Update in Drug Hypersensitivity

Katharine Woessner M.D., F.A.A.A.A.I.
Program Director
Scripps Clinic
Woessner.katharine@scrippshealth.org
Adverse Drug Reactions (ADR)
Any untoward reaction to a medication

- **Type A**: predictable, dose dependent, related to pharmacological action of the drug e.g. gastritis with NSAIDs (80-85% of all ADRs)
- **Type B**: unpredictable, dose-independent, unrelated to pharmacologic activity of the drug, only occur in susceptible individuals (10-15% of ADRs)
  - Drug intolerance (e.g. tinnitus with 1 dose ASA)
  - Drug Allergy
  - Pseudoallergic reactions
Risk Factors for Drug Hypersensitivity

- Drug administration
  - Dose, route of administration, duration of treatment, repetitive exposure to drug

- Drug-specific
  - Molecular weight
  - Complexity
  - Chemical properties of drug
Immune Recognition of Drug Antigens


Courtesy M. Dykewicz MD
Mechanisms (Gell and Coombs)

Type I - Immediate Hypersensitivity
IgE mediated (e.g. anaphylaxis)

Type II - Cytotoxic Reactions
IgG/IgM antibody and complement mediated hemolytic anemia, thrombocytopenia, granulocytopenia.

Heparin induced thrombocytopenia from antibody responses to heparin-platelet factor 4 complex, associated with thrombosis

Courtesy M. Dykewicz MD
Type III - Immune Complex

Serum-sickness reactions

• Immune response: IgG/IgM, complement
• 1-4 weeks after anti-sera (classic) or drugs
• Presentation variable
  – Fever: nearly 100%
  – Skin lesions: 95%
  – Arthritis/ arthralgias (10-50%)
  – Lymphadenopathy (10-20%)
• Treatment: antihistamines, corticosteroids

Lawley. NEJM 1984;311:1407

Courtesy M. Dykewicz MD
# Type IV: Delayed Type Lymphocytic Reactivity: Extended Classification

<table>
<thead>
<tr>
<th>Type IVa</th>
<th>Th1 (IFN-γ)</th>
<th>Monocyte activation</th>
<th>Eczema</th>
</tr>
</thead>
<tbody>
<tr>
<td>Type IVb</td>
<td>Th2 (IL-5, IL-4)</td>
<td>Eosinophilic inflammation</td>
<td>Maculopapular, bullous exanthema</td>
</tr>
<tr>
<td>Type IVc</td>
<td>CTL (perforin &amp; granzyme B)</td>
<td>CD4+ and CD8+ mediated killing of cells (e.g. keratinocytes)</td>
<td>Eczema, maculopapular, bullous, pustular exanthema</td>
</tr>
<tr>
<td>Type IVd</td>
<td>T cells (IL-8)</td>
<td>Neutrophil recruitment and activation</td>
<td>Pustular exanthema</td>
</tr>
</tbody>
</table>

Adapted from: Pichler WJ. Ann Intern Med 2003;139:683-93

Courtesy M. Dykewicz MD
Bullous Exanthema

- Combination of Type IVb and Type IVc mechanisms
- Erythema multiforme minor
- Erythema multiforme major
- Stevens-Johnson syndrome < 10% body surface
- Toxic epidermal necrolysis > 30% body surface
Case History: Exantham

- 7 yo girl seen by pediatrician with CC: burning during urination, no other complaints, no significant PMH or FH
- No fevers/chills, hematuria, no prior medication allergies and not currently on any medications
- PE: afebrile, no rashes, unremarkable
- Labs: Urinalysis: WBC and microscopic hematuria
- Started on 10 d course of amoxicillin
- 8 days after starting medication an itchy rash developed which progressed over next 24h
- Presented back to pediatrician with symmetrical eruption, no blisters, fevers, arthralgias, or purpura.
Morbilliform drug eruption is a non-immediate type IV allergic reaction involving drug-specific T cells (CD4+) with direct cytotoxic effects and release of pro-inflammatory factors.
**Penicillin: Beta Lactam Antibiotics**

- Skin testing most reliable to make diagnosis.
- RAST testing not recommended
- Must haptenate to become active, majority is penicilloyl (95%) = major determinant (pre-pen) minor determinants: penicilloate and penilloate (not cross-reactive)
- “aged” PCN does not spontaneously form minor determinants
- PCN Skin test negative to PRE-PEN and PCN G (10,000 u/mL) similar reaction rates to PCN challenge as those tested with the full panel
- Risk of sensitization with skin testing very low (<3%)\(^1\)
- Resensitization is very rare, if PCN allergic, tolerated an oral course, do not need to repeat each subsequent course of PCN (consider repeat testing if high dose parenteral PCN)\(^2\).

---

Cephalosporins

Patients allergic to amoxicillin should avoid cephalosporins with identical R-group side chains (cephalexin, cefaclor, loracarbef).

Monobactam (Aztreonam) only x-reacts with ceftazidime.

Carbapenems: low level of cross-reactivity with PCN
  - PCN skin test positive or history + : give via graded challenge.
Acetylator Phenotypes and Sulfonamide Sensitivity

• Slow acetylators almost twice as likely to develop sulfa allergy

Cross reactivity between antibiotic and non-antibiotic sulfonamides?

**Sulfonamide antimicrobials**
- aromatic arylamine group
- metabolized to hydroxylamines
- partial cross-reactivity among sulfa antibiotics

**Sulfonamide derivatives**
- e.g., celecoxib, diuretics, sulfonylureas, sumatriptan
- \( \text{(SO}_2\text{-NH}_2 \rangle \), “nonaromatic amines” (no arylamine)
- not immune cross reactive with sulfa antibiotics

Figure adapted from MEDSCAPE
Vancomycin Reactions

• Red man syndrome
  – Rate related histamine release
  – Reduce rate (< 10 mg/min)
  – Use H1 (not H2 blockers)

• IgE mediated anaphylaxis

• Linear IgA bullous dermatosis
Linear IgA Bullous Dermatosis (LABD)

- Vancomycin most frequent cause
- Bullous disease, annular, may confuse with TEN, skin sloughing may result
- IgA deposited in basement membrane zone

Photographs courtesy Y. Hurley, MD, Beth Levy, MD, Saint Louis University
Reactions TO NSAIDS

1. **Allergic**: single drug anaphylaxis
2. **Pseudoallergic**: result of inhibition of COX-1 enzyme
3. **Idiosyncratic**: aseptic meningitis, hypersensitivity pneumonitis, thrombocytopenia, interstitial nephritis, erythema multiforme, fixed drug eruptions, toxic epidermal necrolysis, Stevens Johnson syndrome, erythema nodosum, maculopapular eruptions, and bullous leukocytoclastic vasculitis
Pseudoallergic Reactions to NSAIDs

- **Type 1**: NSAID-induced asthma and rhinosinusitis — Aspirin exacerbated respiratory disease (chronic rhinosinusitis, polyps, asthma)
- **Type 2**: NSAID-induced urticaria/angioedema (CIU) in pts with chronic urticaria
- **Type 3**: NSAID-induced urticaria/angioedema in otherwise asymptomatic individuals
- **Type 4**: Blended reactions: otherwise asymptomatic, involve skin and respiratory tract triggered by COX-1 inhibition

Allergic Reactions to NSAIDs

- Elicited by single NSAID or rarely, by more than one if share similar molecular structures
- Need prior exposure to get sensitized
- Seen most often with ibuprofen
- Types of reactions
  - Urticaria and angioedema
  - Anaphylaxis (no confirmed cases to ASA)
Approach to Cutaneous Reactors to COX-1 Inhibitors

- NSAID-Induced urticaria/angioedema
  - Urticaria triggered by any Cox-1 inhibiting NSAID
  - Normals (no CIU): can be desensitized
  - Patients with Chronic Idiopathic Urticaria/angioedema: cannot be desensitized

Approach to Cutaneous Reactors to COX-1 Inhibitors

- Single drug-induced urticaria/angioedema/anaphylaxis
  - If able to tolerate ASA:
    - Give a different NSAID (full dose challenge)
    - If unknown: ASA challenge (81mg or 325 mg)
      - anaphylaxis: 10mg ASA doubling every 30 minutes in ICU.
- Other/“blended” reactions:
  - Celecoxib (& other highly selective Cox2 inh) typically OK

## Classification of Non-steroidal Anti-inflammatory Drugs by Structural Classes

### ENOLIC ACIDS

**OXICAMS**
- Feldene (Piroxicam)

**PYRAZOLES**
- Butazolidin (phenylbutazone)
- Tandearil (oxyphenbutazone)

### CARBOXYLIC ACIDS

**SALICYLATES**
- Aspirin (acetylsalicylic acid)
- Disalcid (salsalate)
- Dolobid (diffunisal)
- Trilisate (choline magnesium tri salicylate)

**ACETIC ACIDS**
- Indocin (indomethacin)
- Lodine (etodolac)
- Clinoril (sulindac)
- Tolectin (tometin)
- Zomax (zomepirac)
- Voltaren (diclofenac)

**FENAMATES**
- Meclomen (meclofenamate)
- Ponstel (mefenamic acid)

**PYRROLO-PYRROLE**
- Toradol (ketorolac tromethamine)

**PROPIONIC**
- Motrin, Rufen (ibuprofen)
- Naprosyn (naproxen)
- Anaprox (naproxen sodium)
- Oradex (benoxaprofen)
- Nalfon (fenoprofen)
- Orudis (ketoprofen)
Aspirin-Exacerbated Respiratory Disease (AERD)

- Chronic eosinophilic rhinosinusitis, nasal polyposis, asthma
- ASA/NSAIDs induce rhinitis/asthma attacks
- Progressive disease despite careful avoidance of NSAIDs and ASA
Selection of Patients for ASA desensitization

• All AERD patients except those controlled by topical steroids, long-acting beta agonists and LTMDs alone
• Patients with recurrent or chronic sinusitis and nasal polyps
• Individuals who require anti-platelet therapy with ASA or other COX-1 inhibiting NSAIDs
Dosages of ASA for the Treatment of AERD

• 81 mg q.d. OK to remain desensitized for cardiovascular disease prevention
• 325 mg q.d. OK to be cross-desensitized to any doses of all NSAID’s
• 650 mg BID initial starting dose for treatment of AERD; about 50% can decrease to 325 mg BID after 6-12 months

ASA Treatment of AERD

- **Aspirin desensitization as add on therapy:**
  1. Decrease nasal congestion
  2. Decreases need for additional sinus/polyp surgery
  3. Decreases infectious sinusitis (from 5 to 2/year)
  4. Improves sense of smell
  5. Improves asthma control: Direct or indirect
  6. Reduces need for nasal corticosteroids
  7. Reduces need for bursts of systemic steroids
  8. Reduces daily systemic steroids (10.7 to 3.8 mg.)
ACE Inhibitors
Inhibit angiotensin converting enzyme (ACE)

Angiotensin I
- Bradykinins
- Tachykinins

ACE

Angiotensin II

Vagal afferents
Non-myelinated C-fibers

Substance P priming?
TXB2 \( \square \) PGI2 / PGE2 imbalance?
Angiotensin-Converting Enzyme Inhibitor: Cough and Angioedema

- Cough: within hs of first dose to weeks of starting tx. Women, nonsmokers, and Chinese patients higher incidence
  - Resolves 1-3 wks post stopping
- Angioedema: 1 to 7/1,000 pts. African Americans at higher risk. Can occur even after being on drug for years. (mean onset 1.8 y)
  - 1/3 of all cases presenting to ER for angioedema
  - Head and neck, less common: GI tract
  - Mediated by bradykinin\(^1\)
  - Angiotensin II receptor blockers ok, < 10% of patients experience persistent angioedema when switched\(^2\)
  - Management: stop medication, management of airway (antihistamines not helpful) severe cases: FFP

Radiocontrast Media (RCM)

• Anaphylactoid reaction (non-IgE mediated anaphylaxis)
  – 1%-3% ionic RCM studies <0.5% non-ionic RCM studies
  – Fatality rate 1 to 2 per 100,000 procedures

• Risk Factors: female, asthma, hx of prior anaphylactoid reaction (6-10x), beta blocker use, & cardiovascular conditions.

• Not associated with shellfish allergy

• European study: suggested skin testing helpful in some patients not yet confirmed in larger trials\(^1\)

Brockow K et al. Skin testing in patients with hypersensitivity reactions to iodinated contrast media- a European Multicenter Study. Allergy 2009; 64: 234—41.
RCM continued…

- Pretreatment: prednisone 50mg 18, 12 and 6 h before (13, 7 and 1 h)
- Diphenhydramine 50mg IM 1 hour before
- No use of H2-blockers (assoc with ↑ rate of RCM reactions)
- Delayed Reactions: >1h to 1 week 2% of patients pretreatment typically does not work.
- Occ case reports of SJS and TEN
- **Gadolinium**: much less common cause of reactions
  Nephrogenic systemic fibrosis if with renal insufficiency²

Case #2: 45 yo woman with a pustular rash

- 2 d h/o acute-onset, mildly pruritic rash.
- Started in axillae and groin now more generalized
- New onset fever this AM
- Dxd with PNA 4 days prior on azithromycin
- PMH: unremarkable, no personal or FH of psoriasis or drug allergy.
- Non-smoker with 2 young children at home and is a school teacher.
- PE: 102.0° F (38.9° C) p 88 bpm BP 124/76 RR 16
- Fine crackles base of left lung
- Skin Exam: hundreds of nonfollicular pustules on erythematous bases, all over body including face. No crust or scale. No lesions on palms, soles, mucous membranes
This 46-year-old woman developed generalized erythema, most severe on the proximal extremities and trunk, several hours after receiving parenteral normal saline with iron, amin acids, and cobalamin at a medical clinic. Numerous confluent pustules superimposed on the erythematous edematous confluent plaques followed one day later. Although she was afebrile, leukocytosis (18,000/cubic mm) and elevated CRP were noted. A bacterial culture from the pustules was negative. A skin biopsy showed intracorneal pustules with numerous neutrophils and neutrophilic infiltration of the epidermis and upper dermis.

Copyright © Vincent C.B. Lin, MD, Dermatlas; http://www.dermatlas.org
Case 2. Acute Generalized Exanthematous Pustulosis

- Elevated WBC with increased PMNs, can see slight elevation of eos.
- Elevated CRP and ESR
- Culture and Gram Stain of lesions: negative
- Punch Biopsy: spongiform subcorneal pustules, edema of papillary dermis, marked perivascular infiltration of neutrophils, rare eosinophil
AGEP

- Most commonly assoc. with drugs: beta lactams and macrolides (not sulfonamides), mercury, NSAIDs, carbamazepine, acetaminophen
- Infectious assoc: enteroviruses and parvovirus B19
- Acute onset of reaction (can be within hours to days) first edematous erythema followed quickly by appearance of pustules
- Benign disease with self-limited course, pustules resolve spontaneously 4-10 d, usually just need mild supportive care, emollients and topical CCS.
DRESS (Drug-Related Eosinophilia with Systemic Symptoms)

- Synonym: drug (or anticonvulsant) hypersensitivity syndrome
- Causes: anticonvulsants, dapsone, minocycline, sulfamethoxazole, sulfasalazine, allopurinol
- Severe systemic disease: lymphadenopathy, fever, skin eruptions, eosinophilia in >90%, fatal in 10%
- Activated T cells in circulation
- Inherited deficiency of epoxide hydrolase
Clinical Evaluation and Diagnosis of Drug Hypersensitivity

- **History**
  - Current and past drug use
  - Known toxicity/allergenicity of drugs used
  - Interval between drug therapy and reaction

- **General physical exam**

- **General lab studies**: e.g. CBC, liver, renal studies

- **Drug specific immunologic testing**
  - Immediate-type skin testing
  - Patch testing
  - Lymphocyte proliferation assays
Management and Prevention of Drug Hypersensitivity Reactions

- Anaphylaxis: epinephrine, adjunctive agents
- Stop suspect drugs
- Antihistamines
- Glucocorticosteroids
- Induction of tolerance (desensitization) when drug essential
- Slower graded challenge regimens
- Prevention of allergic reactions:
  - Take drug allergy history, avoid cross-reactive drugs
  - Use predictive skin tests when appropriate
  - Proper and prudent drug prescribing
  - Use oral in preference to parenteral drugs