ALLERGY FOR THE DERMATOLOGIST PART II

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DISCLOSURES

• Astra Zeneca
• Pfizer
• Sanofi Genzyme
• Regeneron
ALLERGIC DISEASE STATES DERMATOLOGISTS CAN ENCOUNTER

• Urticaria – presented in an earlier lecture
• Angioedema
• Drug Allergy
• Insect Allergy
• Atopic Dermatitis
• Contact Dermatitis – patch testing is the gold standard for testing and given dermatologist’s familiarity of this disease, will not address here
ANGIOEDEMA

Adapted from Janjua at DermnetNZ.png
ANGIOEDEMA

• Manifests as bouts of asymmetric nondependent swelling involving cutaneous or mucosal surfaces
• Typically is not pruritic
• Usually mast cell–mediated, often seen with urticaria
• Many of the same treatments and principles apply as with urticaria, so will defer to lecture on urticaria
• Hereditary angioedema and bradykinin angioedema are other types of isolated angioedema independent of urticaria. Will not be covered here
DRUG ALLERGY (1/2)

Moriilliform drug rash from antibiotics

Adapted from www.dermnetnz.org/topics/cutaneous-adverse-reactions-to-antibiotics
DRUG RASH (2/2)

Urticaria from antibiotics

Adapted from www.dermnetnz.org/topics/cutaneous-adverse-reactions-to-antibiotics
<table>
<thead>
<tr>
<th>Drug Reaction</th>
<th>Examples</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>TYPE A: REACTIONS OCCURRING IN MOST NORMAL PATIENTS GIVEN SUFFICIENT DOSE AND DURATION OF THERAPY</strong></td>
<td></td>
</tr>
<tr>
<td>Overdose</td>
<td>Hepatic failure (acetaminophen)</td>
</tr>
<tr>
<td>Side effects</td>
<td>Nausea, headache (with methylxanthines)</td>
</tr>
<tr>
<td>Secondary or indirect effects</td>
<td>GI bacterial alteration after antibiotics</td>
</tr>
<tr>
<td>Drug interactions</td>
<td>Erythromycin increasing theophylline/digoxin blood levels</td>
</tr>
<tr>
<td><strong>TYPE B: DRUG HYPERSENSITIVITY REACTIONS RESTRICTED TO A SMALL SUBSET OF THE GENERAL POPULATION</strong></td>
<td></td>
</tr>
<tr>
<td>Intolerance *</td>
<td>Tinnitus after a single aspirin tablet</td>
</tr>
<tr>
<td>Idiosyncrasy † (pharmacogenetics)</td>
<td>G6PD deficiency: anemia after antioxidant drugs</td>
</tr>
<tr>
<td>Immunologic drug reactions (allergy)</td>
<td>Anaphylaxis from β-lactam antibiotics</td>
</tr>
</tbody>
</table>

GL, Gastrointestinal; G6PD, glucose-6-phosphate dehydrogenase.
* Side effects at subtherapeutic doses.
† Drug effect not attributable to known pharmacologic properties of drug and not immune mediated.
Adapted from Celik GE; Pichler WJ, Adkinson NF. Middle's Principles of Allergy and Immunology 1
DRUG ALLERGY – WHO DEFINITION

• World Allergy Organization recommends:
  • Use of the terms *immediate* and *delayed* to refer to the onset of symptoms
  • Within or later than 1 hour after dosing
  • These are helpful in distinguishing whether the probable immunologic mechanism is antibody mediated (e.g., immunoglobulin E or T lymphocyte mediated)\(^1\)

\(^1\)Johansson SG, Bieber T et al. J Allergy Clin Immunology. 2003
DRUG REACTIONS - INCIDENCE

• ADRs (adverse drug reactions) affect 10% to 20% of hospitalized patients and up to 25% of outpatients\(^1\)

• Most are type A reactions

• Type B reactions are much less common, with an estimated frequency of 10% to 15% of all ADRs

• Immune-mediated drug reactions may constitute 6% to 10% of ADRs

\(^1\)Gomes ER, and Demoly P. Curr Opin Allergy Clin Immunol 2005
DRUG REACTIONS – MOST COMMON CAUSES

• The most common drugs causing hypersensitivity reactions: β-lactam antibiotics and nonsteroidal antiinflammatory drugs (NSAIDs)\(^1\)

• Others common causes: radiocontrast media, neuromuscular blocking agents, and antiepileptic drugs

Most common cutaneous eruption is a generalized maculopapular exanthem which accounts for up to 90% of all cutaneous eruptions caused by drugs 1,2,3

Most severe reactions are Stevens–Johnson syndrome and toxic epidermal necrolysis

In diagnosing drug allergy, the history is very important

Diagnosis of drug allergy is largely based on clinical history because diagnostic tests are limited

1 Stern RS. N Engl J Med 2012
2 Khan DA, Solensky R. J Allergy Clin Immunol 2010
3 Abrams EM, Khan DA. Diagnosing and managing Drug Allergy. 2018
STEVEN JOHNSON’S SYNDROME/TOXIC EPIDERMAL NECROLYSIS

[Image]

ww.dermnetnz.org/topics/stevens-johnson-syndrome-toxic-epidermal-necrolysis/
Penicillins, cephalosporins, and carbapenems share a bicyclic nucleus which conveys an appreciable but variable immunologic cross-reactivity in immune responses to these drugs.

Cephalosporins are similar to penicillins immunochemically, but individual immune responses vary greatly.\textsuperscript{1}

\textsuperscript{1}Torres MJ, and Blanca M. Med Clin North Am 2010
ANTIBIOTIC DRUGS THAT CROSS REACT (2/3)

• Third-generation cephalosporins (e.g., ceftazidime) appear less likely to have cross-reactivity responses than first-generation cephalosporins (e.g., cephalothin)¹

• Carbapenems have a similar degree of cross-reactivity by skin testing to 1st generation cephalosporins² but studies have consistently shown that penems are well tolerated clinically

¹Romano A, Gaeta F et al. J Allergy Clin Immunol 2010
ANTIBIOTIC DRUGS THAT CROSS REACT (3/3)

• The monobactam class (aztreonam) very weakly cross-reactive with other β-lactams

• Aromatic sulfonamides, often with antimicrobial activity (i.e., sulfamethoxazole, sulfadiazine, sulfisoxazole, and sulfacetamide), differ from other sulfonamide-containing medications. Based on chemical structure, cross-reactivity between these two groups of sulfonamides is considered unlikely, and studies have indicated this is rare.

1Hernstreet BA, and Page RL. Pharmacotherapy 2006
ONE MEDICATION CAN HAVE MULTIPLE TYPES OF REACTIONS – GELL AND COOMBS - PENICILLIN

<table>
<thead>
<tr>
<th>Gell-Coombs Classification</th>
<th>Mechanism</th>
<th>Examples of Adverse Penicillin Reactions</th>
</tr>
</thead>
</table>
| I                          | Anaphylactic (IgE-mediated)              | • Acute anaphylaxis  
• Urticaria                                                          |
| II                         | Complement-dependent cytolysis (IgG/IgM)  | • Hemolytic anemias  
• Thrombocytopenia                                              |
| III                        | Immune complex damage                    | • Serum sickness  
• Drug fever  
• Some cutaneous eruptions and vasculitis                          |
| IV                         | Delayed or cellular hypersensitivity     | • Contact dermatitis  
• Morbilliform eruptions  
• SJS/TEN  
• Hepatitis                                                          |

Immunopathologic Penicillin Reactions
• *Ig*, Immunoglobulin; SJS, Stevens-Johnson syndrome; TEN, toxic epidermal necrolysis

*Adapted from Celik GE; Pichler WJ et al.. Middle’s Principles of Allergy and Immunology*
PENICILLIN ALLERGY

• + PCN skin test results do not occur more frequently for atopic individuals\(^1\)

• ~10% of the US population reported allergies to penicillin

• Clinically significant IgE-mediated or T lymphocyte-mediated penicillin hypersensitivity rates are <5%

• IgE-mediated penicillin allergy wanes over time, with 80% of patients becoming tolerant after a decade\(^2\)

\(^1\)Adkinson NF: J Allergy Clin Immunol 1984
\(^2\)Shenoy ES, Macy E. JAMA. 2019
PENICILLIN AND CEPHALOSPORINS

• An oral challenge with amoxicillin in patients with low-risk penicillin allergy histories: optimal method to confirm current tolerance

• Clinically significant immunologically mediated penicillin-cephalosporin cross-reactivity is rare

• May still avoid using a b-lactam with a shared side chain in an individual with proven IgE-mediated b-lactam-associated anaphylaxis (Ex: avoiding ceftriaxone in someone with cefepime anaphylaxis; or avoiding cefotaxime in someone with history of cefuroxime anaphylaxis)¹

¹Macy E., Vyles D. Ann Allergy Asthma Immunol. 2018
ALLERGY TO CORTICOSTEROIDS

• Allergic reactions to corticosteroids: rare, testing complicated by the need to test for excipients too
  • Li et al reported on a study of 64 patients - evaluated through skin tests and drug provocation testing – only 9 (14%) were allergic, most cases due to an excipient\(^1,2\)
    • In all cases confirmed sensitive to methylprednisolone, due to the excipient polyethylene glycol.
    • In at least 2 cases positive to triamcinolone, due to carboxymethylcellulose

\(^1\)Schatz M. Sicherer S et al. J Allergy Clin Immunol Pract. 2018
LOCAL ANESTHETICS (1/2)

• Local anesthetic agents are relatively good sensitizers when applied topically (i.e., contact allergy)\(^1\)

• Antibody-mediated allergic reactions to these agents are rare events\(^2,3,4\)

• Nonallergic responses to local anesthetics, particularly in dentistry, often lead to allergy consultations

LOCAL ANESTHETICS CONTINUED (2/2)

• Vasovagal syncope may mimic anaphylaxis - dental settings.
  • Paresthesias and lightheadedness can be explained on the basis of the pharmacologic toxicity of the “caines,” and the symptoms are more common in drug-intolerant patients¹

• Episodes of anxiety or panic associated with a procedure contribute to some reactions

• IgE responses to local anesthetics are rare²

• Intradermal skin testing followed by a series of provocative dose challenges is the recommended approach to diagnosis and management²,³

¹Ring J, Franz R et al. Chem Immunol Allergy 2010
CONTACT ALLERGY TO ANESTHETIC

Adapted from www.dermnetnz.org/topic/allergy-to-bezocaine
## NSAIDS

<table>
<thead>
<tr>
<th>Timing of reaction</th>
<th>Clinical manifestations</th>
<th>Type of reactions</th>
<th>Underlying Disease</th>
<th>Putative mechanism</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acute (immediate to several hours after exposure)</td>
<td>Rhinitis/asthma (AERD)</td>
<td>Cross-reactive</td>
<td>Asthma/rhinosinusitis</td>
<td>Cox-1 inhibition</td>
</tr>
<tr>
<td></td>
<td>Urticaria/angioedema (AECD)</td>
<td>Cross-reactive</td>
<td>Chronic urticaria</td>
<td>Unknown-probably cox inhibition</td>
</tr>
<tr>
<td></td>
<td>Urticaria/angioedema</td>
<td>Multiple NSAID-induced</td>
<td>No underlying chronic diseases</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Urticaria/angioedema/anaphylaxis</td>
<td>Single drug induced</td>
<td>Atopy</td>
<td>IgE mediated</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Food Allergy</td>
<td></td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>Drug allergy</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Various organs involved</td>
<td></td>
<td>Usually none</td>
<td></td>
</tr>
</tbody>
</table>

| Delayed-type (more than 24 hours after exposure) | Various organs involved | | |
| | | | Type IV delayed-type Cytotoxic T cells, NK cells, other |

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LIP ANGIOEDEMA FROM DICLOFENAC IN A WITH CHRONIC SPONTANEOUS URTICARIA AND ANGIOEDEMA

Adapted from Park HS, Kowalski ML, et al. Middleton: Principles and practice. 2013
NONSTEROIDAL ANTIINFLAMMATORY DRUGS (NSAIDS)

• Up to 35% of patients with chronic spontaneous urticaria (CSU) experience exacerbation of skin symptoms when exposed to ASA/NSAIDs. The term AECD (aspirin exacerbated cutaneous disease) has been recently proposed for this condition.

• Urticaria and angioedema appear ~ 1 to 4 hours of drug ingestion, although late reactions occurring up to 24 hours after can occur.
NSAIDS

• Delayed or non-immediate reactions involving the skin and other organs develop more than 6 hours after drug ingestion.
  • Symptoms usually emerge several days to weeks after initiation of a new drug; but they can develop earlier when induced by reintroduction of the drug.
  • The recovery period lasts from several days to weeks.
NSAID INDUCED MACULOPAPULAR EXANTHEM

Adapted from Park HS, Kowalski ML, et al. Middleton: Principles and practice. 2013
• Immediate-type skin testing has been usefully applied to β-lactam antibiotics and a variety of other immunogenic drugs, but the rate of clinically false-negative test results is well established only for penicillins\textsuperscript{1,2}

• Although a positive cephalosporin skin test result implies the presence of drug-specific IgE antibodies, a negative result does not exclude immediate hypersensitivity\textsuperscript{3,4}

\textsuperscript{1}Kränke B, and Aberer W. Immunol Allergy Clin North Am 2009
\textsuperscript{2}Salkind AR, Cuddy PG et al. JAMA 2001
\textsuperscript{3}Antunez C, Blanca-Lopez N et al. J Allergy Clin Immunol 2006
\textsuperscript{4}Romano A, Gueant-Rodriguez RM et al. Clin Exp Allergy 2005
DRUG ALLERGY TESTING (2/3)

• + results for intradermal skin tests have been reported for imipenem and other β-lactams, but validated skin testing protocols are not available.

• Sulfonamidoyl poly- l -tyrosine, a synthetic multivalent sulfonamide antigen, has been shown to elicit positive type I skin test results in a few patients with sulfonamide allergy by history.1,2

1Macy E. J Allergy Clin Immunol 1995
• Only with penicillin allergy have in vitro test results been systematically compared with those of skin tests¹

• Potential IgE-mediated reaction -> validated skin testing reagents exist only for penicillin and not for any of the other low-molecular-weight drugs²,³

• Immunoassays for documenting IgE antibodies to quinolone antibiotics, rocuronium, and other drugs have been reported, but their validity is unknown⁴,⁵

³Joint Task Force on Practice Parameters; AAAAI; ACAAI; Ann Allergy Asthma Immunol 2010
INSECT BITES

Adapted from www.dermnetnz.org/topics/insect-bite-images/
INSECT BITES

• Few credible reports of allergic reactions to biting insects
• Sensitization to salivary proteins from insects can cause abnormal local swelling following insect bites
• Anaphylaxis is rarely reported with insect bites\(^1\)

• Registry at the American Academy of Allergy and Immunology:
  • Only a small number of cases with a convincing history of systemic reactions and detectable allergen-specific IgE antibodies were found

\(^{1}\text{Golden DBK: Insect allergy. Middleton's allergy: principles and practice 2003}\)
CULICOIDAE (MOSQUITO)

• Few cases of anaphylaxis have been reported

• There has also been increased recognition of the clinical impact of large local reactions to mosquito bites in children (i.e., Skeeter syndrome)

• Mosquito extracts commercially available are of unreliable composition and activity, not useful

¹Peng Z, Ho MK, Li C, and Simons FE. Ann Allergy Asthma Immunol 2004
MOSQUITO REACTIONS

- Current research is looking at the major allergens in mosquito extracts, they have also looked at recombinant allergens.
- Natural desensitization may occur with frequent and numerous bites\(^1\).
- Treatment with second-generation antihistamines can be used to prevent and treat reactions to mosquito bites\(^2\).

\(^1\)Peng Z, Ho MK et al. Ann Allergy Asthma Immunol 2004
Left: Delayed local reactions 56 hours after mosquito bites in a 5-year-old child. Note the small central papules (1 × 2 mm with surrounding erythema (8 × 10 mm). Right: delayed (60 hours) large local reaction with vesicular center (10 × 10 mm) with surrounding erythema (50 × 50 mm) in a 4-year-old child.

Adapted from Crisp HC, Johnson KS. Annals of Allergy, Asthma & Immunology 2013.
TRIATOMA (KISSING BUG, CONE-NOSE BUG)

- Most common confirmed cause of systemic reactions to insect bites is the kissing bug\(^1\)
- Found throughout the areas of the southwest states and California
- Feed exclusively by sucking the blood of vertebrate animals, may find shelter in homes at night
- Bite causes an erythematous plaque, but because it is painless, the person may be unaware of the cause of an allergic reaction
- Immunotherapy had success in a small group of patients\(^2\)

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OTHER INSECT BITES

• Tabanidae (Horsefly, Deerfly)
  • Tabanid species are large flies that suck blood and inflict painful bites.
  • Widespread distribution in rural and suburban areas.
  • Affects humans and animals.
  • Allergic reactions to insect bites from horseflies and deerflies have been reported.
• Allergic reactions to other insects – usually large local reactions, rarely anaphylaxis, for example with black flies
• Flea bites unusual in humans, more in pets. Reactions, usually papular urticaria, above the ankle and can last for weeks, sometimes months
VENOM ALLERGY

Adapted from Golden DBK: In Adkinson NF, Yunginger JW, and Busse WW (eds): Middleton's allergy: principles and practice. 2003
VENOM STINGS

• Types of venom – paper wasp (Polistes spp.), honeybee (Apis mellifera), yellow jacket (Vespula spp.), white faced hornet (Dolichovespula maculata), yellow hornet (Dolichovespula arenaria)

• Anaphylaxis to insect stings occurs in 3% of adults and 1% of children, and even the first reaction can be fatal\(^1\)

• Cutaneous-systemic reactions are most common in children

• Hypotensive shock is most common in adults

• Respiratory complaints occur equally in all age groups.

\(^1\)Golden DBK: Insect allergy. In Adkinson NF, Yunginger JW, and Busse WW. Middleton's allergy: principles and practice. 2003
VENOM – HONEY BEE

VENOM STINGS (1/3)

• Chance of a systemic reaction to a sting is low in those with large local reaction and in children with mild (cutaneous) systemic reactions; in adults it varies from 25% to 70% depending on the severity of previous systemic sting reactions.

• Venom skin tests are most accurate for diagnosis, but the specific IgE test can be an important complementary test.
  
  • Degree of sensitivity on skin or serum tests does not predict the severity of a sting reaction. History is important because venom sensitization can be detected in up to 25% of adults.
VENOM STINGS (2/3)

• Venom immunotherapy is 75% to 98% effective in preventing sting anaphylaxis

• Large local reactions are not usually a precursor of systemic reactions. The risk of eventual anaphylaxis in those with large local reactions is only 5% to 10%.

• Prevalence rates are up to 3.3% in the United States.

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VENOM STINGS (3/3)

• Indication for Venom Immunotherapy (VIT):
  • History of previous systemic allergic reaction to a sting AND evidence of venom-specific IgE antibodies with a + venom skin test result or increased specific IgE level.
  • Some patients with + skin test results do not require VIT because they are judged to be at relatively low risk for anaphylaxis.
  • Those with recent and severe anaphylaxis are at highest risk (40% to 70%)
  • Low risk (<10%) has been found for children and adults with a history of large local reactions\(^1,2\) and for children with reactions limited to cutaneous signs and symptoms but with no respiratory or vascular manifestations\(^3\)

\(^3\)Hoffman DR:. In Levine MI, and Lockey RF (eds): Monograph on insect allergy, 4th ed. AAAAI. 2003
VENOM STING IMAGES

Left: wasp sting. Right: bee sting

adapted from https://www/dermnetnz.org/
FIRE ANTS

• Anaphylaxis to fire ants has been reported
• Currently there is no standardized IT for fire ants
• Although has been reported to be effective, there have been no trials with placebo controls\textsuperscript{1}

\textsuperscript{1}Eberlein B et al. J Allergy Clin Immunol 2012
ATOPIC DERMATITIS AND ALLERGIC TRIGGERS

Adapted from www.dermnetnz.org/topics/atopic-dermatitis/
• Patients with AD and + food allergen skin tests could have negative food challenges to the implicated allergen, this distinguishes between symptomatic and asymptomatic hypersensitivity

• Triggers for clinical disease cannot be predicted by testing alone

• Double-blind placebo-controlled food challenges have demonstrated that food allergens can cause exacerbations in a subset of patients with AD

¹Sampson HA, and McCaskill CC. J Pediatr 1985
ATOPIC DERMATITIS AND FOODS (2/4)

• About 1/3 of infants and young children with AD will show clinically relevant reactivity to a food allergen\(^1\)

• Lesion induced by single + challenges are usually transient

• Repeated challenges can result in eczematous lesions.

• Food-specific T cells have been cloned from lesional skin and peripheral blood of patients with AD\(^2,3\)

• Elimination of food allergens results in amelioration of skin disease and a decrease in spontaneous basophil histamine release\(^4\)

• Food allergy testing usually done more for an immediate type reaction

• In AD that is resistant, if food is being considered a trigger, a limited panel of foods may be tested

• An avoidance diet:
  • Indicated in patients clearly identified as food allergic by an appropriate diagnostic food challenge
  • After adequately informing the family of the limited benefits, and possible harms of an elimination diet

1Eigenmann PA, Beyer K et al.. Pediatr Allergy Immunol. 2019
• Food-avoidance can improve AD but does not cure it\(^1\)
  • It can have detrimental effects:
    • Progression to an immediate type reaction
    • May reduce the quality-of-life of the patient and the family.

\(^1\)Eigenmann PA, Beyer K, Lack G, Ong PY, Sicherer SH, Sampson HA. Pediatr Allergy Immunol. 2019
ATOPIC DERMATITIS

ATOPIC DERMATITIS AND AEROALLERGENS (1/3)

• Evidence supports a role for aeroallergens in AD. These findings include both allergen-specific IgE antibodies and allergen-specific T cells

• Exacerbation of AD can occur with house-dust mites, animal danders, and pollens.

• It has been estimated that as many as a third of AD patients with HDM hypersensitivity experience worsening of AD or respiratory symptoms with dust exposure

In DBRPCT, a subgroup of patients with AD underwent bronchoprovocation with a standardized house-dust mite extract. They developed unequivocal cutaneous lesions after inhalation of dust mite.

All the patients with dust mite–induced atopic dermatitis had a history of asthma, so it’s possible the respiratory route may be important in the induction and exacerbation of AD.

ATOPIC DERMATITIS AND AEROALLERGENS (3/3)

• Direct contact with inhaled allergens can also result in eczema lesions\(^1\)

• Using the atopy patch test, Langeveld-Wildschut and coworkers\(^2\) showed that positive reactions to house-dust mite were associated with IgE ² Langerhans cells in the epidermis of AD patients.

• The severity of AD has been correlated with the degree of sensitization to aeroallergens\(^3\)

• Environmental control measures aimed at reducing dust mite allergen have shown clinical improvement in AD patients\(^4\)

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SUMMARY

• Drug allergy – we do not have very good testing. Best testing we have is for Penicillin. The most important diagnostic tool we have is the history

• Insect allergy – usually localized

• Venom allergy – usually when it is a systemic reaction, immunotherapy has a good outcome in reducing the recurrence of another systemic event. Localized reactions do not predict systemic reactions

• Atopic dermatitis – although airborne allergens as well as food sensitization can be involved, need to be careful about what we remove from patient’s diets