I’m Not Making this Up! - Unusual Allergy/Immunology Conditions You’ve Never Heard Of”

Ronald Ferdman, MD, MEd

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• I do not intend to discuss an unapproved / investigative use of a commercial product / device in my presentation.

Learning Objectives

After completion of this activity, participants will be able to:

• Recognize some of the multiple, widely varied and sometimes rare ways in which allergic and immunologic reactions can manifest

• Integrate the possibility of rare and/or unusual allergic reactions into the differential diagnosis of patients with perplexing clinical presentations
Let’s Get Physical…

• Physical Urticarias
  – Estimates that up to 20-30% of cases of chronic urticaria are due to physical trigger
• Temperature - heat, cold
• Pressure: abrasion, pressure, vibration
• Exercise
• Sunlight
• Water

Dermatographism

• Estimated 2%-5% of population
• “Simple” dermatographism
  – Erythematous wheal after firm stroking of skin
  – Starts within 5-7 min and fades after 15-30 min
  – A “finding” rather than a “disease”
• “Symptomatic” dermatographism
  – Faster onset, longer duration
  – Inciting event oftentimes unperceived
  – Itching may be first symptom, followed by wheal at site of scratching
• Treatment is avoidance of trigger and H1-blocker
Urticaria
Heat & Cold

Some say the world will end in fire,
Some say in ice...
-Robert Frost

A 43-year-old woman presented with a 10-month history of an urticarial rash induced by cold, particularly when she was swimming.

Cold Induced

- Familial (autosomal dominant)
  - Delayed cold urticaria
  - Familial cold autoinflammatory syndrome
- Acquired
  - Positive cold test (“ice cube” test)
    - Primary cold urticaria, secondary due to cryoglobulins, infections, leukocytoclastic vasculitis
  - Atypical or negative cold test
    - Systemic cold urticaria, cold-dependent dermatographism, cold-induced cholinergic urticaria, delayed cold urticaria, localized cold reflex

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Cholinergic Urticaria

- Triggered by rise in core body temperature
  - Sweating
  - High temps, exercise, hot water, spicy foods
  - Emotional factors?
- Estimates that ~15% of population will have at least 1 episode
- Average duration of symptoms 7.5 years

Can You Be Allergic to Yourself?

- Many punctate 1-3 mm wheals with large surrounding flares - may coalesce
  - Typically start on neck/trunk, spread to arms
  - Very itchy
- Often preceded by tingling, itching or burning sensation at site
- Rare angioedema, hypotension, bronchospasm
- Treatment is avoidance of heat, H1 blockers, other agents (danazol, beta-blockers), desensitization with purposeful hot baths

Dice JP . Immunol Allergy Clin NA 2004;24:225
Allergic to Your Own Sweat?

- Patients with cholinergic urticaria
- Collect each patient's sweat
  - Sterilize & freeze at -80°C
- Skin test positive to own sweat
- Histamine release positive


Chronic Idiopathic Urticaria

- Chronic Urticaria
  - Daily (at least 3-5 times a week) for over 6-8 weeks
- Incidence ~ 0.5% of population
- Mean duration of symptoms 3-5 years
  - 50% >6 months, 20% >10 years (adults)
- “Idiopathic” in 80-90% of cases
  - 30-40% of “idiopathic” may be autoimmune


Autologous Serum (Plasma) Skin Test

Step 1:
- Draw patient's blood
Step 2:
- Isolate serum (plasma)
Step 3:
- Allergy skin test patient with his/her own serum (plasma)
Autoimmune Chronic Urticaria

- ~30-40% of patients with chronic “idiopathic” urticaria
  - Not present in healthy controls, or those with non-urticarial skin diseases
- Most are anti-IgE receptor antibodies (anti-FceRI)
- Others reported
  - Anti-IgE antibody
  - Anti-CD63 on basophils

Solar Urticaria

- Urticaria caused by exposure to sunlight
- Very rare
  - ~0.5% of urticaria cases
- Symptom onset 7-11 years old
  - Diagnosis ~17 years old in most
- Persistent for years
  - Natural course uncertain & variable
- On sun-exposed areas of skin only
  - Can occur through thin clothing

Solar Urticaria

- Typical appearing urticaria
  - Occasionally erythema, itching, burning
- Develop within minutes after exposure, resolve in <24 hr after removal from sun
- Rare systemic symptoms with prolonged exposure or large surface area exposure
- Areas frequently exposed to sun become "hardened" and less likely to react
  - More common in skin areas not usually exposed to sun


Solar Urticaria

- Unidentified photoallergen?
- Dx by "phototesting": broad spectrum light source (slide-projector light), or sequential monochromatic light source
  - Can classify based on wavelength triggering sx (“action spectrum”)
    - Not clinically useful
  - Treatment: “avoidance”, H1 blockers, PUVA may give transient relief


Sun Sensitivities
(Photodermatoses)

- Group 1: Immunologically mediated photodermatoses
  - Solar urticaria (4%)
  - Polymorphous light eruption (69%)
  - Chronic actinic keratosis (23%)
  - Actinic prurigo (3%)
  - Hydroa vacciniforme (1%)
- Group 2: Exogenous or endogenous photosensitizer
  - Phototoxic (non-immunologic)
    - Porphyrias
  - Photoallergic (immunologic)

Sun Sensitivities (Photodermatoses)

- Group 3: Genophotodermatosis (genetically determined defect in DNA repair)
  - Xeroderma pigmentosum
  - Trichothiodystrophy (IBIDS syndrome)
  - Rothmund-Thompson syndrome
  - Kindler syndrome
- Group 4: Photoaggravated disorders (occur independent of UV exposure, but worsened or triggered by UV light)
  - Lupus (SLE), rosacea, atopic dermatitis
  - Others

Polymorphous Light Eruption (PMLE)

- Most common photodermatosis
- Up to 10-20% of population
  - Most commonly young females
  - Onset at beginning of the sunny season for locale
  - Severely itchy skin in sun-exposed skin
  - May be papular, papulovesicular, plaque
  - In an individual patient, usual monomorphic
  - "Juvenile spring eruption"- localized variant mostly in boys, classically on ear pinna
  - Hypothesized due to a delayed-type hypersensitivity reaction to UV-converted antigen precursors in skin

Solar Urticaria vs Polymorphous Light Eruption

<table>
<thead>
<tr>
<th></th>
<th>Solar Urticaria</th>
<th>Polymorphous Light Eruption</th>
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</thead>
<tbody>
<tr>
<td><strong>Prevalence</strong></td>
<td>Rare</td>
<td>Common</td>
</tr>
<tr>
<td><strong>Interval between sun exposure and onset rash</strong></td>
<td>Minutes</td>
<td>Hours</td>
</tr>
<tr>
<td><strong>Duration of rash after removal from sun</strong></td>
<td>Hours</td>
<td>Days</td>
</tr>
<tr>
<td><strong>Action spectrum</strong></td>
<td>Visible &gt; UVA or UVB</td>
<td>UVA &gt; UVB or Visible</td>
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</table>
Actinic Prurigo
- Rare, except in Indians of the Americas (up to 3.5% of population)
- Usual onset in childhood, and may remit in early adulthood
- Macules, papules, eczematous plaques on UV-exposed skin (esp. face and nose bridge)
  - May also have cheilitis, conjunctivitis
- Itchy all year round with exacerbations in spring and summer

Hydroa Vacciniforme
- Very rare
- Begins early childhood and remits in late teenage years
- Recurs each spring and summer
- Boys 2x > girls
- Sporadic, deep-seated, sometimes hemorrhagic vesicles on sun-exposed skin, especially face and ears
- Heal with necrosis and varioliform scars and dyspigmentation

Defects in The Heme Synthesis Pathway The Porphyrias
- Metabolic disorders of heme synthesis pathway
- Result in build up of porphyrins
  - Group of lipophilic molecules
  - Some are transformed by light to an excited state
  - Cause photooxidative damage to skin
- There are other, non-photosensitive serious manifestations of these conditions (hepatobiliary, brain, blood, intestinal)

Porphyrias Associated with Photosensitivity
- Erythropoietic protoporphyria
  - AD: ferrochelatase and rarer XL: 5-aminolevulinic acid synthase
  - Rare somatic mutation with adult onset
- Congenital erythropoietic porphyria
  - AR: uroporphyrinogen III synthase
- Porphyrina cutanea tarda
  - AD: uroporphyrinogen III decarboxylase
  - Most common acquired (80%)
- Variegate porphyria
  - AD: protoporphyrinogen III oxidase
- Hereditary coproporphyria
  - AD: coproporphyrinogen III oxidase
- Pseudoporphyria
  - Unknown
Allergic to The Moon?

“Dust is the No. 1 environmental problem on the moon,” said Apollo 17 astronaut Harrison Schmitt, who reported having a severe allergic reaction (“hay fever”) to moon dust during his mission in 1972.

Astronaut Harrison Schmitt collects samples during the Apollo 17 mission to the moon. Lunar dust covers the lower third of his spacesuit.

Exercise-Induced Urticaria

- Exercise, regardless of body temperature
  - Can occur with mild exercise
  - Not always reproducible with same activity
- Within 5-10 minutes of starting exercise
  - Skin may be prodromal phase and may progress to anaphylaxis (angioedema, wheeze/stridor, hypotension, syncope, colic/N/V)
  - Lasts 30 min to 4 hour.
  - Occasionally late phase of HA, fatigue, warmth lasting 24-72 hours

Exercise-Induced Urticaria

- Food independent
- Food dependent (within < 3 hour of eating food)
  - Any food (usually skin test negative to all associated foods - not type I mechanism)
  - Specific food or food combination - usually skin test positive (type I mechanism)
    - Multiple foods described: celery, shellfish, chicken, hazelnut, apples, peaches, grapes, wheat, grain flours, cabbage
- Also reported associated medication use (ASA/NSAID), menstruation

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Exercise-Induced Urticaria

- Not typically familial, associated with atopy in at least 50% of cases
- Mechanism unknown - but elevated serum histamine & tryptase suggest mast cell release
  - Maybe an allergen is released by exercise?
- Treatment
  - Avoid foods or eating (or meds, menstruation) if appropriate
  - Limit intensity, or at least slow down when symptoms start
  - Exercise with a buddy
  - Have epinephrine available
  - Antihistamines may block mild skin, but not anaphylaxis

Aquagenic Urticaria

- Very rare
- Typical onset slightly after puberty
- Familial cases have been reported
- Due to direct skin contact with water (distilled, tap or saline) (irregardless of temperature or pH of water), not other solvents (eg alcohol)
- Occur rapidly w/in 20-30 after contact with water, then fade w/in 30-60 minutes after removal of water from skin

Aquagenic Urticaria

- Refractory period of hours after an attack
- Repeated purposeful exposure leads to exhaustion of wheal response
- Often reported to occur in conjunction with other physical urticarias (dermatographism, cholinergic, cold)
- Unclear pathogenesis - probably water has to penetrate stratum corneum, may solubilize an antigen already in existence in skin?
- Aquagenic Pruritus
  - Just itching upon exposure to water, no urticaria
New Ways to Bug You

Unusual encounters with the animal kingdom

Ear cleaning with grub (don't let go!). Irian Jaya, Indonesia

Man Eating Bugs - The Art and Science of Eating Insects
Peter Menzel and Faith D'Aluisio

Scales of Justice

- Patient presents with 2 months of rhinconjunctivitis symptoms occurring only at home
  - Skin testing for routine indoor allergens negative
- Family had recently obtained a green iguana
- Extracts from scales and urine obtained
- IgE to scales (less so to urine) detected
- Skin test to scales positive (negative in 10 controls)
- Nasal challenge to scales was positive
- Symptoms resolved after removal of iguana from home
- Also case report of allergy to chameleon


Green Iguana

Ergenia cunningami
Big Cockroach Allergy

- Subject reported itchy watery eyes and nose, sneezing and rash after exposure to cockroach
- First, a digression....

Cockroach (CR) in Inner City

- National Cooperative Inner-City Asthma Study
  - Collected dust from children's bedrooms
    - 85% had detectable levels of CR allergen (Bla g 1)
    - 50% had what was considered high levels (>8 U/g)
  - 98% of homes in Gary, IN had detectable CR allergen
  - 56% of homes in New Orleans had high levels of CR allergen
  - 50% of homes in NY & Chicago - Bla g 1 >2 U/g
  - In schools in NY, Detroit, Houston, Birmingham levels of CR allergen exceeded sensitization thresholds
  - Significantly higher levels of CR allergen in inner-city homes compared to urban homes in the same city

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Cockroach (CR) in Inner City

• Exposure to CR allergen is associated with asthma in children
  – Similar data for rodents
• Sensitization is associated with increased:
  – Incidence
  – Symptoms
  – Unscheduled physician visits
  – Emergency department visits
  – Increased hospitalization

Sheehan WJ. J Allergy Clin Immunol 2010;125:575

What is in House Dust?

• Various inert organic particulates
  – Dirt, rocks, sand, ash, wood, etc.
• Various inert inorganic particulates
  – Fibers from clothes, carpets, etc.
• Multiple allergenic organic material
  – Dust mites
  – Fungal elements
  – Pollens and other plant-derived matter
  – Animal dander and hair (cat, dog, etc)
  – Insects - cockroach, cricket, grasshopper, and many others

Not Just Cockroaches...

• Study of allergic asthmatic children from Cincinnati, OH - detected specific insect IgE:
  – 43% to moth
  – 19% to cricket
  – 19% to grasshopper
  – 23% to house fly
• 24/25 controls had no IgE to any insect, and 1/25 had IgE to moth only
Ladybug Lore

In Europe, during the Middle Ages, swarms of insects were destroying the crops. The farmers prayed to the Virgin Mary for help. Soon thereafter the Ladybugs came, devouring the plant-destroying pests and saving the crops. The farmers called these beautiful insects "The Beetles of Our Lady", and - over time - they eventually became popularly known as "Lady Beetles", and in the US, "ladybugs".

Ladybugs are considered lucky in virtually every culture.

Very Lucky In Colorado

- Jefferson County, Colorado 2009
- Swarm of Asian Ladybugs

Asian Ladybug Allergy

Harmonia axyridis

- Imported 1916 as a agricultural pest control predator
  - 1 ladybug can eat 5000 aphids in lifetime
- By 1988 first feral colony detected
- First allergy reported 1998
- In endemic areas, anywhere from 3.6-20% of population has IgE to ladybug
  - Rhinconjunctivitis, asthma, urticaria/angioedema
- 1839 skin tests in a West Virginia:
  - 21% ladybug, 24% cat, 27% cockroach, 40% dust mite
- Of those with a single positive allergy test (12%)
  - 8% ladybug, 8% cat, 12% cockroach, 31% dust mite

Yarbrough JA. J Allergy Clin Immunol 1999;104:704; Goetz DW. Allergy Asthma Pro 2009;29:123
Source of Allergens

- Ladybug major allergens Har a 1 & Har a 2
  - Hemolymph secreted from tibiotemporal joints
- Cat (Fel d 1) (skin & fur are main reservoirs)
  - Sebaceous, salivary and perianal glands
- Dog (Can f 1) (hair is main reservoir)
  - Salivary lipocalin
- Rat (Rat n 1), mice (Mus m 1)
  - Urinary albumin
- Dust mites (Der p 1, Der f 1)
  - Fecal protease
- Cockroach (Bla g 2, Per a 1)
  - Feces (whole body)

[Graph showing Shrimp IgE (kU/L) vs. Cockroach exposure, Bla g 1 (U/gram dust)]


“Pan-Invertebrate Allergen”

- Tropomyosin - highly conserved muscle protein found in both vertebrates and invertebrates
- Invertebrate tropomyosin:
  - Allergenic
  - May be cross-sensitizing
    - Arachnids (dust mites)
    - Insects (cockroach)
    - Crustaceans (shrimp, lobster, crab, crawfish)
    - Mollusks (squid)
- Vertebrate tropomyosin:
  - Non-allergenic
Big Cockroach Allergy

- Subject reported itchy watery eyes and nose, sneezing and rash after exposure to cockroach
- Some of allergens cross-reacted with typical German and American cockroaches

Madagascar Hissing Cockroach

Morgan M. Ann Allergy Asthma Immunol 2007;98:258

Occupational Animal Allergy

- 19 year old volunteer zookeeper
- Immediate onset of urticaria after petting a Rothschild’s giraffe (Giraffa camelopardalis rothschildi)
- Did not occur when she petted bison, zebra, goat, ibex or elephant.


Revenge of the Lab Rat

- Estimates range from 11% to as many as 46% of lab workers will become allergic to mice and/or rats
  - Median estimate ~ 1/3 of all workers
  - 10-20% in the first <1 year
- Allergic rhinoconjunctivitis, asthma and urticaria/angioedema

Occupational Animal Allergy

- Laboratory workers, veterinarians, zoo workers, animal farmers & hunters
- Cat, dog, mouse/rat, hamster, horse, cattle, pig, sheep, goat, deer
- Survey of California veterinarians
  - 20% had hand animal related skin disease
  - 60% had work-related rhinitis
  - 43% had work-related asthma-like symptoms
- In Finland, cow dander is the most common cause of occupational contact urticaria
  - More than latex

Hymenoptera Reactions Via Oral Exposure

- Wine-Induced Anaphylaxis
  - 5 patients with symptoms (oral allergy, flushing, anaphylaxis) after drinking grape juice or wine
  - Hymenoptera venom in juice/wine proven by immunoblot inhibition and challenge studies
- Multiple reports or allergic reactions to honey or royal jelly
  - Most thought to be due to pollens, rarely other insect-related non-venom proteins

Anaphylaxis After Eating Pancakes

Mites present in pancake mix eaten by the patient. Suidasia species mites are stained in yellow (arrows), and wheat flour appears in red. Fuscin red staining was used.
You Are What You Eat

Unusual food-related allergic conditions

Something’s Fishy Here

9 y/o boy goes out with his grandparents to celebrate their 40th wedding anniversary. He orders the Mahi-Mahi with roasted peanut coating, rice pilaf with almond slivers and shrimp in coconut milk.

Within 10 minutes after starting the meal, he complains of a “funny taste” in mouth, mouth & throat itching, then a “tight” throat, wheezing, severe abdominal pain/cramps and an itchy rash.

Additional Information

• No previous known food allergies in child
• Skin testing to fish, shrimp, nuts all negative (as was to all other ingredients)
• Serum IgE (“RAST”) to all foods also negative (<0.35 kU/L)
• One other person at table, who had same dish, had similar symptoms
Scrombroid Poisoning

- Common fish associated with scrombroid:
  - Tuna, mackerel, mahi-mahi, sardines, anchovies, herring, and many others
- With improper refrigeration, naturally occurring histidine in fish is decarboxylated by marine bacteria to histamine
- “Histamine Poisoning”:
  - Similar to the symptoms of anaphylaxis
  - Flushing; sweating; N/V/D; cramps; headache; palpitations; urticaria; dizziness; metallic, sharp or peppery taste; hypotension & bronchospasm
- FDA ‘safe’ histamine < 450 mcg/100g tuna
  - Scrombroid poisoning: 2500-250,000 mcg/100g reported

Itchy Mouth

- 16 year old female complains of itchy mouth, lips, tongue and throat after eating fresh apples, peaches and bananas. Has never had any concomitant skin respiratory or GI symptoms.
  - Has no reaction if she eats apple pie, canned peaches or frozen bananas
- She is otherwise well except for seasonal allergic rhinitis

1. What is her diagnosis?
2. Why does she have this pattern of food sensitivity?

Oral Allergy Syndrome

- Itching and/or burning, erythema, mild swelling of oropharynx upon eating certain fresh fruits, vegetables and nuts
  - Rarely expands beyond oropharynx or causes respiratory symptoms, may progress in some (<10%)
- Begins in childhood to adolescence, but typically lasts a lifetime
- >50% associated with pollen allergy
  - May be worse in pollen season
- Diagnosis: history and fresh food skin testing (prick-prick test)
Oral Allergy Syndrome

- Labile proteins in fresh fruits and vegetables (profilins) homologous to plant pollens
  - Destroyed by heat, digestion, freezing, canning
  - Contrast to allergy to non-specific lipid transfer proteins (nsLTP) for vegetable/fruit/nut allergies not associated with pollens - nsLTP are very stable and resistant to processing.
- Treatment: avoidance of offending fresh fruit or vegetable
  - Either complete avoidance or processed, peeling may help in some cases
  - May improve with pollen immunotherapy

Example of Fruit/Vegetable - Pollen Cross Reactivities

Ragweed
- Cantaloupe, honeydew, watermelon, zucchini, cucumber (Cucurbitaceae family); bananas (Musaceae family)
- Birch tree
  - Apple, peach, apricot, cherry, plum, pear, almond, hazelnut (Rosaceae & Betulaceae families); carrot, celery, parsley, caraway, fennel, coriander, aniseed (Apiaceae family);
  - Soybean, peanut (Fabaceae family)
- Mugwort
  - Rosaceae family; Apiaceae family; mustard, cauliflower, cabbage, broccoli (Cruciferae family); bell pepper, black pepper, garlic, onion
- Grass
  - Peach, cherry, potato, tomato

Latex as a Food Allergen

- 10 year old boy developed anaphylaxis (angioedema/urticaria, cough, dyspnea, hypotension) 10 minutes after eating a cream-filled donut at “shop A”
  - “Often” had similar donut from “shop B” with no reactions
- 2 previous episodes of reactions to latex glove at dentist and from blowing up a balloon.
  - Use of latex gloves standard in “shop A”
- Skin test negative to all raw ingredients
- Skin test + to donut from “shop A” only
- Challenge test to donut from “shop A” positive, with negative reaction to donut from “shop B”
- Able to eat donuts “ad lib” from “shop B”
- Several additional cases of latex in multiple foods have been reported, including stirring drink with finger of gloved hand

The Incredible Adventures of “Alpha Gal”!

This Week’s Episode:
“THE ATTACK OF THE VEGETARIAN TICKS”

Our Story Begins…in Oncology Clinics Throughout the USA….

- Up to 20% of patients having severe allergic reactions to cetuximab
  - Chimeric (mouse/human) monoclonal antibody against epidermal growth factor receptor (EGFR)
- The weird part...
  - Reactions with first infusion
  - Patients who reacted had pre-existing IgE antibodies to cetuximab
  - Reported only in southeast US states - Tennessee, North Carolina, Arkansas, Virginia, southern Missouri

At The Same Time, in Allergy Clinics Throughout the World.....

- Reports of patients with anaphylaxis after eating meat
  - Despite having tolerated food for years in the past
- The weird part...
  - Delayed onset of symptoms → 3-6 hours after eating
  - Only beef, pork, lamb → not chicken, turkey, fish
  - Reported in states from roughly the same parts of southeast US
The Plot Thickens…

- IgE was **not** against a protein, but rather a glycosylation site on the Fab fragment of the cetuximab monoclonal ab
  - Oligosaccharide
  - Galactose-alpha-1, 3-galactose
  - AKA “alpha-gal”

- What is alpha-gal?
  - Blood group substance of non-primate mammals


The Crucial Clue…

- A astute allergist noted that his blood level of alpha-gal IgE skyrocketed after he received multiple tick bites while hiking
- >90% of subjects with elevated alpha-gal IgE had a history of tick bites
- In patients with delayed anaphylaxis, positive response to “have you ever had a local reaction to tick bites that lasted for weeks or longer” correlated with presence of alpha-gal IgE (p<0.001).

Regional positive alpha-gal IgE rates, with distribution of lone star tick superimposed

Why Now?

- Retrospectively, clinical reports of patients with symptoms for > 20 years
- Alpha-gal IgE detected in stored serum samples as far back as 1980’s
- Major natural host is white-tailed deer
  - By 1880’s, white-tailed deer nearly extirpated in some eastern states
  - Changes in hunting laws, decreased hunting, efforts to re-stock population have allowed deer population to soar
  - An as-of-yet unidentified change in composition of saliva or presence of a new symbiotic organism
**How Did the Lone Star Tick Get Its Name?**

![Image of Amblyomma americanum tick]

Amblyomma americanum

CDC Public Health Image Library

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**Mango Madness**

- 27 year old male developed a “handprint” shaped red, itchy, weepy rash on medial aspect of right thigh
- 3 days earlier, was on vacation on tropical island and was peeling and eating mangos
  - Phone call - rested left hand on right leg

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**Contact Dermatitis**

Mango - Poison Ivy/Oak

Tucker MO. NEJM 1998;339:235

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Mango Madness

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- 3 days earlier, was on vacation on tropical island and was peeling and eating mangos
  - Phone call - rested left hand on right leg
- *Oleoresins in poison oak/ivy cross-react with sap in mango rinds*

More Mango Madness

- 29 year old nurse walks into Allergy Clinic covered with patches of red, very itchy, oozing rash
  - Ate mango earlier that day
- Developed “recall” “contact” dermatitis at sites of old poison ivy/oak rashes
- Also can occur with oils in cashew shells

Mango - Poison Ivy/Oak Cross-reactivity

- Both patients have a past history of severe poison ivy or poison oak.
- Patient 1 had ‘direct’ contact dermatitis from mango rind sap that came in contact with his skin
- Patient 2 had “recall” dermatitis (“systemic contact dermatitis”) at sites of past contact dermatitis from ingestion of mango rind
Mango – Poison Ivy/Oak Cross-reactivity

- Contact dermatitis from poison ivy, oak (and sumac) is due to sensitivity to oleoresins in plant called ‘urushiol’
- Poison ivy/oak and mango trees belong to the same family - Anacardiaceae
- Urushiol in poison ivy/oak is cross-reactive with oleoresins in mango rind (also leaves and vines of mango tree), but not mango fruit
- Other plants (including cashew) in same family can cross-react, but are rare in U.S.

You’re gonna need an ocean, of calamine lotion...

The Coasters

Mohan J. Proc Natl Acad Sci U S A. 2006;103:9086

Cell Phone Allergy


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Dermatitis due to ingestion of coin containing nickel

Can Dietary Nickel Induce Systemic Reactions In Nickel Sensitive Patients?

- As much as 10% of population has a nickel allergy
- 1% of nickel allergic patients would have systemic reactions to nickel content in a normal diet (220-530 mcg)
- 10% would react to 550-1320 mcg
- ~50% to >2500 mcg

Sample Nickel Content in Foods

- Soybean, boiled - 1 cup = 895 mcg
- Cocoa - 1 tbsp. = 147 mcg
- Cashew - 18 nuts = 143 mcg
- Figs - 5 figs = 85 mcg
- Lentils, cooked - 1 cup = 61 mcg
- Other foods with high contents
  - Whole grains / oats
  - Peanuts + other legumes (red kidney beans, peas)
  - Dried fruits, raspberry
  - Canned foods
  - Lobster
“Lime” Disease

- Flight attendant on route to Caribbean
- Extensive sun exposure during layover
- 24 later, onset of burning erythema, bullae by 48 hours

http://emedicine.medscape.com/article/1119566-overview

Phytophotodermatitis

- A phototoxic reaction to light-sensitizing botanical substance
  - Acute (24-48 hours): burning erythema, blisters,
  - Chronic (wks-mos): hyperpigmentation for months
- Not immune mediated
  - Any person, no prior sensitization necessary
- Mostly UV-A
- Furocoumarins
  - Psoralens, angelicin, bergaptol, xanthotal bergamottin, dihydroxybergamottin
  - Limes most common - also celery, fig leaf, multiple other plants

Random Fact Alert!!

These are the two major components that cause the “grapefruit juice effect” – interfere with metabolism of medications through inhibition CYP 3A4 (and other) enzymes

- bergamottin, dihydroxybergamottin

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The Following Slides May Be Presented in A Conference That Has Useful Information

Allergy advisory label on a cupcake mix for a children’s home bake toy oven, manufacturer’s recommended age 8-15 year

Not Entirely Unlike a Helpful Warning

- May contain
- May contain traces of
- Manufactured in a facility that also processes
- Manufactured on shared equipment with products containing
- Manufactured on a line that processes
- Packaged in a facility that also packages products containing
- Processed on equipment that makes products containing
- Produced in a plant which manufactures products containing
- Allergy information: produced in a facility that handles
- Made on equipment that also processes
- Allergen information: Good manufacturing practices used to segregate ingredients in a facility that also processes

At least 25 different terminologies.....

This slide may contain some useful information.....

- Survey of 20,241 unique products in US supermarkets for presence of a food advisory label → 17% had an advisory label

Pieretti MM. J Allergy Clin Immunol 2009;124:537
This slide may contain some useful information.....

Hidden Allergens

- 9/99 - 3/00 FDA audit of ice cream and bakery manufacturers in Wisconsin and Minnesota
  - 25% contained undeclared peanut residue
  - 10% contained undeclared egg residue
  - 400 inspectors for 57,000 US food plants

http://www.fda.gov/Food/LabelingNutrition/FoodAllergensLabeling/GuidanceComplianceRegulatoryInformation/ucm106779.htm

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I'll Drink To That.....
Adverse reactions to alcoholic drinks

• Non-immunologic reactions
  – Long-term consequences on liver, weight...
  – Just plain drunkenness
  – Low activity of alcohol/acetaldehyde dehydrogen.
  – Reactions to additives (sulfites)
• Immunologic reactions
  – Increases IgE production, TH-2 response
  – In pregnancy: increased atopic markers in babies
  – Allergic reaction to ETOH or other components in alcoholic beverages

Beer Anaphylaxis

• Anaphylaxis to beer without reactions to other alcoholic beverages (+ skin test)
  – Malt (barley)
    • May tolerate barley in other forms
  – Rice, wheat, corn, rye
  – Yeast: Saccharomyces cerevisiae, S. uvarum
• Gluten (celiac disease)
  – Not anaphylaxis, but an itchy skin rash + GI

Allergy To Alcoholic Drinks

• Survey of ~4200 people in Copenhagen, 13.9% had ever had an “allergic” symptom
  – Upper airway (rhinitis) in 7.6%
  – Lower airway (asthma) in 3.2%
  – Skin symptoms (rash/hives) in 7.2%
  – Red wine > other wines, beer, spirits
• Majority of reactions likely “enzymatic” and not “immunologic”
• IgE-mediated reactions to ETOH unlikely
• IgE reactions to grains, fruits, yeast

Linneberg A. Chin Exp Allergy 2007;38:145

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Unusual allergic reactions to pharmaceuticals and other therapeutics

Allergic Reactions to The Things Prescribed to Treat Allergic Reactions

- Glucocorticoids
- H1-antihistamines
- Bronchodilators

Contact Dermatitis to Topical Corticosteroids

- Increasingly recognized in adults and kids
- Can be clinically indistinguishable from underlying atopic dermatitis
- Up to 6% of cases of allergic contact dermatitis in children
- Cross-reactions within allergy groups

Lee PW. Curr Opin Pediatr 2009;21:491
Allergic Reactions to Systemic Corticosteroids

- Multiple reports of anaphylaxis to variety of systemic steroids - enteral and parenteral
- Usually specific to a particular glucocorticoid
  - Most commonly hydrocortisone, methylprednisolone
  - Patients can usually tolerate other glucocorticoids
- “Succinylated” corticosteroids frequently implicated:
  - Allergy: methylprednisolone succinate (Solu-Medrol©), hydrocortisone succinate (Solu-Cortef©)
  - Not allergic: methylprednisolone (Medrol©), hydrocortisone (Cortef©)


Allergy to Diphenhydramine

- Relatively common:
  - Contact dermatitis
  - Fixed drug eruption
- Uncommon
  - Systemic contact dermatitis
  - Photoallergic contact dermatitis
- Can you have anaphylaxis?

Photo: emedicine.medscape.com/article/1336702-differential

Anaphylaxis to other antihistamines

- Rare case reports of urticaria reported to hydroxyzine, cetirizine, levocetirizine, loratidine, desloratidine, fexofenadine, others
### Adverse Reactions To Albuterol

- **Pharmacologic**
  - Tachycardia, hypertension, trembling, arrhythmia, hypokalemia
  - Tachyphylaxis
- **Idiopathic**
  - Paradoxical bronchoconstriction -
    - Due to propellant, preservative or pH
    - Usually specific to single agent
- **True IgE- mediated allergic reactions are rare**

### Allergy To Albuterol

- Adult patient treated with formoterol only (LABA)
- Took albuterol for an acute exacerbation, within 15 minutes went into respiratory arrest
- Skin test and inhalation challenge positive to albuterol, terbutaline and pirbuterol
- Tolerates LABA: formoterol and salmeterol

Generalized erythema and eyelid and palmar swelling after challenge with nebulized salbutamol.


Bonniaud P. Allergy 2007;62:1219

### Adverse Drug Reactions

- **Type A - Predictable (80% of ADRs)**
  - Dose dependent, related to known pharmacologic actions, occur in otherwise healthy people
  - Side effects, secondary effects, toxic effects, interactions
- **Type B - Unpredictable**
  - Dose independent, unrelated to pharmacologic actions, occur only in susceptible people
  - Immune and non-immune mediated
- **Type C - long-term adverse effects**
- **Type D - carcinogenicity and teratogenicity**
Drug - Infection Interactions

Drug Hypersensitivity Reactions Related to Infections

- Penicillin + syphilis
  - Jarisch-Herxheimer reaction
    - Release of endotoxin from spirochetes
      - Also other spirochete and non-spirochete infections (Lyme, relapsing fever, Q fever, bartonellosis, brucellosis, others)
- Amoxicillin + EBV infections
  - Exanthematous rash seen in >70%-100%
  - Mechanism unknown: ?lymph. activation

Leung AKC. Int J Derm 2003;92:553

Drug-Related Eosinophilia with Systemic Symptoms (DRESS)

AKA Drug Induced Hypersensitivity Syndrome (DIHS)

- Erythematous maculopapular exanthem and swelling + significant eosinophilia, starting >3 wks into treatment (often at dose increases)
  - Leukocytosis (>11,000), atypical lymphs (>5%)
- Systemic symptoms
  - Fever, malaise, LAD, hepatitis (50%), interstitial nephritis (10%)
  - Less commonly colitis, interstitial pneumonitis, pancreatitis (IDDM), myocarditis, thyroiditis, encephalitis/meningitis, other serositis
- Symptoms may persist, recur or worsen for weeks-months after drug is withdrawn
  - Can be fatal (~10%), usually due to liver failure
- Treatment
  - Empiric supportive therapy, glucocorticoids


Drug-Related Eosinophilia with Systemic Symptoms (DRESS)

AKA Drug Induced Hypersensitivity Syndrome (DIHS)

- Causative drugs
  - Anticonvulsants (very high rate of cross-reactivity)
    - Carbamazepine (CBM), phenytoin, phenobarbital, zonisamide, lamotrigine
  - Allopurinol, Sulfonamides, Minocycline
- Associated with reactivation of herpes viruses (HHV-6, HHV-7, EBV, CMV)
  - The detection of HHV-6 reactivation is proposed as a diagnostic marker for DRESS
- May also be a genetic predisposition...


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Pharmacogenetics

- Carbamazepine: SJS/TEN, DIHS
  - HLA-B*1502 in ~100% of Han-Chinese (and descendants in other countries), and majority of Thai & Indians (75%)
  - Japanese, Caucasians = 0%
    - Japanese - 25% HLA-B*1511
  - Similar to other aromatic amine anticonvulsants
- Allopurinol: SJS/TEN, DIHS
  - HLA-B*5801 in ~100% of Han-Chinese, Thai and majority of Japanese Caucasians
- Abacavir: Hypersensitivity (SJS/TEN & DIHS - like)
  - HLA-B*5701 in ~50% Caucasians, 15% African American, 0% Japanese
  - Nevirapine: HLA-B*3505 ~15% Thais, Cw8 ~40% Japanese

Phillips EJ. Pharmacogenomics 2010;11:973; Aihara M. J Dermatol 2011;38:246

Might as well face it you’re addicted to love....
Robert Palmer, 1986

Unusual allergic reactions for mature audiences only

THE FOLLOWING SLIDES HAVE APPROVED FOR APPROPRIATE AUDIENCES BY THE MPAA (MOST PRACTICING ALLERGISTS OF AMERICA)

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The following slides have been rated

PG-13 PARENTS STRONGLY CAUTIONED

Some Material May Be Inappropriate for Children Under 13

CRUDE AND SEXUAL CONTENT

Kiss of Death?

Just one problem, it was not true...

People Magazine. December 19, 2005, Vol. 64, No. 25

Allergic Reactions to Foods Without Eating

• 1139 patients self-reported food allergy
  – 17% in kitchen with food handled by others
  – 13% when sitting beside a person who is eating the food
  – 12% when in close physical contact (kissing) with a person who recently ate the food

Wrong on Many Levels….

- 20 y/o female with shellfish allergy, yet worked at a seafood restaurant
  - Recurrent urticaria from touching seafood
- Developed a romantic relationship with a co-worker
- Within <1 minute of a kiss at bedtime, developed severe anaphylaxis
- Her boyfriend ate shrimp 1 hour earlier

Food Allergy From Kissing

- 379 subjects with self-reported food allergy
  - 5.3% (20-16 F, 4 M) experienced reactions through kissing
- Of 17 who could be contacted:
  - All had local reactions at site of kiss in <1 min including urticaria and lip/tongue angioedema
  - 4 had wheezing
  - 1 had systemic anaphylaxis

Not Just Peanuts…

- Several foods have been reported to cause allergic reaction via kissing
  - Peanuts
  - Tree nuts
  - Seafood
  - Kiwi
  - Milk
  - Pea

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Not just foods....

- 45 y/o woman developed angioedema of lips & mouth 30 mins after being kissed by husband who took an ampicillin tablet 2 hrs earlier
- 22 y/o woman developed oropharyngeal edema several minutes after kissing boyfriend who took amoxicillin a few minutes earlier
- 31 year old mother had anaphylaxis after kissing the lips of her 5 year old who ingested amoxicillin 3 hours earlier

Liccardi G. Lancet 2002;359:1700; Pellevy-Catala C. Contact Derm 2001;44:251; Mancuso G. Contact Derm 2006;54:256

Not Just People...

- Family owned a green-cheeked parakeet
- Trained to give “kisses” on cheek
- Fed the parrot peanuts
- Peanut-allergic child developed a local reaction after a “peck on the cheek”

When and How Does Peanut Sensitization Occur?

- ~75% of young children (<14 mo) with peanut allergy react to their first known oral exposure
  - How does sensitization occur?
- Risk of peanut allergy may be related to household (not direct) consumption of peanuts
  - Especially in children with eczema

Exposure to food antigens through non-oral routes increases sensitization

- Through skin via peanut oil products
- (Via inhalation)
- Via kissing?

How Much Peanut in Once Kiss?

- Estimate 88.8 mcg of peanut protein per kiss
  - Similar to amount needed to sensitize mice in an experimental epidermal barrier disruption to model eczema

"We acknowledge that kissing is essential for a child's social and emotional development and do not advocate avoidance of kissing but caution against high-saliva-volume kisses soon after peanut consumption in infants with eczema"

Interventions to Reduce Peanut Exposure Through Saliva

- 38 subject ingested 2 tbls of peanut butter
  - Saliva collected at various time points and analyzed for peanut via monoclonal-based ELISA for Ara h1
- At another time, samples were collected after 5 interventions:
  - Waiting 60 minutes, brushing teeth, brushing & rinsing, rinsing only, chewing gum for 30 minutes and waiting for 30 more minutes
Don’t Make This Our Last Kiss…

• Salivary peanut levels peaked at 5 minutes
• Large within & between individual range in median peak salivary levels
• All interventions reduced levels
• Waiting only: 87% undetectable after 1 hour
• None had detectable levels after 1 hour and eating a non-peanut meal

Maloney JM. J Allergy Clin Immunol 2006;118:719

Don’t Make This Our Last Kiss…

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Kissing - Is it Worthwhile? (from a purely allergic standpoint)

• Adult subjects (eczema & allergic rhinitis) allergic to house dust mite + Japanese cedar pollen
• Each subject brought a spouse or an intimate friend for a 30 min session of “free kissing” privately while listening to soft music
  – Control subjects were allowed to embrace for 30 minutes without kissing
• Skin prick test wheal size (pre vs post) diminished by 28-34% in the kissing group compared to control
• Decreased allergen-specific IgE production with skewing of cytokine pattern toward Th1 type


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Allergy To Sex

• Latex allergy: condoms, diaphragms
  – Urticaria, angioedema, anaphylaxis, contact dermatitis

• Spermicides, lubricants, medications, sanitary napkins
  • Urticaria, angioedema, anaphylaxis, contact dermatitis

  – Others....

Human Semen Allergy
Review of 80 Cases

• Modal age of onset 20-29 years
  – 16% started in teens, 7% started after 50 years old

• 79% had personal history of atopy

• 41% on “first” intercourse

• 3 cases reported allergic to just one particular man and no other partners
  – 6 occurred with multiple partners (up to 5)

Shah A. Clin Exp Allergy 2004;34:827
Human Semen Allergy
Review of 80 Cases

- Type of reaction:
  - 31% systemic
  - 39% systemic and local
  - 28% local
- 87% occurred during or < 30 minutes after intercourse
- 36% required an ED visit
  - No fatalities

Shah A. Clin Exp Allergy 2004;34:827

Human Semen Allergy
Rare Manifestations

- Systemic Vaculitis
  - 19 year old developed progressively worse urticaria, arthritis, generalized pruritus, colitis (bx proven)
  - Elevated C3, C4, immune complexes
  - Multiple recurrences related to sex, prevented by condom
  - Skin test to husband’s semen was negative, but had delayed reaction 8 hours later consistent of angioedema, rash, arthritis and diarrhea

- Fixed Cutaneous Eruption
  - 33 y/o developed pruritic erythematous macules, vesicles and bullae → hyperpigmented macular lesions in same areas
  - Progressed over 2 years, with time of onset decreasing from 2 days to 2 hours


Human Semen Allergy
Diagnosis and Treatment

- Diagnosis:
  - Suggestive clinical history
    - Rule out more common - latex, etc.
  - Symptoms prevented by condom
  - Skin test with partner’s semen
  - Serum semen IgE (“RAST”)

- Treatment:
  - “Avoidance” - abstinence, condom
  - Immunotherapy (vaginal better than SQ)
Not just seminal proteins...

- 3 episodes of acute urticaria in 1 week
  - Each occurred < 30 minutes after intercourse
  - No condoms, barriers, creams etc.
- Partner was taking dicloxacillin
- Patient had a childhood history of penicillin allergy
- Skin test + to penicillin, negative to semen
- Resolved with condom use, and after partner stopped dicloxacillin

Seminal Transfer of Allergens

- Allergic reactions in women from partner taking:
  - Dicloxacillin (skin infection)
  - Thioridazine (schizophrenia)
  - Vinblastine (stage II B Hodgkins)
  - Walnuts (hungry)
- Case report of allergy via oral exposure
  - Cephalexin

Bronchospasm during sex

- Patients with pre-existing asthma
  - Severe enough to require mechanical ventilation
- Differentiated from exercise-induced asthma
  - Hypothesized to be due to anxiety, apprehension, heightened emotion

“Sexercise-Induced Bronchorgasm”
Nasal Polyps and Erectile Dysfunction....Really?

• Prospective study, with “normal” control group
  • 35 consecutive men presenting for nasal polyps were approached - 32 agreed to participate!
    - Exclude those with other causes for ED (3) or didn’t want to repeat post-operative ED eval (1)
• Evaluated subjectively and objectively
  - International Index of Erectile Function (IIEF-EF) survey
  - Nocturnal penile tumescence (NPT)
• Pre-operative ED 34.5% (IIEF-EF) and 24% (NPT)
  - Compared to control 3.3% (IIEF-EF & NPT) (p=0.009)
• Post-operative ED 10.3% (IIEF-EF) (p=0.014) and 6.9% (NPT) (p=0.037)

Gunhan K. Am J Rhinol Allergy 2011;25:112