Drug, Food Allergies and Anaphylaxis:

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Prevalence: Adverse Drug Reactions (ADR)

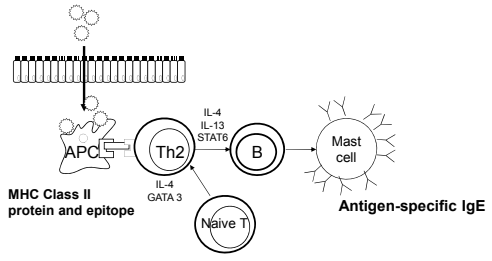
- ADR hospital admission rate:
  - children: 4.1% (IQR 0.16-5.3%)
  - adults: 6.3% (IQR 3.9-9.0%)
  - elderly: 10.7% (IQR 9.6-13.3%)
- Allergic reactions make up a minority (6-10%) of all adverse reactions
- Higher rates if study employs multiple ADR detection methods, such as medical record review and patient interview
- Risk in general population: ≈1-3%/drug

Kongkaew et al. Ann Pharmacother. 2008 Jul 1.

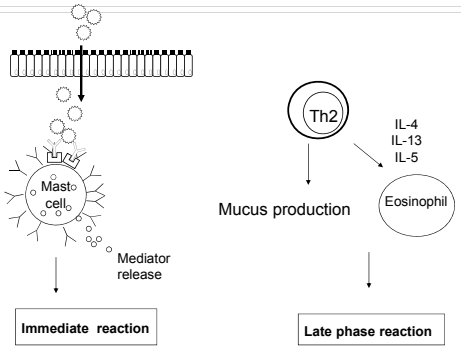
Coombs and Gell Classification

Classification	Immune Mechanism	Clinical Manifest.
Type I	Mast cell-mediated immediate generalized reactions IgE-dependent (anaphylactic) IgE-independent (anaphylactoid)	Anaphylaxis, urticaria, angioedema, asthma, rhinitis
Type II	Ab-mediated cytotoxic reactions IgG or IgM antibodies Complement often involved	Immune cytopenias Some types of organ inflammation
Type III	Immune complex-mediated rxns. Complement involved	Serum sickness Vasculitis
Type IV	T cell-mediated ($CD4^+$ cells) Lymphokines involved DTH	Contact dermatitis Some exanthems Some organ inflammation

Immunological Mechanisms: Allergic Sensitization



Immunological Mechanisms: Reexposure



IgE-Dpdt Release of Inflammatory Mediators

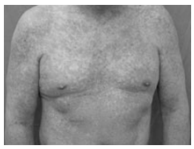
- Immediate Release: Granule contents
  - Histamine
  - TNF-α
  - Proteases
  - Heparin
- Over Minutes: Lipid mediators
  - Prostaglandins
  - Leukotrienes
- Over Hours: Cytokine production
  - IL-4
  - IL-13

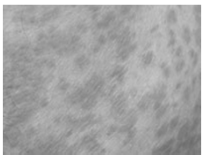
Drugs as Immunogens

- Low MW substances (<4 KD)-poor immunogens
  - Eg. PCN, cisplatin
  - Linked to larger macromolecule to elicit immune response
    - usually covalently
    - thereby facilitates antigen processing/presentation
- High MW substances
  - Multiple epitopes
  - Direct binding of drugs to TCR and MHC-peptide interaction
  - Eg. L-asparaginase and murine OKT3

Dermatologic Drug Reactions

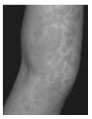
- Morbilliform/maculopap. rash: most common
  - usually appears <1 wk of starting drug
  - begins on trunk and pressure areas; symmetric spread





Dermatologic Drug Reactions

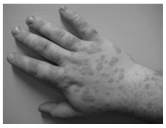
- Urticaria/Angioedema: 2nd most common
  - immediate IgE mediated
  - late appearing serum sickness-like reaction



•"Hypersensitivity Syndrome"
morbill. rash, fever, arthralgias, hepatitis
late onset (wks)
implicated: anti-convulsants, sulfas, allopurinol

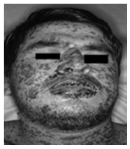
Erythema Multiforme

- Erythema multiforme (EM minor)
  - symmetric erythematous eruptions hands/feet ("target" lesions)
  - minimal mucous membrane involvement
  - minimal constitutional symptoms
  - self-limiting: resolves in 2-4 wks.
  - Precipitated by infection: HSV



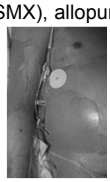
Stevens-Johnson Syndrome

- Mucous membrane ulceration, extensive truncal involvement, fever, H/A, malaise
- May involve epithelium of respiratory and GI tracts
- Pathology
  - Ig/C3 deposition
  - activated $CD8^+$ T cells invading vessel walls
- Implicated: sulfas, anticonvulsants, PCN

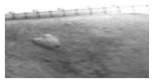


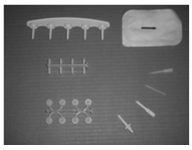
Toxic Epidermal Necrolysis

- Pathology
  - Massive keratinocyte necrosis
  - Cleavage at basal layer of epidermis (loss of entire epidermis)
- Onset extensive (≥30% surface area), explosive: over 1-3 days
- Implicated: sulfas (esp. TMP/SMX), allopurinol, anticonvulsants, NSAIDs



Diagnostic Allergy Testing





Diagnosis of Drug Allergy

- Hx
  - correlate symptoms with timing of agents administered/withdrawn
  - Time of onset:
    - most btw 1-4 wk. of initiation
    - sooner if previously sensitized
- Lab tests:
  - Contact sensitivity: patch testing
  - HA:
    - Coombs test
    - drug-specific IgG/IgM tests if avail.
  - Anaphylaxis: β–tryptase
  - Type III (serum sickness-like): C3, C4, CH50

Drug Allergy Testing

- Skin testing: Has limits
  - validated for relatively few agents: eg. PCN's
  - immune response may be to unknown drug or metabolite
  - non-specific irritant effect or mast cell degranulation
    - false positives
    - Eg: morphine, vancomycin
- Drug challenge
  - oral or parenteral incremental dosing starting at 0.1-10% dose (depending on severity of reaction)
  - can raise dose raised 5-10 fold in intervals
- Contraindicated in SJS, TEN, immune cytopenia

Variables That Affect Skin Test Results

Controllable

- Medications:
  - H1 antihistamines
  - H2 antihistamines
  - Antidepressants
  - Corticosteroids
- Immunotherapy
- Relation to adjacent positive reactions
- Extract quality
- Skin testing devices

Uncontrollable

- Chronobiology:
  - Diurnal
  - Seasonal
- Menstrual Cycle
- Age:
  - Specific IgE
  - Histamine reactivity
- Location on body:
  - Variations on back
  - Back vs. forearm

β-Lactam Allergy

- 10-20% of hospitalized patients claim history of previous reaction
- True PCN allergy 0.3-3%
- Classes of reaction:
  - IgE-mediated: urticaria, anaphylaxis
  - Non-IgE-mediated: maculopapular/morbilliform rash, SJS, serum-sickness, drug fever, AIN, vasculitis

Graff-Lonnevig V et. al. *Arch Dis Child. 1998;63:1342–1346*
Surtees SJ et. al. *BMJ. 1991;302:1051–1052*

Case 1

- A patient is suffering from severe sinusitis, and is unable to tolerate quinolones and macrolide antibiotics. He developed urticaria following penicillin approximately 15 years ago. You consider prescribing a second generation cephalosporin. In making your decision, you recall that the cross-reactivity between penicillin and first generation cephalosporin is approximately:

Cross-reactivity between penicillin and first generation cephalosporin is approximately?

1. <<7%
2. 7%
3. 10%
4. 30%

β-Lactam Cross-Reactivity

•**2%** btw PCN skin test pos. pts and 1st/2nd generation cephalosporin (using data **after** 1980)

•For first-generation cephalosporins, the attributable increased risk is 0.4%

•For the AAP-endorsed agents for sinusitis and acute otitis media (cefuroxime, cefpodoxime, and cefdinir), the risk is nearly nil.

•Problems with earlier studies:
- cephalosporins produced <1980 contained trace amts of PCN (via Cephalosporium mold)
- didn't include PCN skin testing

Pediatrics Vol. 115 2005;
Adverse Reactions to Drugs, Biologicals and Latex Committee 5/09

β-Lactam Cross-Reactivity

- 1% btw PCN skin test positive patients and 3-4th gen. cephalosporin
- <45% btw PCN skin test pos patients and carbapenums (Imipenum)
- 1% btw PCN skin test pos pts and monobactams (Aztreonam)

Pichichero, Pediatrics Vol. 115 2005;
Adverse Reactions to Drugs, Biologicals and Latex Committee 5/09

Case 1, continued

- The patient's sinusitis improves nicely on the cephalosporin. But in the process of his evaluation, it is noted that he has a new and elevated RPR titer and you prefer to treat with penicillin. The next course of action is to:

The next course of action is:

1. Reject the idea of prescribing penicillin, and treat with doxycyxline
2. Decide against treating with any antibiotic
3. Refer to an allergist for skin testing to penicillin
4. Refer to an allergist for desensitization to penicillin
5. Test for anti-penicillin antibodies in the sera

Prevalence of Skin Test Pos ("truest") PCN Allergy

- 14% of pts. with history of urticaria to PCN
- 25% of pts. with history of anaphylaxis to PCN
- Reactivity may be lost over time
  - ≈10% per year following exposure
  - 20-30% remain long-term reactors

Desensitization

- Proven Applications:
  - IgE-mediated hypersensitivity to PCN, insulin, heterologous antisera
  - Sensitivity (non-IgE-mediated) to TMP/SMX, ASA, plavix, allopurinol
- Mast cells rendered unresponsive specifically to drug of interest
- Post-desensitization therapy phase
  - drug-specific serum IgE and IgG rise
  - loss of skin-test reactivity
  - Increase in Tregs
- Chronic desensitized state maintained by almost daily drug administration

Drug Fever

- Immune mechanism unclear
- Presentation
  - height of temp. does not distinguish it from infectious source
  - disparity between temp. and clinical appearance a clue?
- Labs:
  - leukocytosis with left shift
  - elev. ESR
  - elev. LFT's
  - +/- eosinophilia
- Diagnosis:
  - fever subsides with drug withdrawal, recurs with reintroduction

Adverse Reactions to Food: Immunologic Spectrum

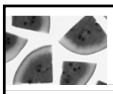
IgE-Mediated ⇨ Non-IgE Mediated

- **Oral allergy syndrome**
- **Anaphylaxis**
- **Urticaria**
- **Eosinophilic esophagitis**
- **Eosinophilic gastritis**
- **Eosinophilic gastroenteritis**
- **Atopic dermatitis**
- **Protein-induced enterocolitis**
- **Protein-induced enteropathy**
- **Eosinophilic proctitis**
- **Dermatitis herpetiformis**

AAAAI Adverse Reactions to Foods Committee

Pathophysiology: Food Allergens

- Proteins
  - 10-70 kD glycoproteins
  - Heat resistant, acid stable
- Major ones (>85% of allergy)
  - Children: milk, egg, soy, wheat
  - Adults: peanut, nuts, shellfish, fish
- Single food > many food allergies



Oral Allergy Syndrome

- Oral pruritus, rapid onset, IgE-mediated, rarely progressive
- Usually fresh fruits and vegetables
- Heat labile: cooked forms, no reaction
- Cross reactivity with pollens

Pollen	Foods
Birch	**Apple, apricot, carrot, cherry, kiwi, plum**
Ragweed	**Banana, cucumber, melon, watermelon**
Grass	**Cherry, peach, potato, tomato**

AAAAI Adverse Reactions to Food Committee

Latex-Fruit Syndrome

- 30-50% of those with latex allergy are sensitive to some fruits due to cross-reactive IgE
- Most common fruits: banana, avocado, kiwi, chestnut; also other fruits and nuts
- Can present as anaphylaxis to fruit
- Warn latex-sensitive patients of potential cross-reactivity
- Some fruit-allergic patients may be at risk for latex allergy

Case 2

- A newborn presents with bloody stools and excessive vomiting of her formula. The pediatrician, who suspects cows milk allergy, should explain:

The pediatrician should explain:

1. Most cows milk allergy remits in later childhood
2. The child is not at greater risk of allergy to any other foods
3. The likelihood of outgrowing cows milk allergy is similar to the likelihood of outgrowing peanut allergy
4. It's the mother's fault because she did not breast feed

Prevalence of Food Allergy

- Perception by public: 20-25%
- Confirmed allergy (oral challenge)
  - Adults: 1-2%
  - Infants/Children: 6-8% (~1/4 million births)
- Dye / preservative allergy (rare)
- Specific Allergens
  - Milk (infants)- 2.5%
  - Peanut / nuts in general population- 1.1%

AAAAI Adverse Reactions to Foods Committee

Natural History of Food Allergy

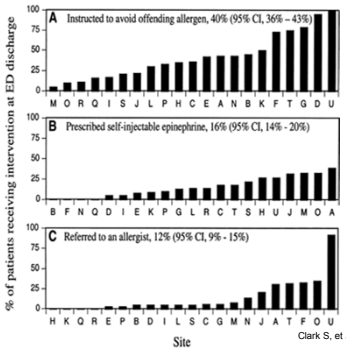
- 50% of children lose their milk hypersensitivity by age 1 year, 70% by age 2 year, 85% by age 3 year
- A negative skin prick test for cows milk by age 1 year has good prognostic value
- Children diagnosed with food allergy after age 3 year most likely will have it persist
- Only approximately 20% (but not 0%) of peanut allergy remits

Food Allergy Practice Parameters vol 96
March 2006

Pan-allergens

- Proteins in food, pollen or plants that possess homologous IgE binding epitopes across species
- Tropomyosins:
  - Important food allergen in crustacea, dust mites, cockroach, mollusks
- Parvalbumins: major fish allergens
- Bovine IgG: beef, lamb, venison, cow's milk
- Lipid transfer protein:
  - fruits (peach, apple), vegetables, peanut, tree nuts
- Profilin: fruits, vegetables
- Chitinases: fruits, wheat, latex

Emergency Department Management of Food Allergy



Clark S, et al. J Allergy Clin Immunol 2004.

First Documented Case of Anaphylaxis

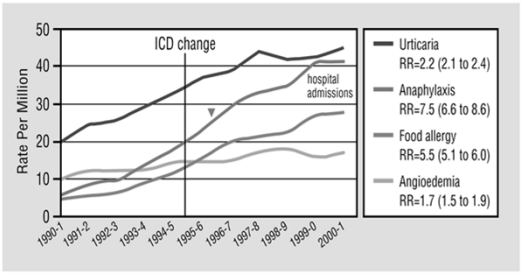
- K. M. (aka King Menes of Egypt)
- Middle aged man, age unknown
- Occupation: King of ancient Egypt
- Date: 2641 B.C.
- Was carrying out his royal duties
- Dropped dead after wasp sting
- Documented via hieroglyphics
- Autopsy: deferred

Susceptible to Misdiagnosis

- Retrospective series; n=19,122 presenting to Mayo Clinic E.R. over 4 months; 17 cases of anaphylaxis diagnosed
- 13/17 (76%) cases were not documented by E.R. physicians
- Most common original diagnosis (and code used) was "allergic reaction" in 9/17 (53%) cases

Klein J.S. Yocum M.W. J. Allergy Clin. Immunol. 1995; 95:637-8

Incidence Continues to Increase (UK)



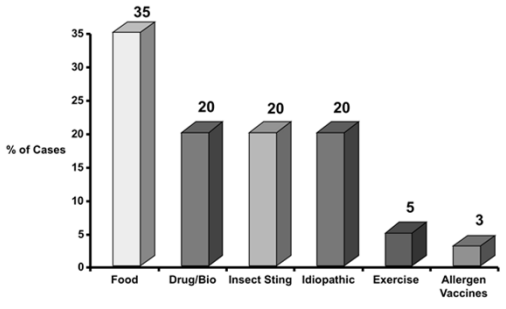
Gupta R et al. BMJ 2003;327:1142

American College of Allergy, Asthma and Immunology Epidemiology of Anaphylaxis Working Group

- Data on anaphylaxis incidence and prevalence:
  - Sparse
  - Often imprecise
  - Based on diverse study designs; not entirely comparable
- Roundtable discussion led to an improved estimation of frequency of anaphylaxis:
  - 50-2000 episodes per 100,000 persons
  - Lifetime prevalence of 0.05% -2.0%

Lieberman, Camargo, Bohlke, Jick, Miller, Sheikh and Simons, Ann. Allergy Asthma Immunol. 2006; 97:596-602

Overview of Anaphylactic Triggers

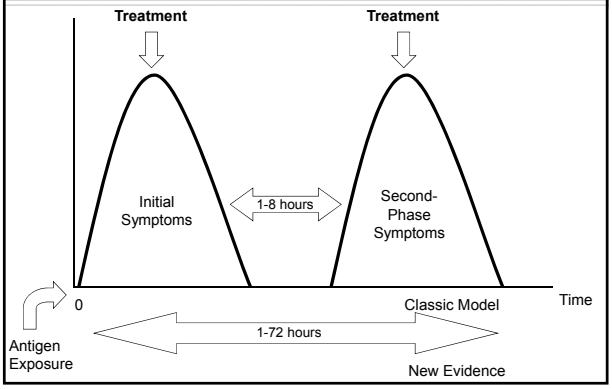


Golden. *Anaphylaxis*, 2004

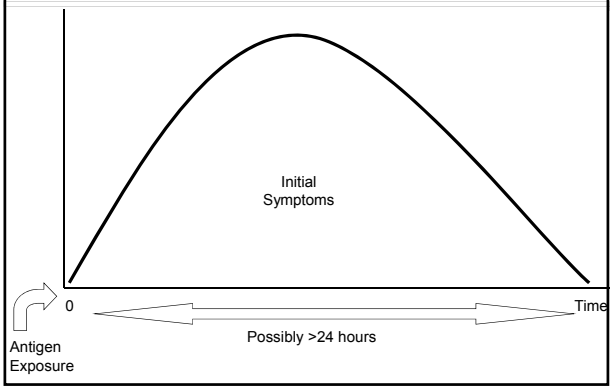
3 Clinical Patterns

1. 50%: acute reaction within minutes of exposure If treated immediately, wont recur
2. 25%: biphasic response:
   - early intestinal or oral symptoms
   - followed 1-2 hours later by respiratory or cardiovascular symptoms
   - at risk of death if discharged from E.R. too soon.
3. 25%: prolonged hypotension and respiratory failure resistant to Rx
   - Must rule out β–blockers

Biphasic Anaphylaxis



Protracted Anaphylaxis



Case 3

- A 7 year old child with peanut allergy and asthma tastes a cookie contaminated with peanuts at a school birthday celebration. He immediately starts wheezing and is escorted to the nurses office. He reminds the school nurse that he has an inhaler in the office. The next course of action is for the nurse to administer:

Next course of action is?

1. solumedrol 50 mg IV
2. glucagon 1-5 mg bolus
3. Epipen Jr
4. albuterol inhaler
5. benadryl 25 mg

Treatment: Must be EARLY and AGGRESSIVE for Everyone!!!!

- Every patient with anaphylaxis should be treated with epinephrine first
  - Old, young, fat, thin, purple
  - INCLUDES those with cardiac disease
  - INCLUDES those on β blockers
  - INCLUDES asthmatics presenting with wheezing (DO NOT GIVE ALBUTEROL 1st)

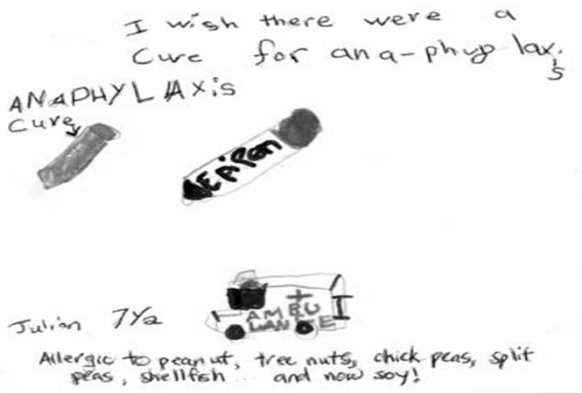
Outdated Epinephrine Loses Efficacy

- As time passes, percent of labeled dose and epinephrine bioavailability are reduced.
- Improper storage and exposure to sunlight and heat increase degradation.
- Degradation often occurs without a color change in the epinephrine solution.

Simons FER et al. J Allergy Clin Immunol 2000;105:1025-30

Treatment (in order of use)

- Epinephrine (1:1000 aq) 0.3-.5 ml IM q 15-20 min
  - inhibits mast cell mediator release
  - reduces target organ response
- Extremity tourniquet
  - extra dose of subcut epinephrine at site
- Volume expanders
- Benadryl or hydroxyzine 50 mg IM or IV
- H2 antagonists
- Solumedrol 50 mg or hydrocortisone 200 mg IV
- Glucagon:1-5 mg IV bolus, 5-15 μg/min
  - consider for idiopathic bradycardia or refractory cases)



http://www.safe4kids.ca/content/art_gallery/art_gallery_dreams.asp