or multiple drugs administered within short period of time to an evolving drug reaction
- Detailed history alone usually adequate to broaden tolerable drugs (usually antibiotics)
- Things not to say to these patients
  - “I’m not sure how we can treat you if you really get sick”
  - “The next time you get an antibiotic you could die”
Multiple Drug Allergic Patients

- **Principles for Patients**
  - Avoid medications as much as possible
  - Take antibiotics only for proven infections
    - Proven by culture preferably (or x-ray)
  - Avoid antibiotics for sinusitis, otitis, and bronchitis (especially since antibiotics typically not needed for these conditions)

Conclusions

- Most cases of drug allergy can be evaluated by the history and physical exam alone
- Skin testing is limited as a diagnostic tool
- Graded challenges and drug desensitizations may be performed safely
- Even multiply drug allergic patients can be managed successfully