Pediatric Allergy& Immunology Board Review May 2009

Mona I Kidon MD

Allergy Unit, Sheba Medical Center

Tel Hashomer

The Children's Health Center, Clalit Health Services

Rishon Lezion

המרכז הרפואי ע"ש ח. שיבא תל-השומר
בית החולים של המדינה

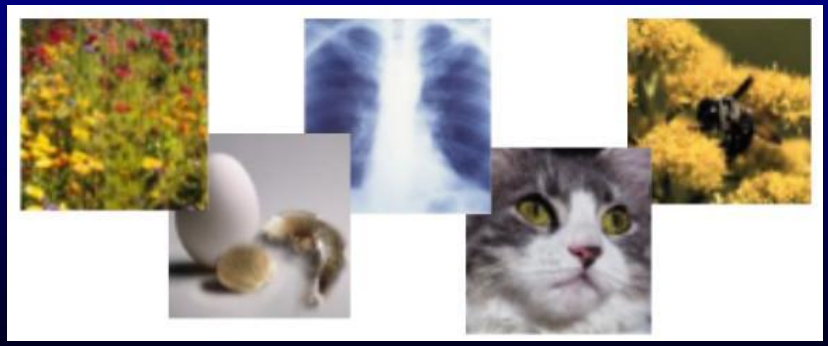
כללית
הכי טובה למשפחה

Pediatric Certification Exam

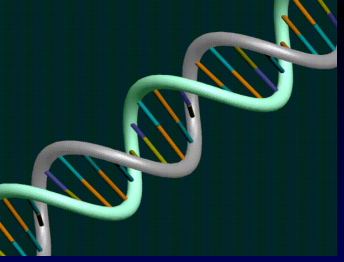
- Allergy and related disorders: 4.5% [ID-5.5%, development 4.5%, neonatology 4.5%]
- www.abp.org: General Pediatrics Exam Information: content outline
- Allergic Rhinitis
- Asthma
- Atopic Dermatitis
- Food Allergy
- Anaphylaxis
- Urticaria, angioedema
- Drug Allergy
- Hymenoptera Allergy
- Diagnosis and treatment of allergic dz
- Immunodeficiency disease

Prevalence of Allergic Diseases

- Atopic dermatitis
  - Up to 15-20% of children
- Allergic rhinitis
  - 20% cumulative prevalence rate in the US (15% in 14yo IS)
- Asthma
  - 5.4% in the US (Similar LAMAS data, 8.4% 14yo)
- Food allergy
  - Up to 8% of children less than 3 years of age
  - Up to 3-4% of adults



Prevalence doubled in the past 20 years!



Genetics of Allergic Diseases

- Complex genetic disease, in contrast to simple mendelian trait such as CF
- Clear hereditary pattern (one parent atopic-risk in child 40%, both parents atopic-70% risk)
- Asthma twin studies: 70-80% of susceptibility due to a genetic component; asthma in twins 4x higher if parents asthmatic
- Susceptibility genes: ADAM33 in asthma, SPINK5 in AD, Fillagrin AD and Asthma, many others
- Gene Environment interactions (CD14)

Bonus!

Factors Influencing the Development of Atopic Allergic Disease

Factors favoring TH1 phenotype

- ✓Developing countries
- ✓Presence of older siblings
- ✓Rural homes, livestock, pet (dog) ownership in childhood
- ✓Poor sanitation, high orofaecal burden
- ✓High helminth burden
- ✓Early exposure to day care
- ✓Tuberculosis, measles, or HAV infection

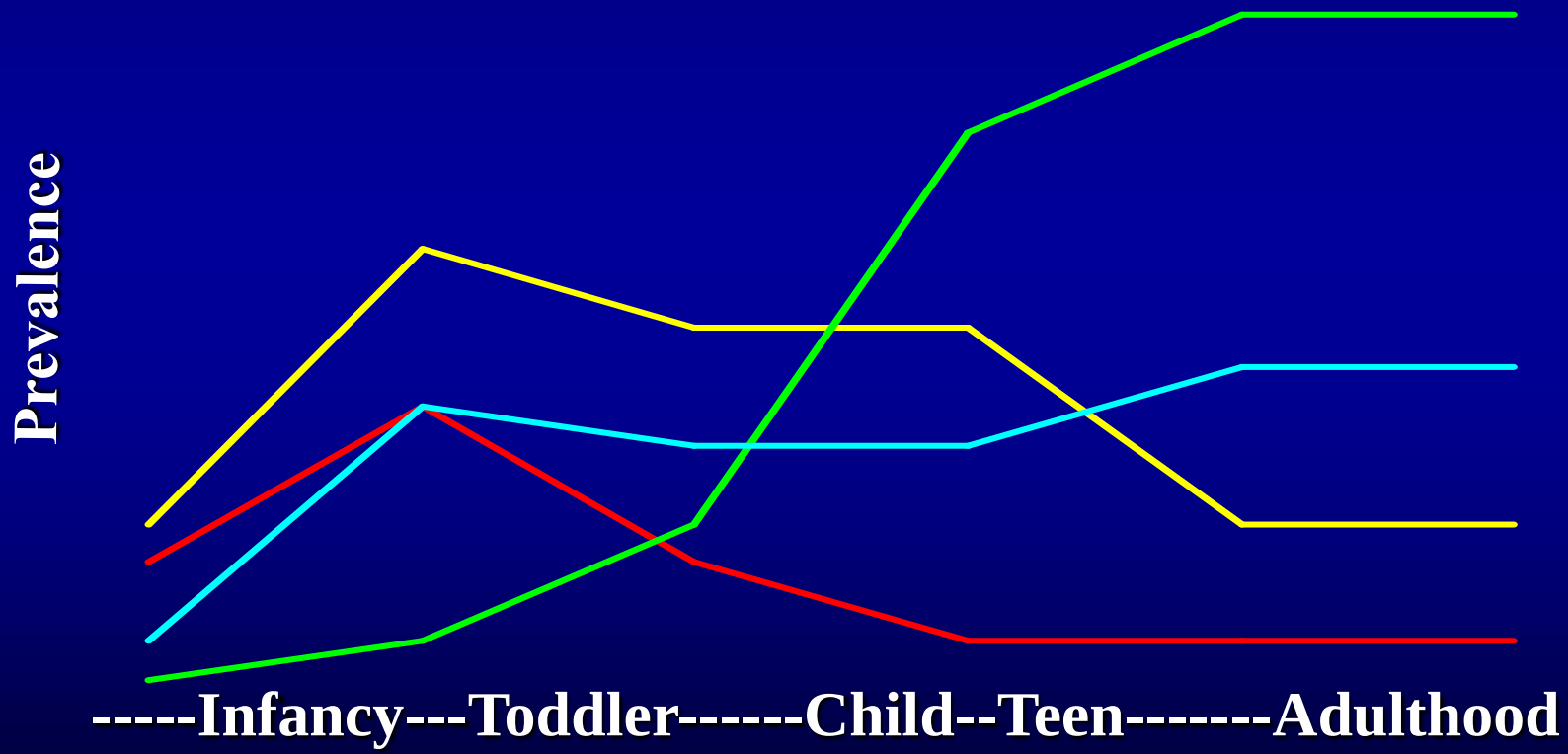
Factors favoring TH2 (allergic) phenotype

- ✓Widespread use of antibiotics
- ✓Western lifestyle
- ✓Urban environment
- ✓Diet
- ✓Early sensitization to house dust mites and cockroaches
- ✓Good sanitation

The Atopic March

Food Allergy/Atopic Dermatitis

Asthma/Allergic Rhinitis

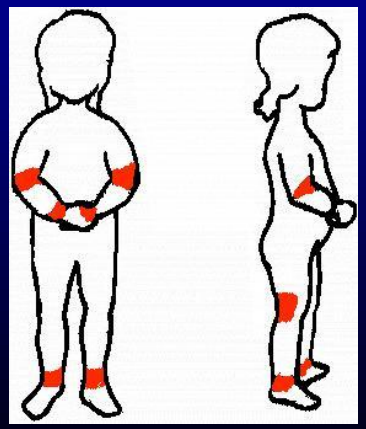


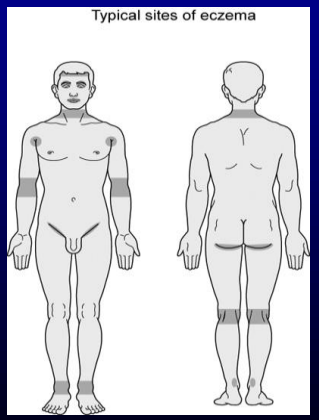
Atopic Dermatitis

- Prevalence:
  - Children: 10-20%, Adults: 1-3%
  - 50% present in the first year of life (but rarely under 2 months, 80% develop by age 5 years
  - Less severe by adolescence in 65%, but only 20% outgrow AD by age 11-13 years
- Pathology:
  - **Acute skin lesions: spongiosis/intercellular edema, of the epidermis. Dendritic APCs (LCs) have surface-bound IgE. marked perivenular T-cell infiltrate. Mast cells are found in normal numbers but in different stages of degranulation. an increased number of cells expressing IL-4 and IL-13**
  - **Chronic lesions: hyperplastic epidermis with hyperkeratosis, and minimal spongiosis. There are predominantly IgE-bearing LCs in the epidermis and macrophages in the dermal mononuclear cell infiltrate. The numbers of mast cells and of eosinophils are increased, also expression of IFN-γ and IL-12**

AD Diagnosis

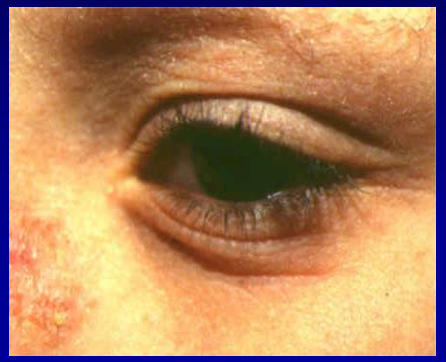
- No objective diagnostic test
- Major criteria [Hanifin & Rajka *Acta Derm Vener* 1980; 92:44]
  - Pruritus
  - Eczematous dermatitis with a Chronic relapsing course
  - Typical distribution of eczema
    - Facial and extensor eczema in infants and children
    - Flexural eczema in adults

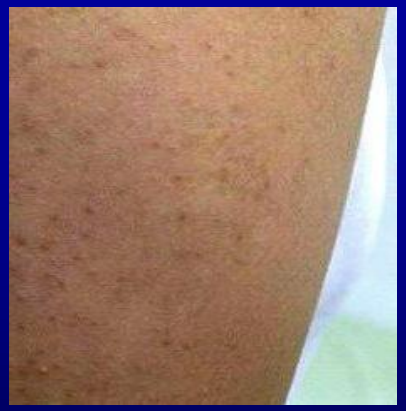




AD diagnosis-minor criteria

- Xerosis
- Atypical vascular response (facial pallor, white dermatographism)
- Perioral or periauricular lesions
- Allergic shiners
- Morgan-Dennie lines
- Keratosis pilaris
- Pityriasis alba
- Palmar / plantar hyperlinearity
- Anterior Capsular Cataracts
- Keratoconus





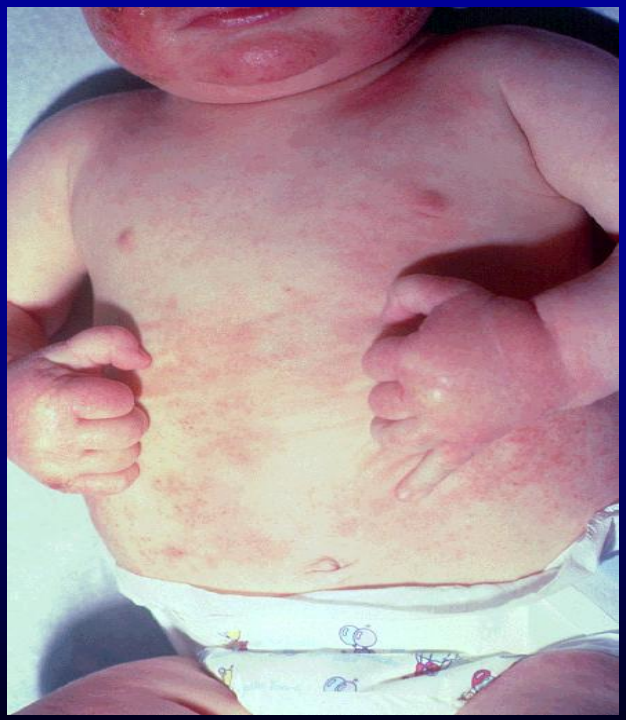
AD rash

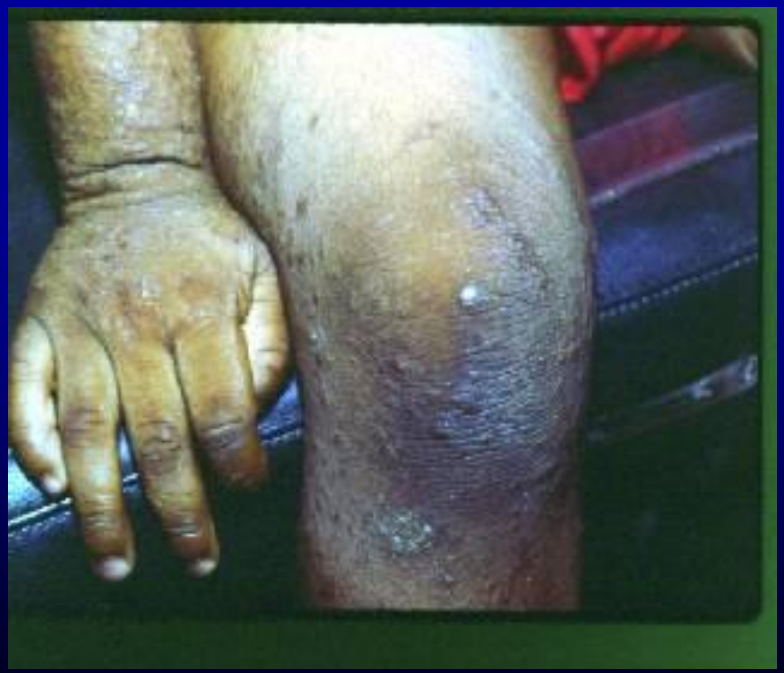
Acute

- Pruritic erythematous papules
- Serous exudation
- Excoriation

Chronic (skin remodelling)

- Lichenification
- Dry fibrotic papules
- Hyperpigmentation





Bonus!

Differential diagnosis of AD

- SCID/Omen Syndrome
- Wiskott-Aldrich Syndrome
- Hyper IgE Syndrome
- Agammaglobulinemia
- Ataxia-telangectasia

- Netherton's Syndrome
- Familial keratosis pilaris

- HIV
- Scabies

- Cutaneous T cell lymphoma
- Letterer-Siwe disease

- Seborrheic Dermatitis
- Nummular eczema
- Contact dermatitis (allergic, irritant)
- Psoriasis
- Ichtyoses

- Dermatitis herpetiformis
- Pemphigus foliaceus
- GVHD
- Dermatomyositis

- Phenylketonuria
- Zinc deficiency
- Vitamin B 6 and niacin deficiency

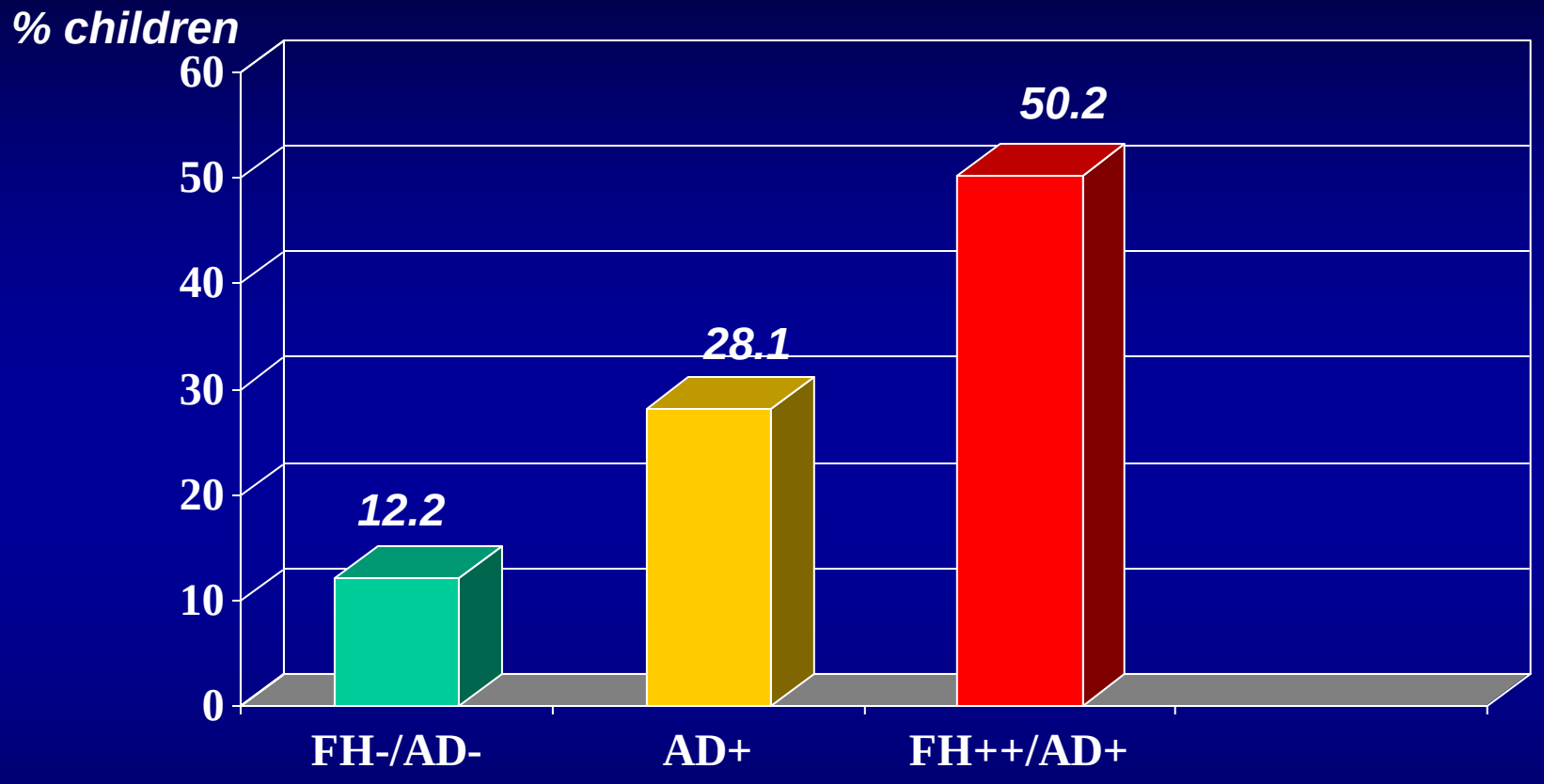
Atopic Dermatitis and Food Allergy

- 40% of children with mod/severe AD have skin symptoms provoked by food hypersensitivity (Eigenman et al, 1998)
- 90% of significant food allergy caused by egg, cow's milk, soy, wheat, peanut, and fish
- Egg allergy is the single most common food allergy
- 7 out of 10 children with AD and egg allergy develop respiratory allergy by age 5 years
- Suspect food allergy in uncontrollable eczema that waxes and wanes without particular association with diet

Atopic Dermatitis and Respiratory Allergy

- Up to 80% have positive skin test to environmental allergens
- Inhalation of dust mites causes AD flare within 24 hours
- Exposure to pollen (tree, grass, ragweed) associated with seasonal AD flares
- Skin contact with animal allergens, dust mites, pollens or molds causes eczema worsening or hives
- Ingestion of foods cross-reactive with birch tree pollen in the birch season associated with AD
- Degree of IgE sensitization to aeroallergens is directly associated with severity of AD

Atopic Dermatitis and Allergic Airway Disease at Age 5 Years

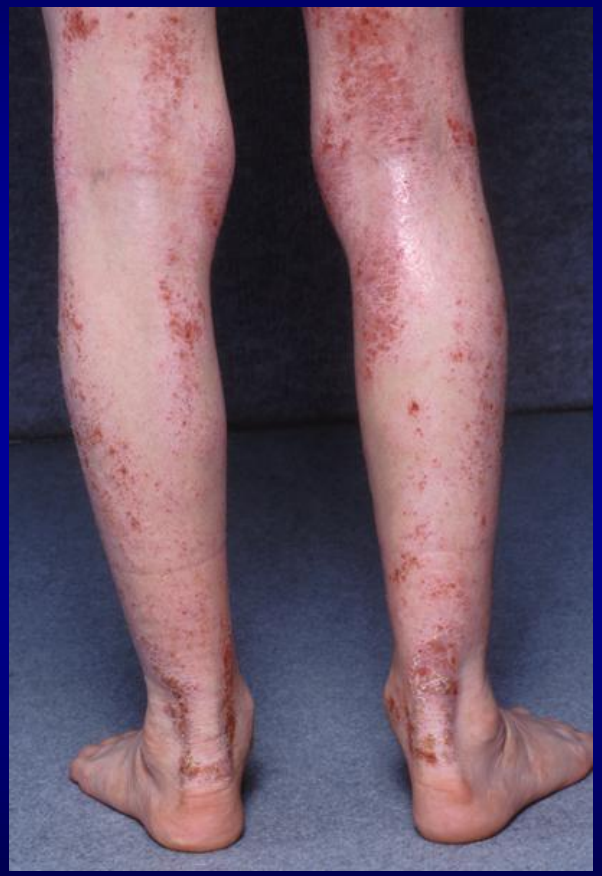


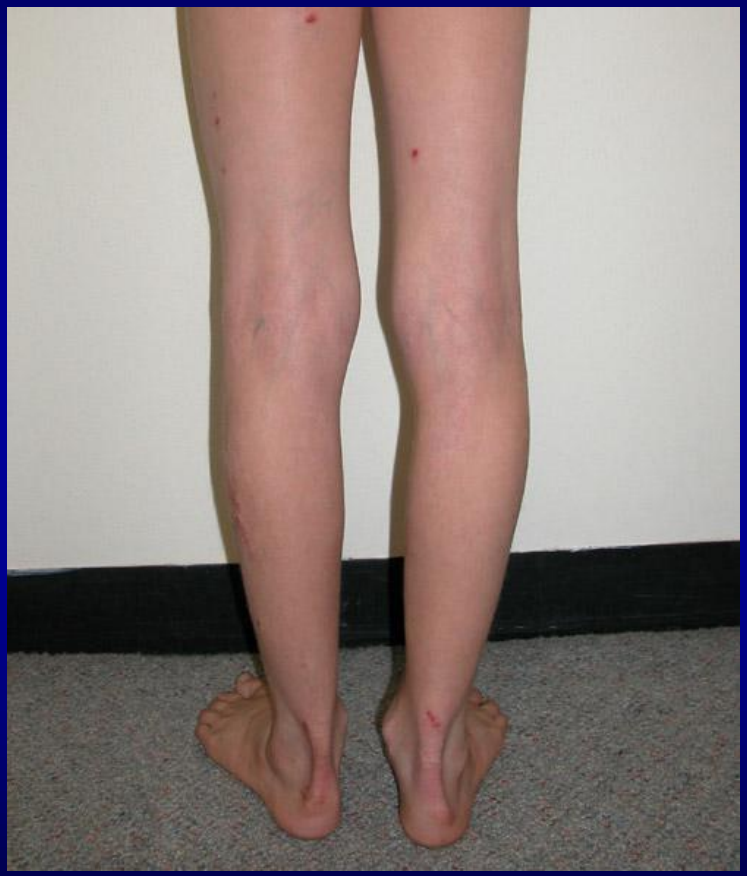
AD+ / AD- in the first 3 months of life

FH++ / FH- at least two atopic family members

Bergmann et al, Clin Exp Allergy, 1998

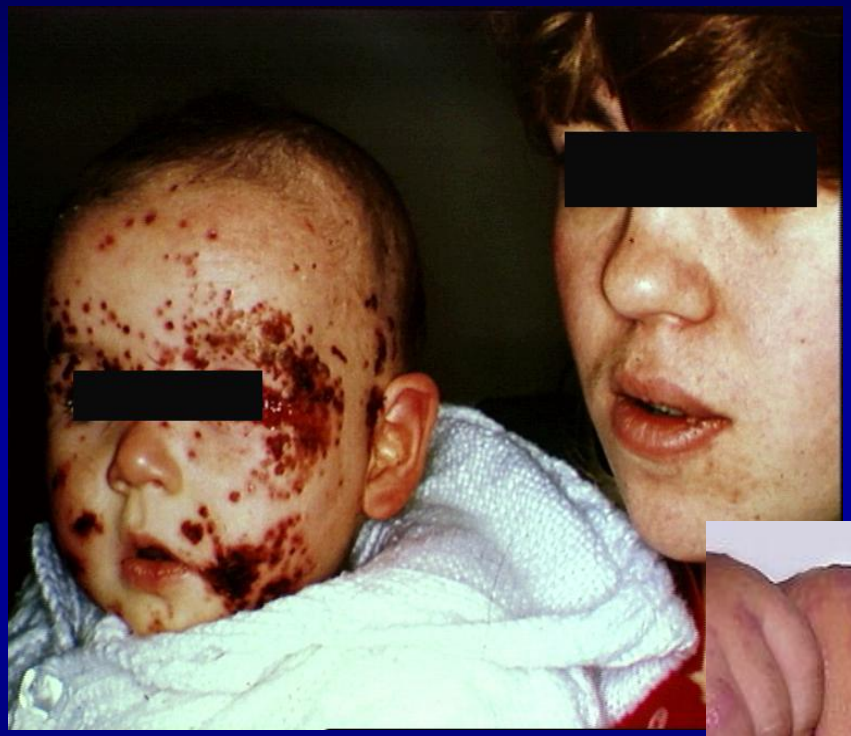
AD - *S. aureus* Superinfection

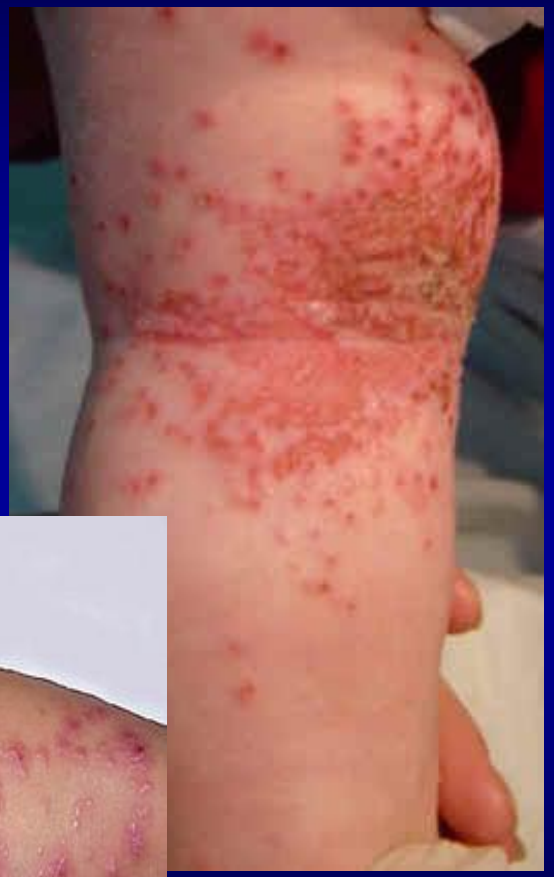




Patients with AD have increased tendency to bacterial, viral, and fungal skin infections.

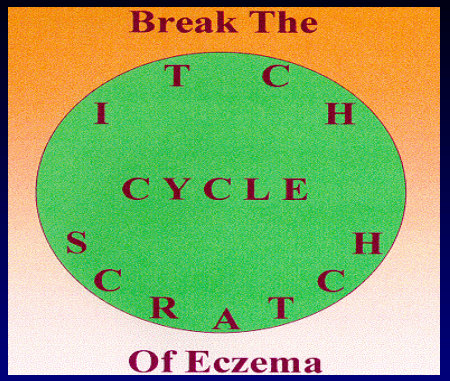
Eczema herpeticum





Bonus!

Atopic Dermatitis Management

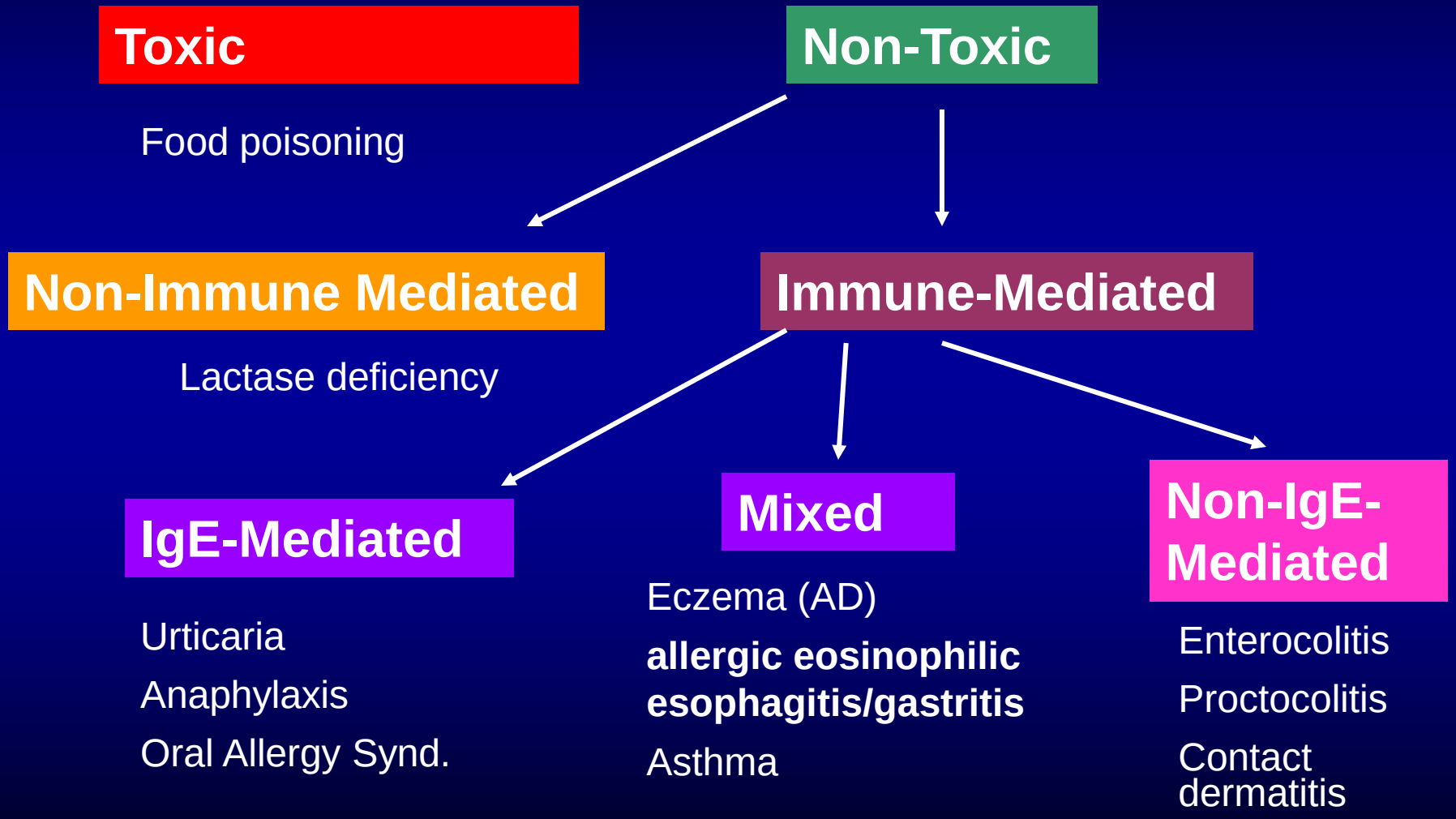


- Identify and avoid relevant food and environmental allergens- EDUCATION
- Avoid irritants: wool and synthetic clothing, sweating, stress, harsh soap, laundry detergent
- Hydration / Lubrication
- Antihistamines: Non Sedating
- Topical anti-inflammatory: steroids, tacrolimus
- Systemic anti-inflammatory: steroids, cyclosporine
- Phototherapy
- Treatment of infections: *S. aureus*, HSV

Food Allergy

- Non-toxic, immune-mediated adverse reaction to food
- Up to 6% of children (in the first 3 y of life)
- Increasing incidence in the Westernized world
- 2.5% of infants <1 year allergic to cow's milk, 85% outgrow by age 3 (Host and Halken, 1994)
- 1.5% allergic to egg
- 40% of children with mod/severe AD have skin symptoms provoked by food hypersensitivity (Eigenman et al, 1998)
- 6% of asthmatic children have food-induced wheezing (Novembre et al, 1988)
- Most children "outgrow" milk and egg allergy, with about ½ outgrowing their allergy within 2–3 yr

Adverse Food Reactions



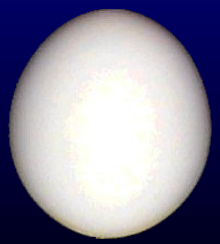
Food Allergens

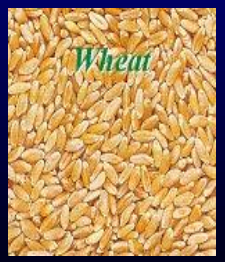
Children

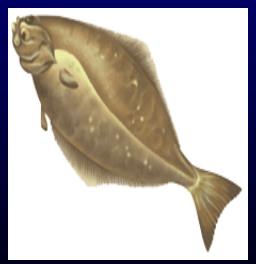
- ✓Milk
- ✓Egg
- ✓Peanut (Sesammee)
- ✓Soybean
- ✓Wheat
- ✓Tree nuts
- ✓Fish
- ✓Shellfish

Adults

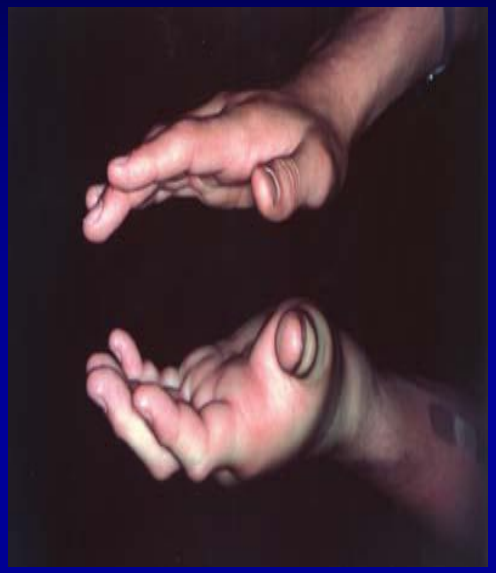
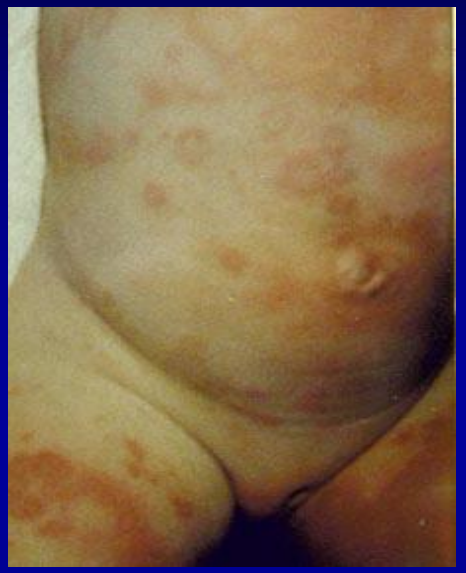
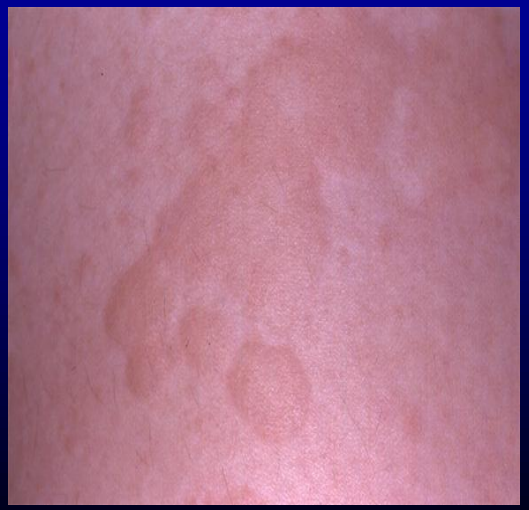
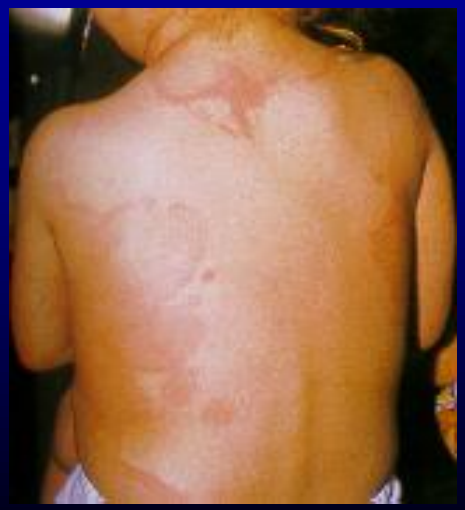
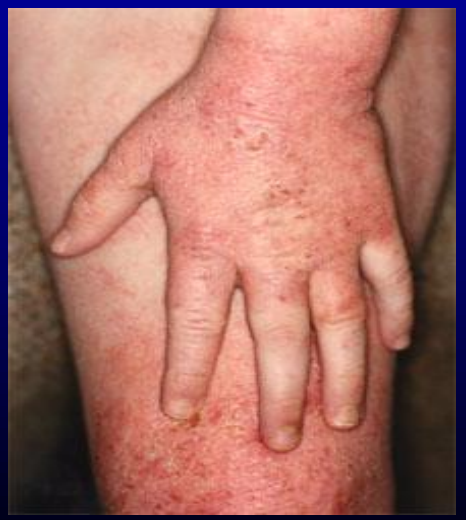
- ✓Peanut
- ✓Tree nuts
- ✓Fish
- ✓Shellfish




Cutaneous Manifestations of Food Allergy

FA points to remember

- Acute urticaria and angioedema are the most common symptoms
- Respiratory FA are uncommon as isolated symptoms
- Wheezing occurs in about 25% of IgE-mediated FA s
- Only about 10% of asthmatic patients have food-induced respiratory symptoms. – risk of severe asthma
- Food allergic reactions are the single most common cause of anaphylaxis seen in hospital emergency departments
- Chronic urticaria and angioedema are rarely due to FA

Risk Factors for Fatal Food Anaphylaxis

- Peanut and tree nut allergy
  Not all allergens are created equal
- Asthma
- Delayed administration of epinephrine
  - Bock, Munoz-Furlong, Sampson, et al, 2001

Bonus!

Treatment of Food Anaphylaxis

- Identification of food
- Strict avoidance, no try and see
- Children reevaluated periodically by an allergist
- Clear emergency treatment plan for the patient
- Prompt recognition of symptoms
- Oral antihistamines – fast acting
- Parenteral epinephrine
  - Self-injectable device
  - EpiPen Jr / Twinject Jr. 0.15 mg, und
  - Epi Pen / Twinject 0.3 mg, over 20 kg
- Follow up in the ED or call 911

Clinical Pearl: FA & Immunizations

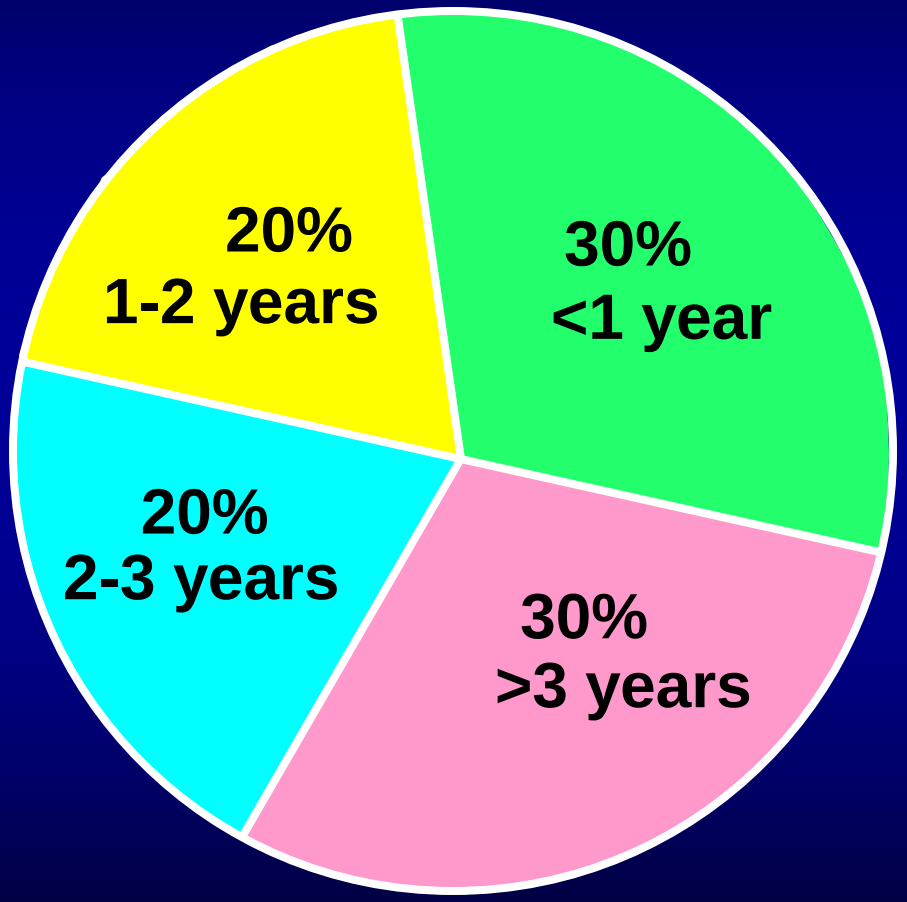
- Children with egg allergy may receive MMR/MMR-V as per routine protocol, no increased risk for allergic reactions
- Influenza vaccine contains egg protein and may cause allergic reactions in egg allergic children
- Children allergic to gelatin may react to gelatin stabilizer in vaccines, i.e. MMR

Asthma-Definition

- Asthma is a chronic inflammatory disorder:
  - Airway inflammation underlies the airway hyper-responsiveness to asthma triggers.
  - The airway hyper-responsiveness leads to airway obstruction that is usually reversible.
  - Obstruction leads to the classic symptoms of asthma: cough, wheeze, and dyspnea.

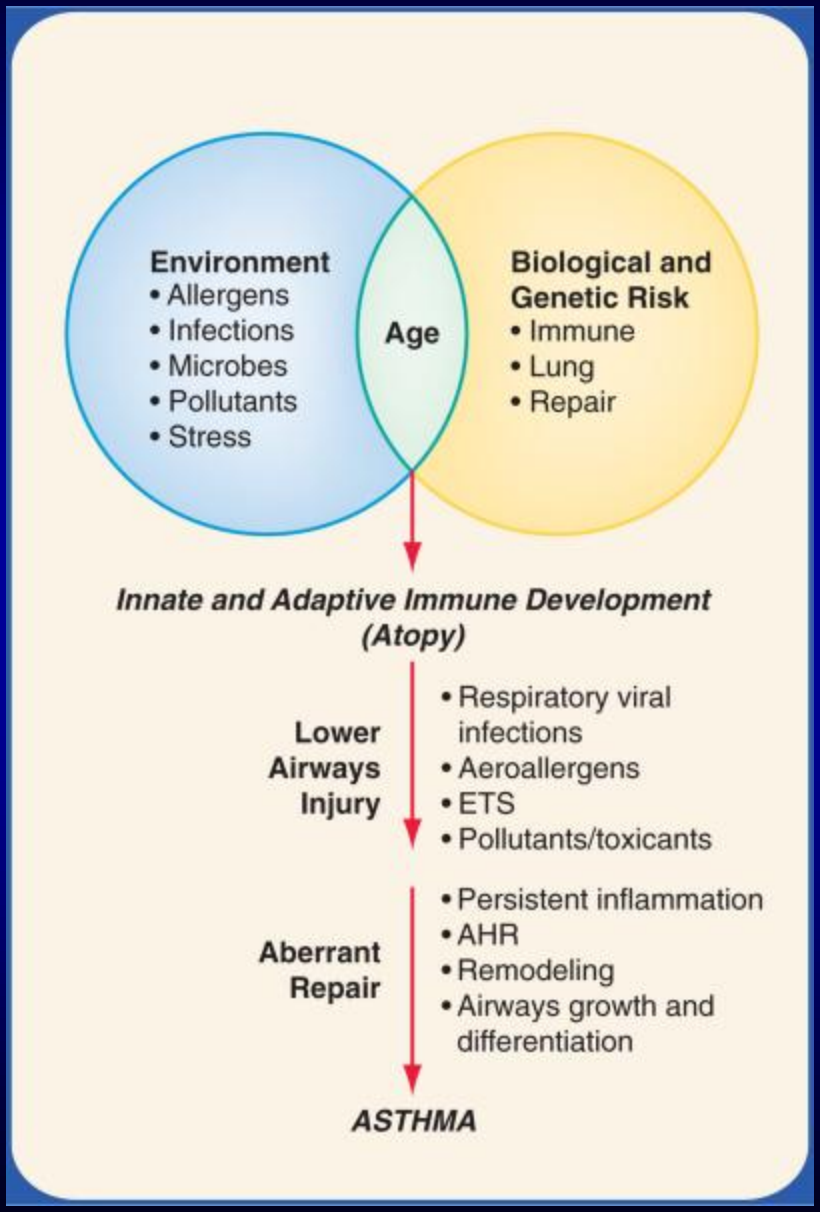
National Asthma Education and Prevention Program. *Highlights of theExpert Panel Report 2: Guidelines for the Diagnosis and Management of Asthma.* Bethesda, MD., May 1997. NIH Publication No. 97-4051A.

Onset of Symptoms in Children With Asthma

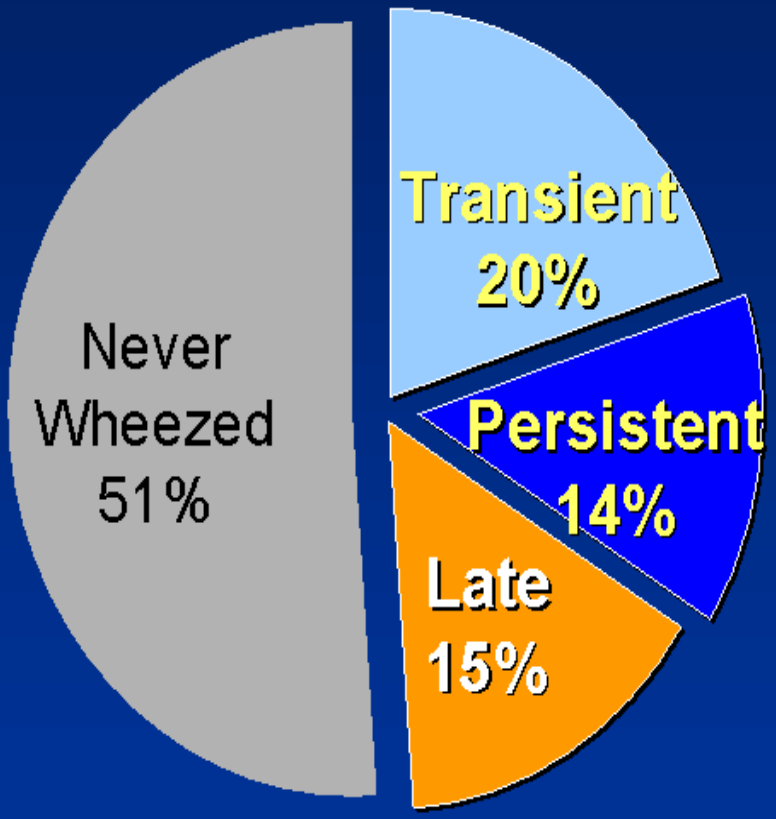


McNicol and Williams. *BMJ* 1973;4:7-11.
Wainwright et al. *Med J Aust* 1997;167:218-222.

Etiology of Asthma



Asthma and Wheezing in the First Six Years
Tucson Children's Respiratory Study



- TRANSIENT:
  wheeze <3 y.o.
  no wheeze at 6 y.o.
- PERSISTENT:
  wheeze <3 y.o.
  wheeze at 6 y.o.
- LATE:
  no wheeze <3 y.o.
  wheeze at 6 y.o.
- Never wheezed
  by age 6 years

(Total n=826)

Martinez et al. *N Engl J Med* 332:133-8, 1995.

Asthma-Natural History

- Approximately 80% of all asthmatics report disease onset prior to 6 yr of age
- Of all young children who experience recurrent wheezing, however, only a minority will go on to have persistent asthma in later childhood
- Early childhood risk factors for persistent asthma are:
  - Parental asthma
  - Allergy: Atopic dermatitis, Allergic rhinitis, Food allergy, Inhalant allergen sensitization, Food allergen sensitization
  - Severe lower respiratory tract infection: Pneumonia, severe Bronchiolitis
  - Wheezing apart from colds
  - Male gender
  - Low birthweight
  - Environmental tobacco smoke exposure
- **Asthma Predictive Index for Children**
  - MAJOR CRITERIA: Parent asthma, Eczema, Inhalant allergen sensitization
  - MINOR CRITERIA: Allergic rhinitis, Wheezing apart from colds, Eosinophils ≥ 4%, Food allergen sensitization
- One major criterion OR two minor criteria provide a high specificity (97%) and positive predictive value (77%) for persistent asthma

Clinical Pearl

- The most common **CAUSE** of wheezing in young children is viral respiratory infection

BUT

- The strongest predictor for wheezing that develops into asthma is ATOPY

Role of Allergens in Asthma

Atopy is one of the strongest asthma risk factors

Indoor allergens

- House dust mites
- Domestic pets
- Cockroaches
- Molds

Outdoor allergens

- Alternaria - a risk factor for childhood asthma (Peat et al. 1993, 1994)
- Ragweed (Creticos et al. 1996) and grass (Reid et al. 1986) associated with seasonal asthma exacerbations

When Is It Asthma?

- Repeated cough, wheeze, chest tightness
- Repeated dx of RAD, allergic bronchitis, or wheezy bronchitis
- Symptoms worsened by viral infection, smoke, allergens, exercise, weather
- Symptoms occur / worsen at night
- Reversible flow limitation (increase in FEV1 by 12% post-bronchodilator)
- Wheezing may or may not be present
- Persistent cough may be the only symptom

DDx - When Is It NOT Asthma?

- **UPPER RESPIRATORY TRACT CONDITIONS**
  - Allergic rhinitis, NA rhinitis, Sinusitis, Adenoidal or tonsillar hypertrophy, Nasal foreign body
- **MIDDLE RESPIRATORY TRACT CONDITIONS**
  - Laryngotracheobronchomalacia, Laryngotracheobronchitis, Laryngeal web, cyst, or stenosis, Vocal cord dysfunction, Vocal cord paralysis, Tracheoesophageal fistula, Vascular ring, sling, or external mass compressing on the airway, Foreign body aspiration, Chronic bronchitis, Toxic inhalations
- **LOWER RESPIRATORY TRACT CONDITIONS**
  - BPD, Viral bronchiolitis, Gastroesophageal reflux, bronchiectasis, Cystic fibrosis, Immune deficiency, Allergic bronchopulmonary mycoses, Chronic aspiration, Kartagener's, Bronchiolitis obliterans, Interstitial lung diseases, Hypersensitivity pneumonitis, Pulmonary eosinophilia, Churg-Strauss vasculitis, Pulmonary hemosiderosis, Tuberculosis, Pneumonia, Pulmonary edema.

Asthma Severity Vs Asthma Control

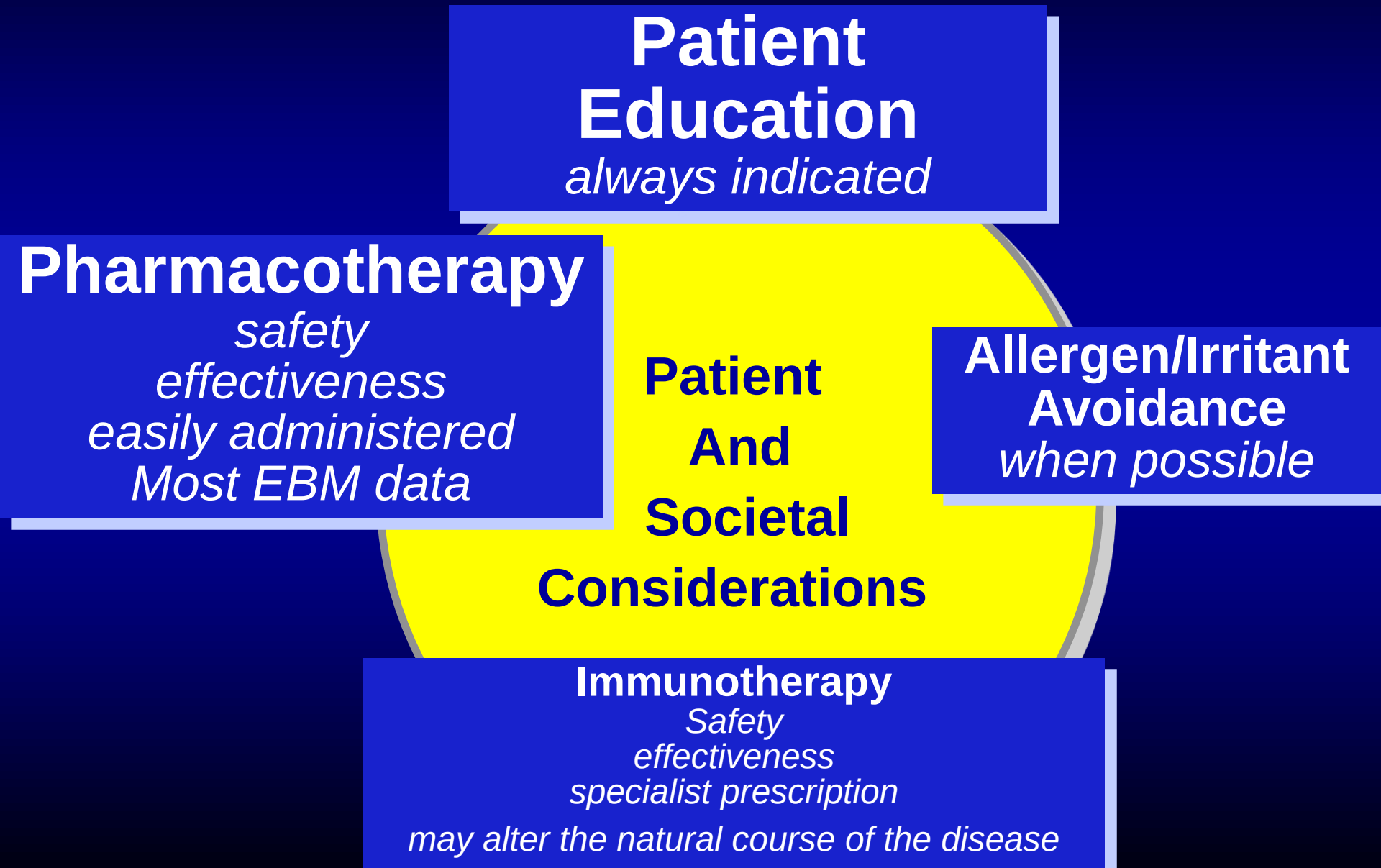
Components of Control		Classification of Asthma Control (Children 5–11 years of age)		
		Well Controlled	**Not Well Controlled**	**Very Poorly Controlled**
Impairment	Symptoms	≤2 days/week but not more than once on each day	>2 days/week or multiple times on ≤2 days/week	Throughout the day
	Nighttime awakenings	≤1x/month	≥2x/month	≥2x/week
	Interference with normal activity	None	Some limitation	Extremely limited
	Short-acting $beta_2$-agonist use for symptom control (not prevention of EIB)	≤2 days/week	>2 days/week	Several times per day
	Lung function ▪ FEV_1 or peak flow ▪ FEV_1/FVC	 >80% predicted/ personal best >80%	 60–80% predicted/ personal best 75–80%	 <60% predicted/ personal best <75%
Risk	Exacerbations requiring oral systemic corticosteroids	0–1/year	≥2/year (see note)	
		Consider severity and interval since last exacerbation		
	Reduction in lung growth	Evaluation requires long-term followup.		
	Treatment-related adverse effects	Medication side effects can vary in intensity from none to very troublesome and worrisome. The level of intensity does not correlate to specific levels of control but should be considered in the overall assessment of risk.		

Bonus!

Goals of Asthma Treatment

- Prevent chronic and troublesome symptoms
- Normal lung function (FEV1 / PEF >80% of predicted/personal best)
- Normal activity / exercise
- Prevent recurrent exacerbations
- Eliminate/minimize ED visits and hospitalizations
- Optimal pharmacotherapy with minimal or no adverse effects; minimal use <1x / day of short-acting beta2-agonist

Principles of Asthma Therapy



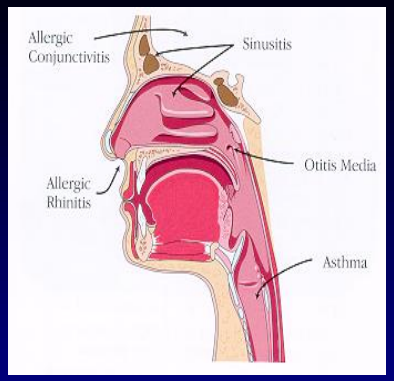
Bonus!

Severity-based Therapy for Asthma

Severity	Preferred	Alternative	PRN
Intermittent	No daily meds	N/A	Oral CS for severe exacerbations
Mild persistent	Low-dose ICS	Cromolyn, leukotriene modifier, nedocromil, OR sustained release theophylline	
Moderate persistent	Low-medium dose ICS AND long-acting beta2-agonist	Increased ICS in medium dose range , OR add leukotriene modifier or theophylline	
Severe persistent	High dose ICS AND long-acting beta2-agonist		

Clinical Pearls

- The most commonly encountered **adverse effects** from ICSs are local: oral candidiasis (thrush) and dysphonia (hoarse voice)
- BUT
- Their incidence can be minimized by using a spacer with MDI ICS and mouth rinsing using a “swish and spit” technique after ICS use



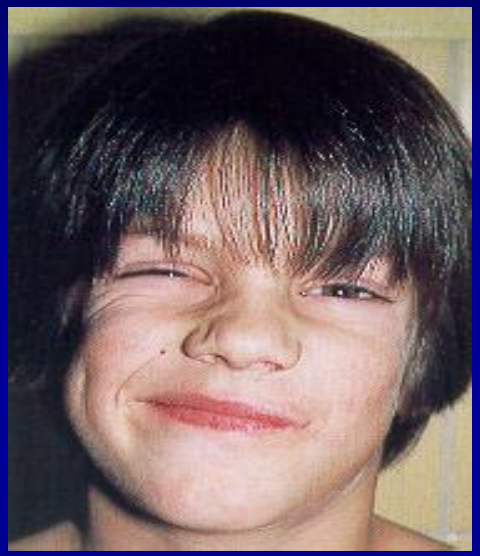
Allergic Rhinitis

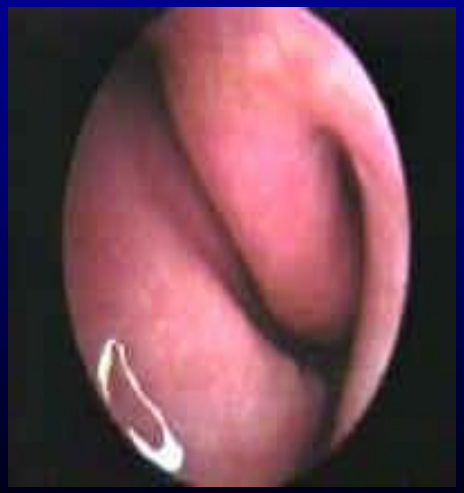
- An IgE mediated chronic inflammatory disorder of the nasal mucosa and respiratory sinuses
- Prevalence 3-19% (IS 15% in 14 yo)
- SAR 10%, PAR 10-20%, Mixed 5 – 10%
- The most common chronic disease in children
- Symptoms develop by 20 years in 80%; 20% by age 2-3 years, 40% by age 6 years, and 30% during adolescence

Allergic Rhinitis: Symptoms

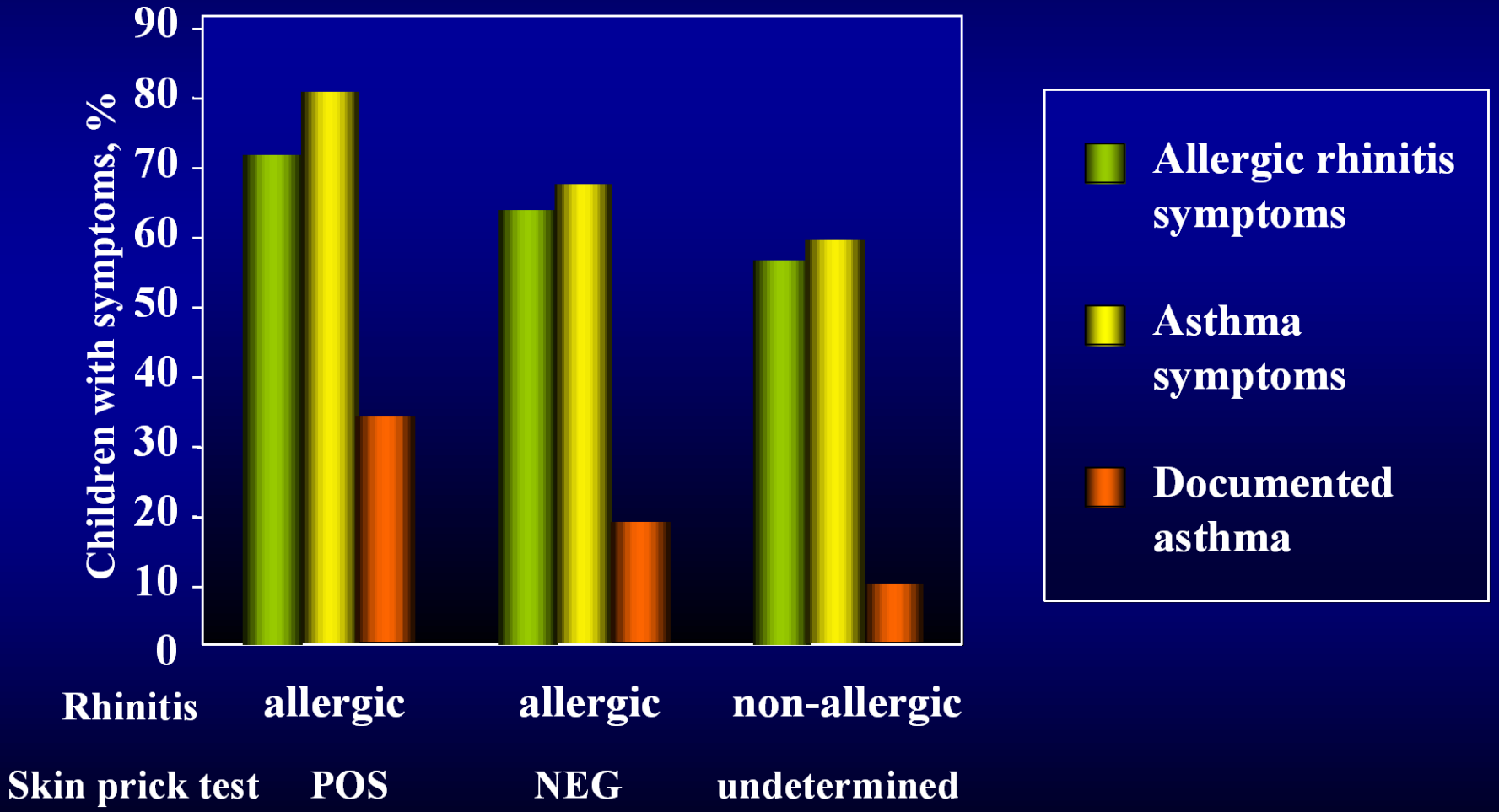
- Sneezing
- Itching
- Rhinorrhea
- Nasal congestion
- Postnasal drip
- Cough
- Halithosis
- Nasal speech
- Itchy, runny eyes

Allergic Rhinitis: Physical Findings



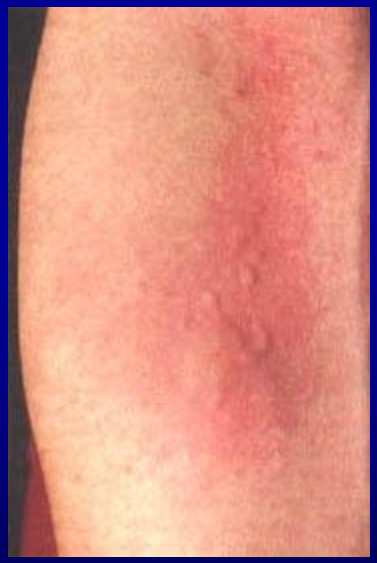
Early Allergic Rhinitis as Risk Factor for Asthma



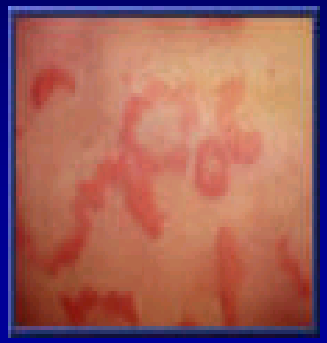
Wright AL, et al. *Pediatrics*. 1994 Dec;94(6)895-901.

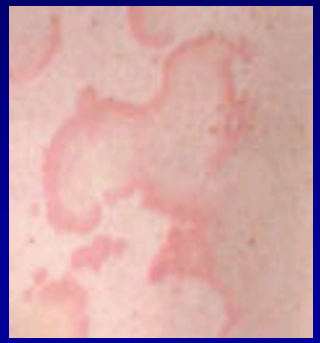
Urticaria and Angioedema

- Transient pruritic rash (welts or hives)
- Acute
  - 10-20% of general population
  - Drugs, food, viral infection, insect bites
- Chronic
  - Over 6 weeks
  - Difficult to identify the trigger,
  - Mostly post-viral/autoimmune
- Evaluation
  - History and physical examination
  - Allergy testing if indicated
  - Skin biopsy if lesions persist in the same location >24 hrs
  - Other: CBC, ESR, Stool O&P, TFTs, etc.

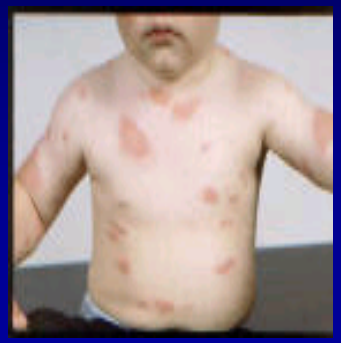


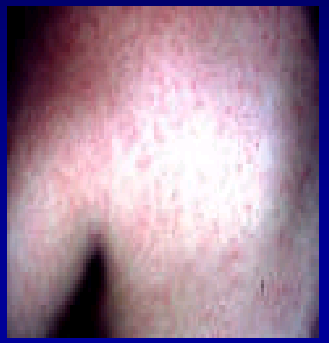
Urticaria



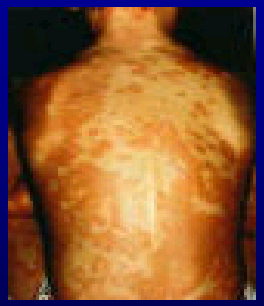


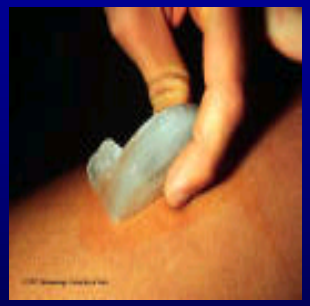
“Classic”



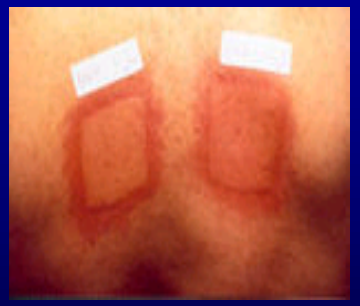


Cholinergic

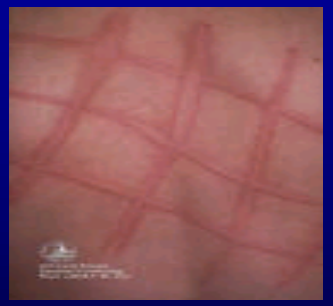




Cold - induced



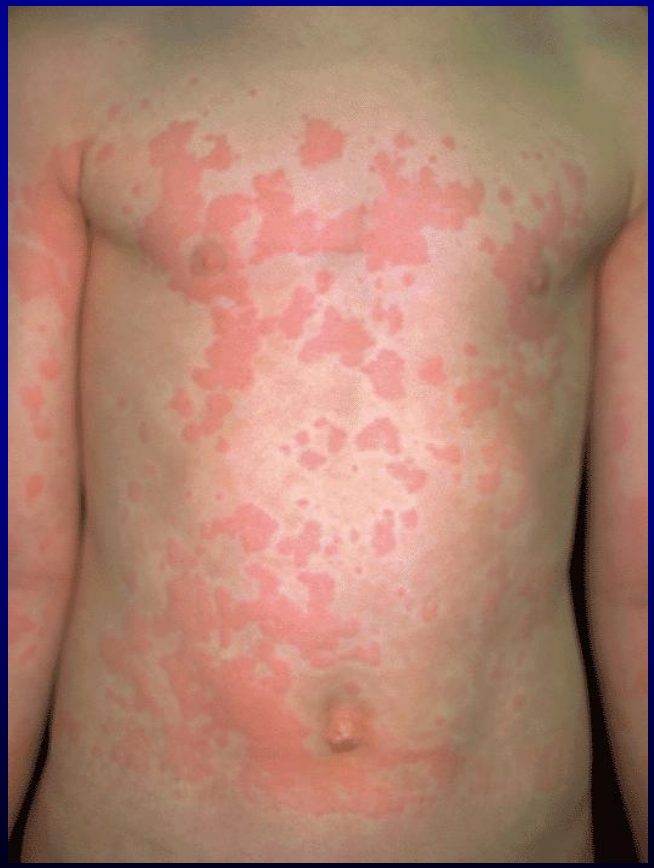
Solar



Dermatographism

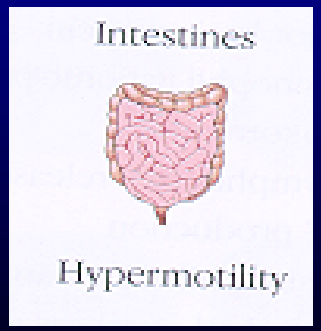
Urticaria -Treatment

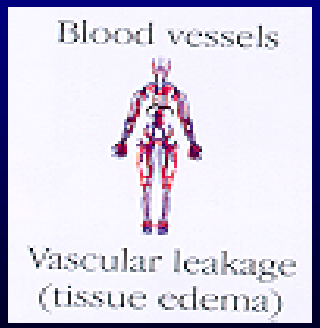
- Remove the offending agent
- Antihistamines
- Avoid ASA or NSAIDs
- Steroids
- Referral



Anaphylaxis

- Systemic immediate hypersensitivity reaction
- IgE / Non-IgE-mediated
- Release of histamine and other mediators from mast cells and / or basophils
- Biphasic course: early and late symptoms
- * Skin symptoms may be absent in up to 10-15% of most severe anaphylaxis





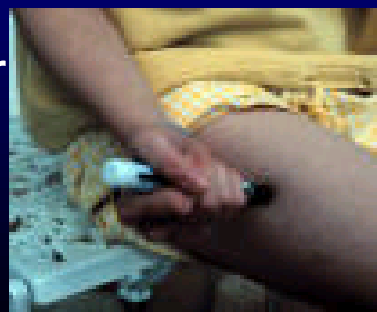
Etiology of Anaphylaxis

- In hospital: medications (ASA and NSAIDs, antibiotics, radiocontrast media, induction anesthetic agents, insulin, protamine, progesterone), latex, foods

- Outside hospital:
  - Yocum et al, 1999: *36% foods*, 17% medications, 15% insect stings
  - Pumphrey et al, 1996: *foods* (peanut and tree nuts) major cause in north-west England
  - Novembre et al, 1998: *foods* responsible for 50% of anaphylaxis in children treated in the ER

Treatment of Anaphylaxis

- Emergency
- Recognize the symptom pattern
- Measure serum tryptase (marker of mast cell degranulation): elevated 30 min up to 18 hours (not usually in food anaphylaxis
- I. M. epinephrine 1:1000, 0.01 mL/kg (0.3-0.5 ml)
- I. V. antihistamine (H1, H2 blockers), steroids, fluids, oxygen
- INH beta-agonists
- **Observation ≥ 4 hours**
- Refer for allergy evaluation to identify the trigger
- Clear emergency treatment plan
- Rx self-injectable epinephrine device

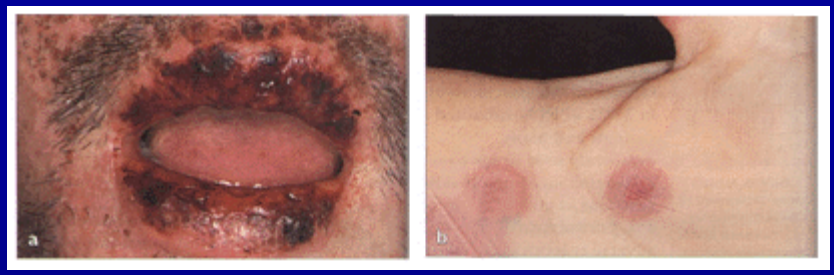


Anaphylaxis

- A 5 year old boy with a severe allergy to milk needs a CT scan with IV and oral contrast. You advise:
  A. Pretreat with prednisone and diphenhydramine.
  B. Pretreat with hydrocortisone.
  C. Desensitization to contrast media
  D. Reassurance
- Risk for a reaction is negligible. Pretreat only if there is a h/o a reaction to contrast media.

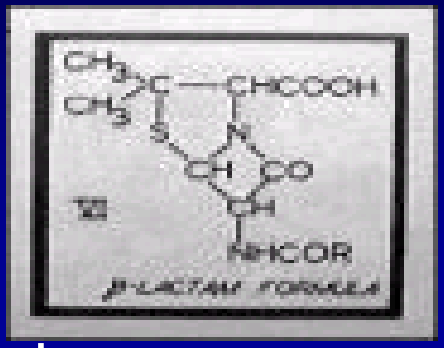
Drug Allergy

- Immune Mediated
  - IgE-mediated (Type I)
    - Hives, anaphylaxis
  - Non-IgE-mediated
    - Maculopapular rash
    - Serum sickness (Type III)
    - Stevens-Johnson (Type IV)
- Non Immune = direct release of histamine
  - Radiocontrast media
  - Vancomycin
  - Opiates

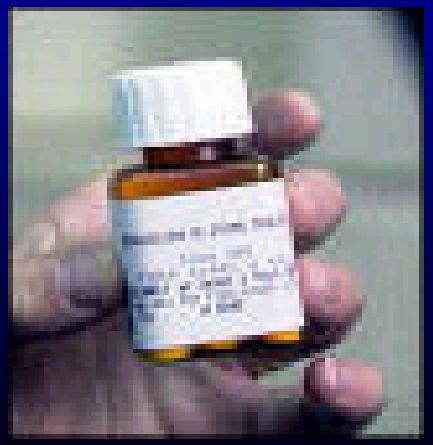


	INTERVAL BETWEEN EXPOSURE AND REACTION	EFFECTOR CELL OR ANTIBODY	TARGET OR ANTIGEN	EXAMPLES OF MEDIATORS	DISORDER	
Type I	Anaphylaxis		IgE	Pollens, foods, drugs, insect venoms		Anaphylaxis
	a. Immediate	<30 minutes			a. Histamine	Allergic rhinitis
	b. Late phase	2-12 hours			b. Leukotrienes	Allergic asthma
Type II	Cytotoxic	Variable (minutes to hours)	IgG, IgM	Red blood cells, lung tissue	Complement	Immune hemolytic anemia Rh hemolytic disease Goodpasture syndrome
Type III	Immune complexes	4-8 hours	Antigen with antibody	Vascular endothelium	Complement Anaphylatoxin	Serum sickness Poststreptococcal glomerulonephritis
Type IV	Delayed type	24-48 hours	Lymphocytes	*Mycobacterium tuberculosis*, chemicals	Cytokines	Contact dermatitis Tuberculin skin test reactions

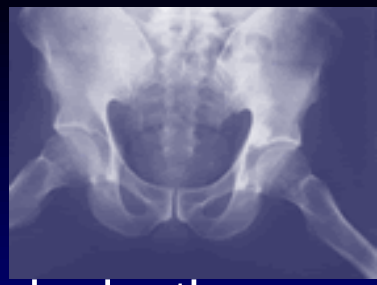
Drug Allergy - Treatment



- Stop the drug
- Use alternatives from a different class
- Skin testing to penicillin, or high molecular drug
- Desensitization (gradual administration)
  - not indicated in SJS, TEN, serum sickness, reactions to anti-convulsants
- Treat through mild reaction



Radiocontrast Media



- Urticaria, angioedema, laryngo/bronchospasm, shock, death
- Incidence 1.7% of IVP
- Recurrence 16% on subsequent administration
- ⇑ risk: atopy, older age, CHD, use of β - blockers, asthma
- Allergy to seafood and sensitivity to iodine are not risk factors
- ⇓ recurrence with newer, non-ionic, lower osmolar RCM
- Pre - medication with prednisone 50 mg po 13, 7, and 1 hours prior to procedure, diphenhydramine 50 mg po 1 hour prior ⇒ ⇓ risk by 5-10x
- Consider pre - medication for high risk patients without h/o prior reactions: strongly atopic, extensive cardiovascular disease

Insect Sting Allergy

- Most common offenders: Yellow Jacket, Hornets, Wasp, Honeybee, Bumblebee, and Fire Ant
- Degrees of severity
  - Local or large local
  - Toxic
  - Delayed
  - Systemic
- Systemic reaction: Rx self-injectable epinephrine device and refer for allergy evaluation
  - Skin testing and serum venom - IgE
  - Venom IT reduces risk from >50% to <2%

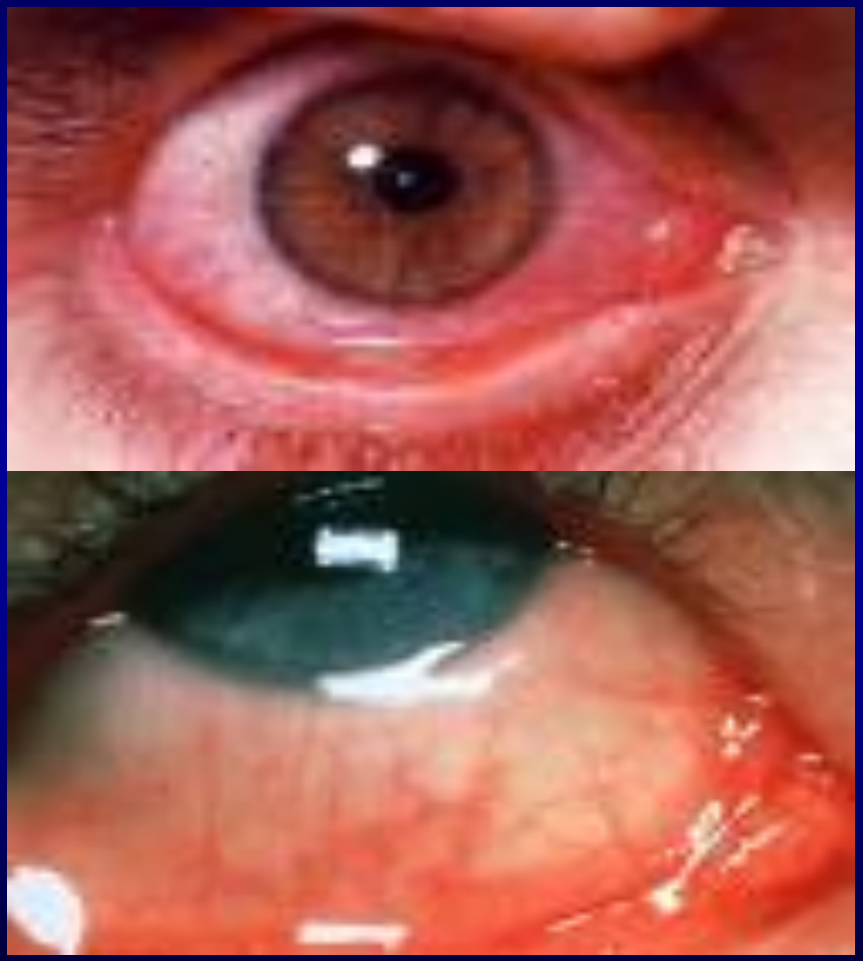
*Under 16 years of age: generalized urticaria is not associated with increased risk for ANA upon subsequent stings, not an indication for VIT

Ocular Allergies

- My involve eyelid or conjunctiva
- Occur when exposed to triggering agent

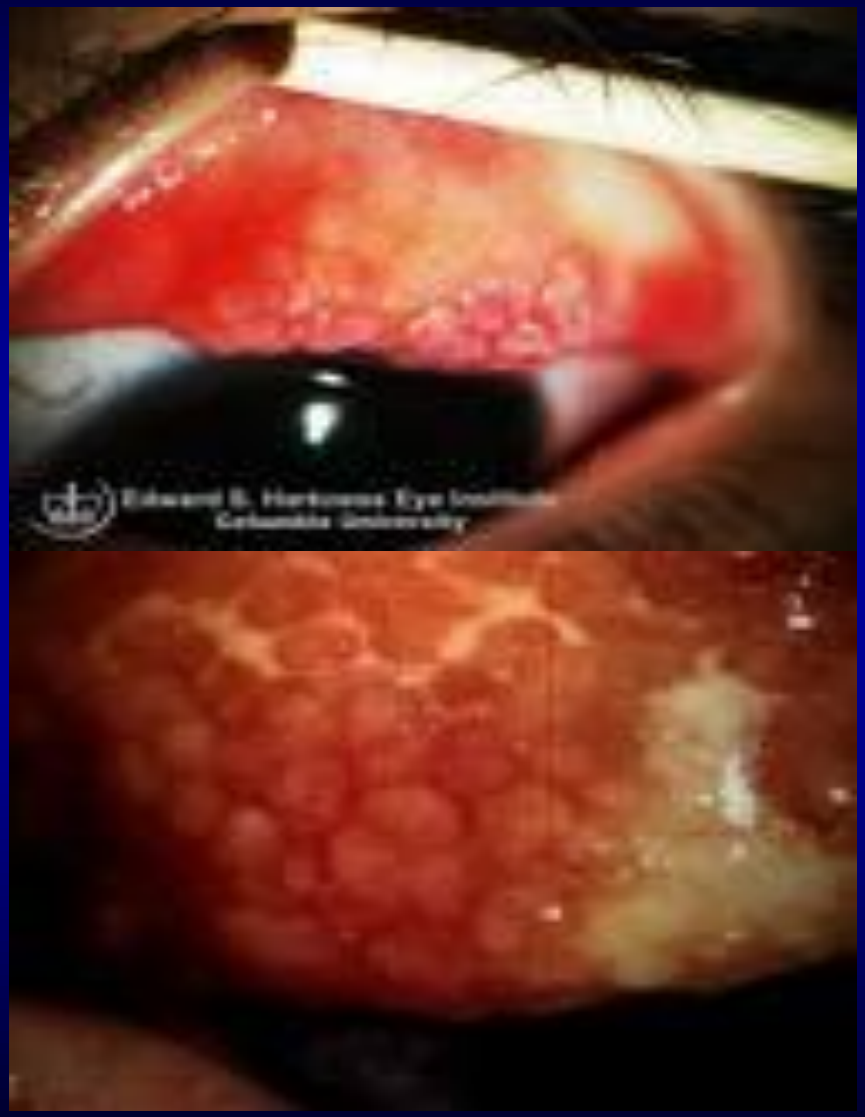
Allergic Conjunctivitis

- Allergic Conjunctivitis
- Acute or Chronic, Seasonal or Perennial
- Itching and Excessive tearing
- Physical Finding: Allergic Cobblestoning with fine granular appearance of the conjunctiva



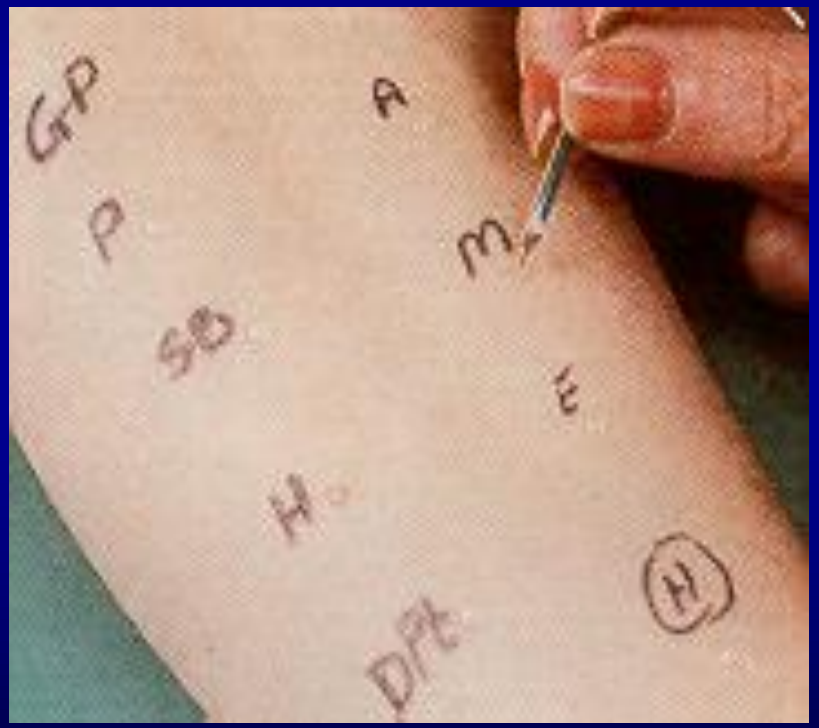
Vernal Conjunctivitis

- Uncommon and Chronic
- Mostly in young atopic boys
- Symptoms: Severe itching, photophobia, blurring of vision, and tearing
- Physical Exam Finding: White, Ropy secretions that contain many eosinophils, may see hypertrophic nodular papillae that resembles cobblestones usually on the upper eyelid.
- May be due to build up on foreign objects being placed in the eyes such as contacts for long durations with chronic exposure



Allergy Evaluation

- History and physical exam
- Prick skin testing
- Serum allergen-specific IgE
- Challenge



Bonus!

Allergy Diagnosis

- **Skin test**
- **Less expensive**
- **Greater sensitivity**
- **Wide allergen selection**
- **Immediate results (10-15 minutes)**

- **Serum Immunoassay**
- **No patient risk**
- **Convenience**
- **Not affected by antihistamines**
- **Quantitative results**
- **Preferable to skin testing in:**
  - **Dermatographism**
  - **Extensive eczema**
  - **Uncooperative patient**

Bonus!

Food Allergen-Specific IgE levels (kU/L) in the Diagnosis of Food Allergy

	Egg	Milk	Peanut	Fish	Soy	Wheat	
Reactive if ≥ (no challenge necessary)	7	15	14	20	65	80	Probability of reaction
Possibly reactive (physician challenge)					30	26	
Unlikely reactive if < (home challenge)	0.35	0.35	0.35	0.35	0.35	0.35	

Sampson HA, JACI, 2001

Allergen Immunotherapy

- Subcutaneous injections of specific allergen in gradually increasing doses: environmental allergens, insect venoms
- Generally indicated for subjects who don't respond well to pharmacotherapy
- Allergen avoidance always recommended
- Useful for AR, asthma, venom allergy; generally not indicated for AD and contraindicated in food allergy

Clinical Features of Immunodeficiency

- Increased susceptibility to infection
  - Chronic / recurrent infections without other explanations
  - Infections with organisms of low virulence (P.carinii, invasive fungal infections, vaccine Polio, BCG infection after vaccination)
  - Severe infections: pneumonia with empyema, bacterial meningitis, arthritis, sepsis, mastoiditis
- Autoimmune or inflammatory disease
  - Target cells: hemolytic anemia, ITP, thyroiditis
  - Target tissues: RA, vasculitis, SLE
- Syndrome complexes

10 WARNING SIGNS OF PRIMARY IMMUNODEFICIENCY

Primary immunodeficiency (PI) causes children and young adults to have infections that come back frequently or are unusually hard to cure. In America alone, up to 1/2 million people suffer from one of the 140 known primary immunodeficiency diseases. If you or someone you know is affected by two or more of the following warning signs, speak to a physician about the possible presence of an underlying primary immunodeficiency.

1. Eight or more new ear infections within 1 year.
2. Two or more serious sinus infections within 1 year.
3. Two or more months on antibiotics with little effect.
4. Two or more pneumonias within 1 year.
5. Failure of an infant to gain weight or grow normally.
6. Recurrent deep skin or organ abscesses.
7. Persistent thrush in mouth or elsewhere on skin, after age 1.
8. Need for intravenous antibiotics to clear infections.
9. Two or more deep-seated infections.
10. A family history of primary immunodeficiency.

ID Syndromes with Increased Sinopulmonary Infections

- Ataxia teleangiectasia:
  - Ataxia, telangiectasia, variable B and T lymphocyte dysfunction, dysfunctional swallow with pulmonary aspiration
- DiGeorge
  - CHD, hypoparathyroidism, abnormal facies; thymic hypoplasia or aplasia; cleft palate, dysfunction of soft palate
- Dysmotile cilia:
  - Situs inversus [Kartagener's syndrome], male infertility, ectopic pregnancy, upper and lower resp. tract infections; immotile cilia
- Hyper-IgE:
  - Coarse facies, exczematoid rash, retained primary teeth, bone fractures, pneumonia; elevated serum IgE, eosinophilia
- Wiskott-Aldrich
  - Thrombocytopenia, eczema, variable B and T lymphocyte dysfucntion

Patterns of Illnesses Associated with Primary ID

- **Antibody**: sinopulmonary inf., GI (enterovirus, Giardia); autoimmune dz
- **T-cell immunity**: pneumonia (bacteria, P. carinii, virus), GI viral inf., skin/mucous membranes (fungi)
- **Complement**: sepsis, meningitis(Strep, Pneumococcus, Neisseria); autoimmune dz (SLE, gromeluronephritis)
- **Phagocytosis**: skin, RES, abscesses (Staphylococcus, enteric bacteria, fungi, mycobacteria)

Antibody Deficiency

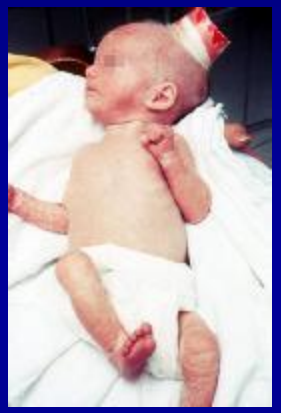
- X-linked agammaglobulinemia*
  - Only boys, infections start by 9-18 months
  - Absence of tonsils and lymph nodes on PE
  - Pneumonia, chronic enteroviral meningitis, vaccine-Polio, mycoplasma/ureaplasma arthritis
- Common variable immunodeficiency*
  - Onset 1st and 3rd decades of life, both sexes
  - Sinopulmonary infections, asthma, chronic rhinitis, IBD, autoimmnue disorders (pernicious anemia, thrombocytopenia); 1.4-7% develop B cell lymphoma
- IgA deficiency
  - Prevalence 1:700 whites; mostly asymptomatic
  - May be associated with chronic bacterial sinusitis, atopy, autoimmne dz (Crohn's, IBD, SLE)
- IgG subclass deficiency
  - IgG2 and IgG4
  - Controversy re: if clinically relevant; may be associated with recurrent sinopulmonary infections
- **Transient hypogammaglobulinemia of infancy**
  - IgG transported via placenta, nadir 3-9 months postnatal life
  - Begins in infancy, resolves spont. By 36-48 months of age
  - Most asymptomatic but may present with recurrent infections
  - Some children have food allergy
  - Typically normal responses to vaccines (IgG to tetanus, diphtheria)

*Treatment: IVIG replacement, antibiotic prophylaxis

Severe Combined Immunodeficiency (SCID)

- Positive family hx (X-linked, parental consanguinity)
- Presentation early in life: first 4-6 months of age
- Severe respiratory infections (interstitial pneumonia)
- Protracted diarrhea
- Failure to thrive
- Persistent oral thrush
- Skin rash, erythrodermia
- Laboratory findings:
  - Lymphopenia (ALC<2000/µl)
  - Reduced CD3+T lymphocytes (<1500/µl)
  - Very low or undetectable levels of serum immunoglobulins (although may be initially normal due to transplacental passage of maternal IgG)
  - Very low to absent *in vitro* proliferative responses to mitogens

Treatment: medical emergency! aggressive tx of infections, PCP prophylaxis, IVIG, isolation, irradiate blood products, BMT!!!



White Blood Cell Defects

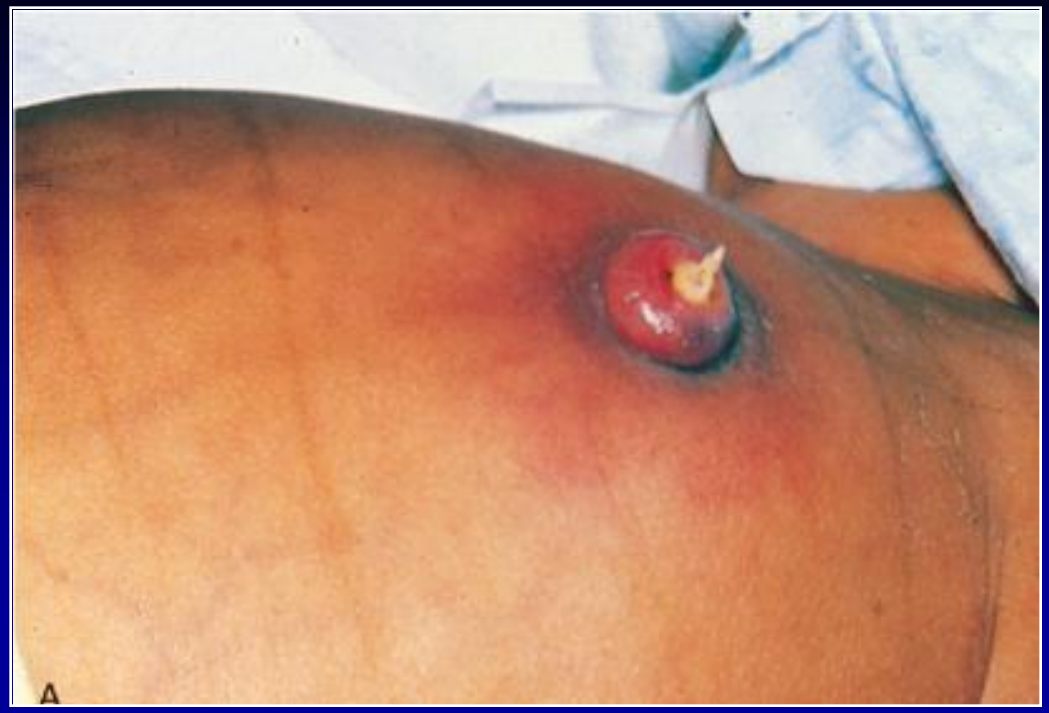
- **Defective oxidative burst: <u>Chronic granulomatous disease*</u>**
  - May be X-linked or AR
  - Recurrent life threatening infections by catalase positive bacteria (Staph aureus, Nocardia, Salmonella, Serratia, Burkholderia cepacia) and fungi (Aspergillus, Candida) and exuberant granuloma formation (liver, gut, GU), abscesses, suppurative adenitis, osteomyelitis;
  - Peripheral blood neutrophilia during the infection
  - Aspergillus pneumonia-major cause for mortality
  - Tx: prophylaxis with Bactrim, itraconazole and IFN-γ
- **Neutropenias**
- **Defective granule formation and content: Chediak-Higashi syndrome**
  - AR, oculocutaneous albinism, pyogenic infections, neurologic abnormalities, late onset lymphoma
- **Leukocyte adhesion deficiency (types 1-4)**
  - LAD 1: AR, deficiency of CD18 and as result of CD11 a-c
  - Defective neutrophil chemotaxis and tight adherence
  - Delayed umbilical cord separation, omphalitis, severe destructive gingivitis and periodontitis, recurrent infections of skin, upper/lower airways, bowel and perirectal area (necrosis, ulceration); *S. aureus*, gram-negative bacilli
  - Peripheral blood leukocytosis >15,000 /µl (baseline), eosinophilia,

Differential Diagnosis

- Allergy
- Cystic fibrosis
- Ciliary dysmotility due to recurrent infections
- Localized abnormalities of anatomy or physiology (i.e., cleft palate, neurological impairment)
- Secondary immunodeficiency; HIV, leukemia/lymphomas, chemotherapy
- Environmental factors:
  - Day care attendance, sick older siblings
  - Exposure to irritants: tobacco smoke, fumes, etc

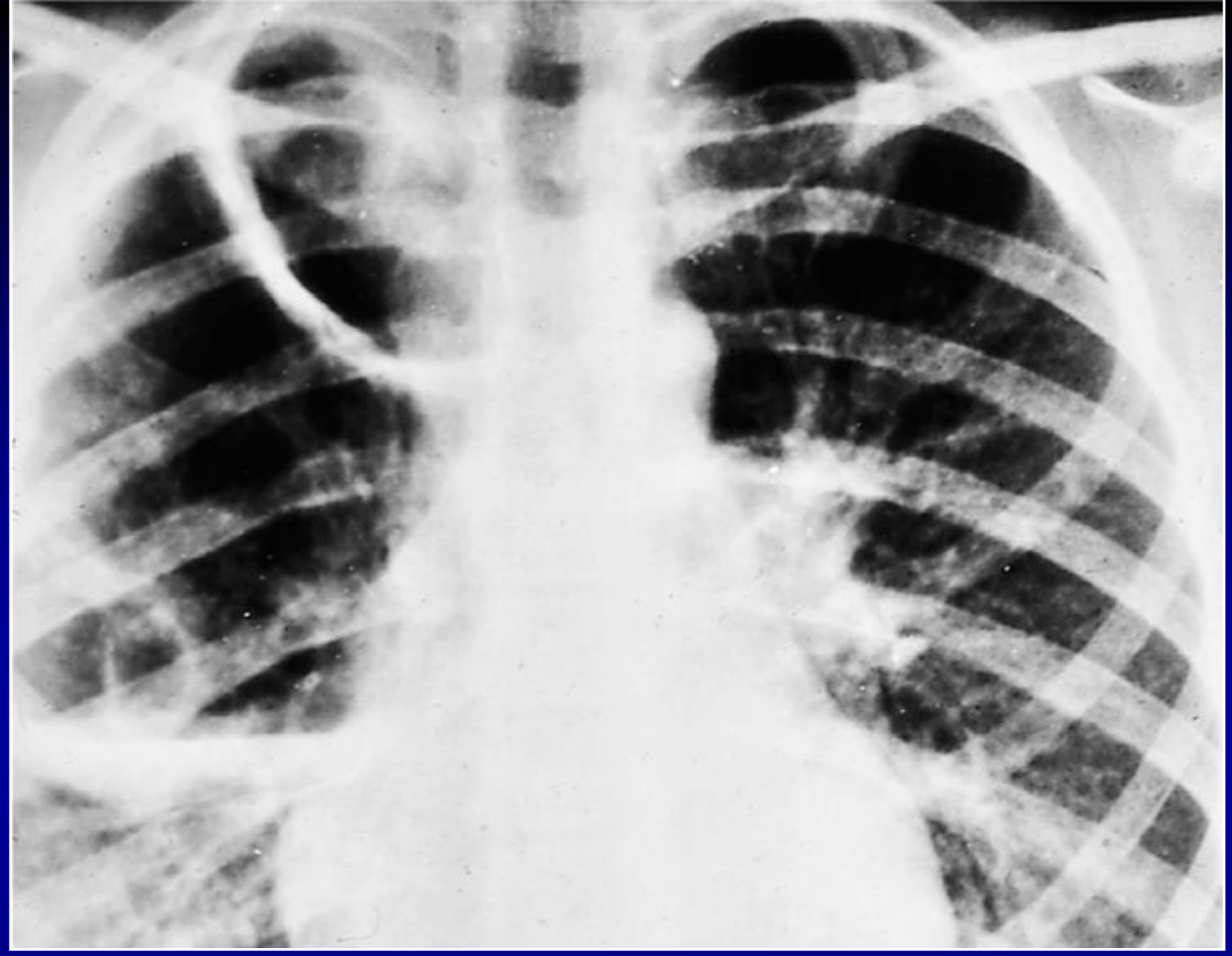
Screening Tests

- Antibody:
  - Serum IgG, IgA, IgM
  - IgG to immunizations: tetanus, diphtheria, Strep. pneumoniae
- T-cell immunity:
  - Lymphocyte count (<2000/ul)
  - T cell enumeration (CD3, CD4, CD8)
  - HIV serology
- Complement:
  - CH50
- Phagocytosis:
  - Neutrophil count
  - Nitroblue tetrazolium test or other tests for oxidative burst



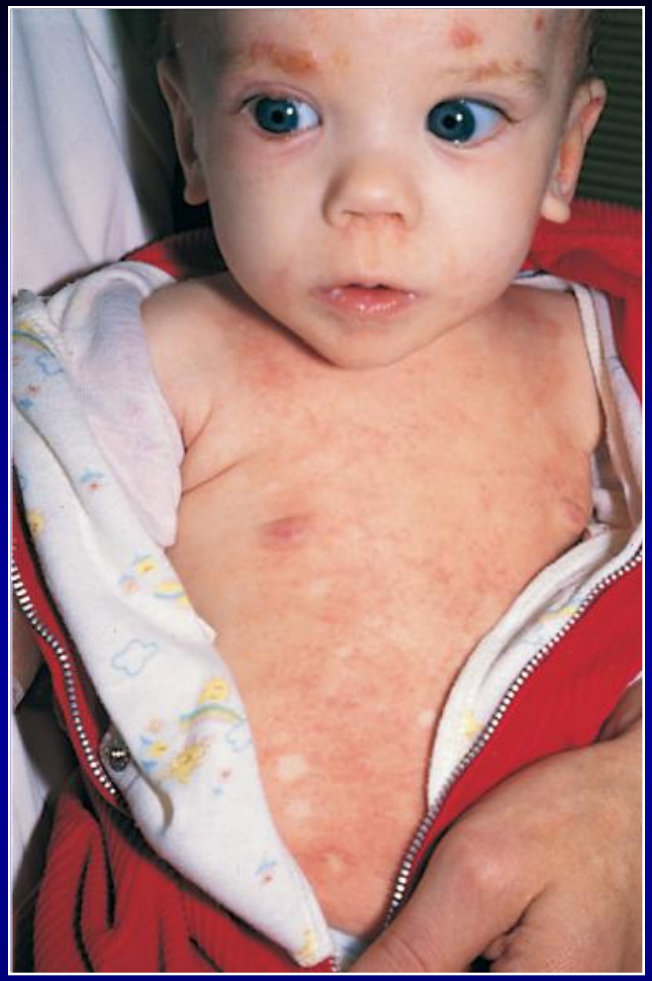
This child had delayed cord separation and developed an umbilical stump infection. What disease might you suspect and what abnormalities would you expect on CBC?

Leukocyte Adhesion Deficiency and elevated neutrophils.



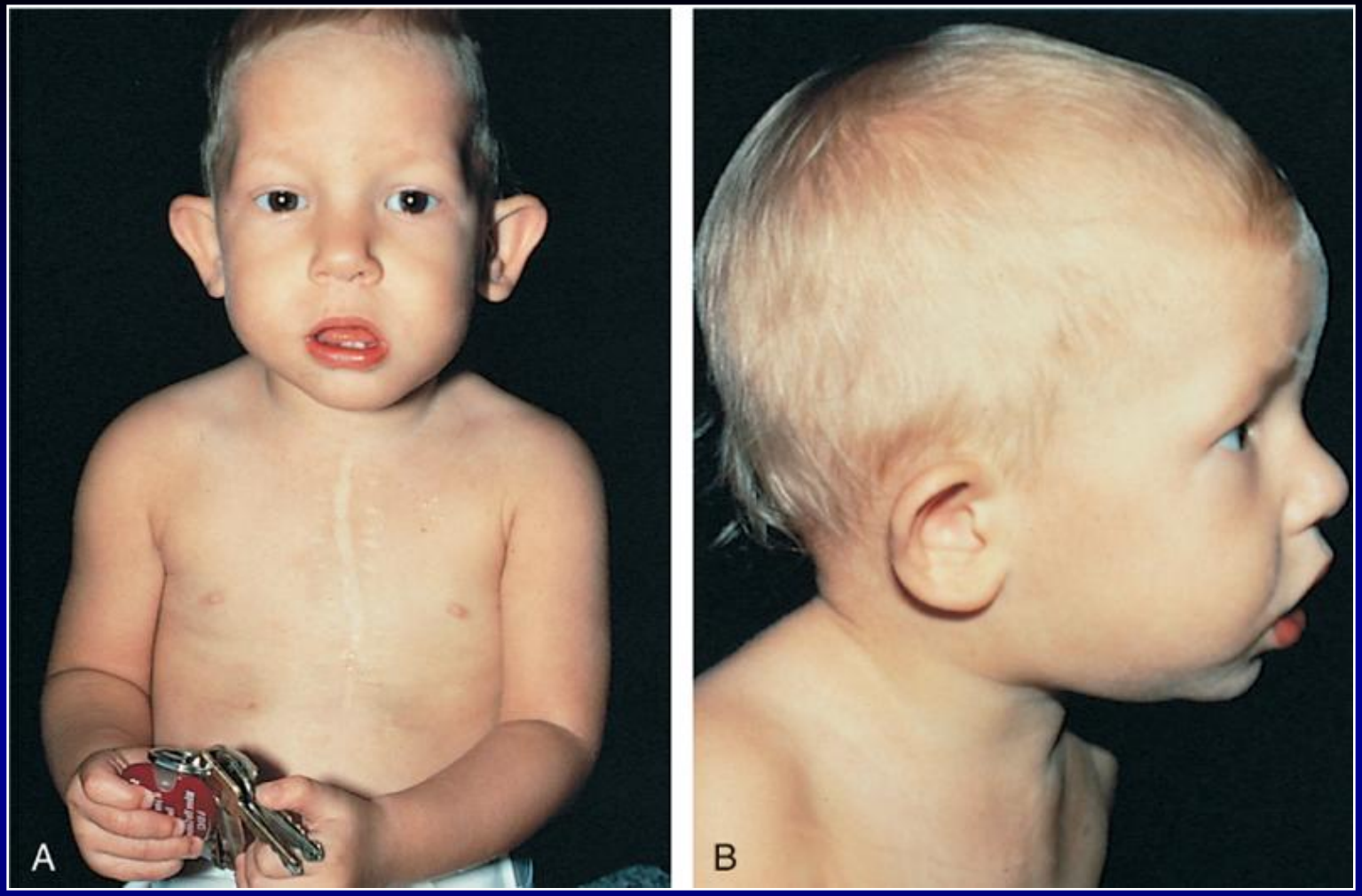
What is organism most likely to cause the chest xray seen above? If this child had frequent pneumonias and maybe skin abscesses what immune deficiency would you suspect? What dental findings might this child have?

S. aureus, Job syndrome (hyper IgE), delayed loss of primary teeth



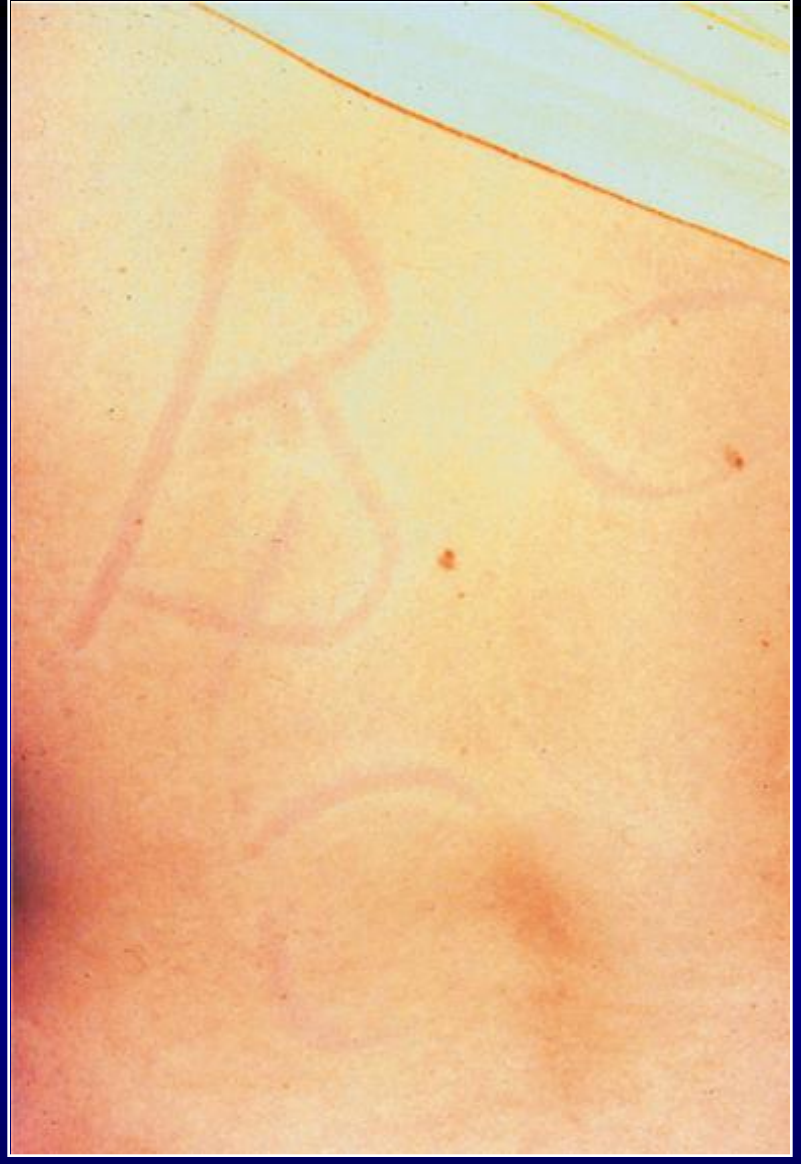
The clinical findings of thrombocytopenia and eczema (as seen here) are characteristic of what disease? What is the inheritance pattern?

Wiskott Aldrich and x linked recessive



This child has velocardiofacial syndrome. What are the common heart defects seen? What is the associated immune deficiency?

VSD, Interrupted arch, TOF, truncus arteriosus. T cell deficiency (lack of thymus)



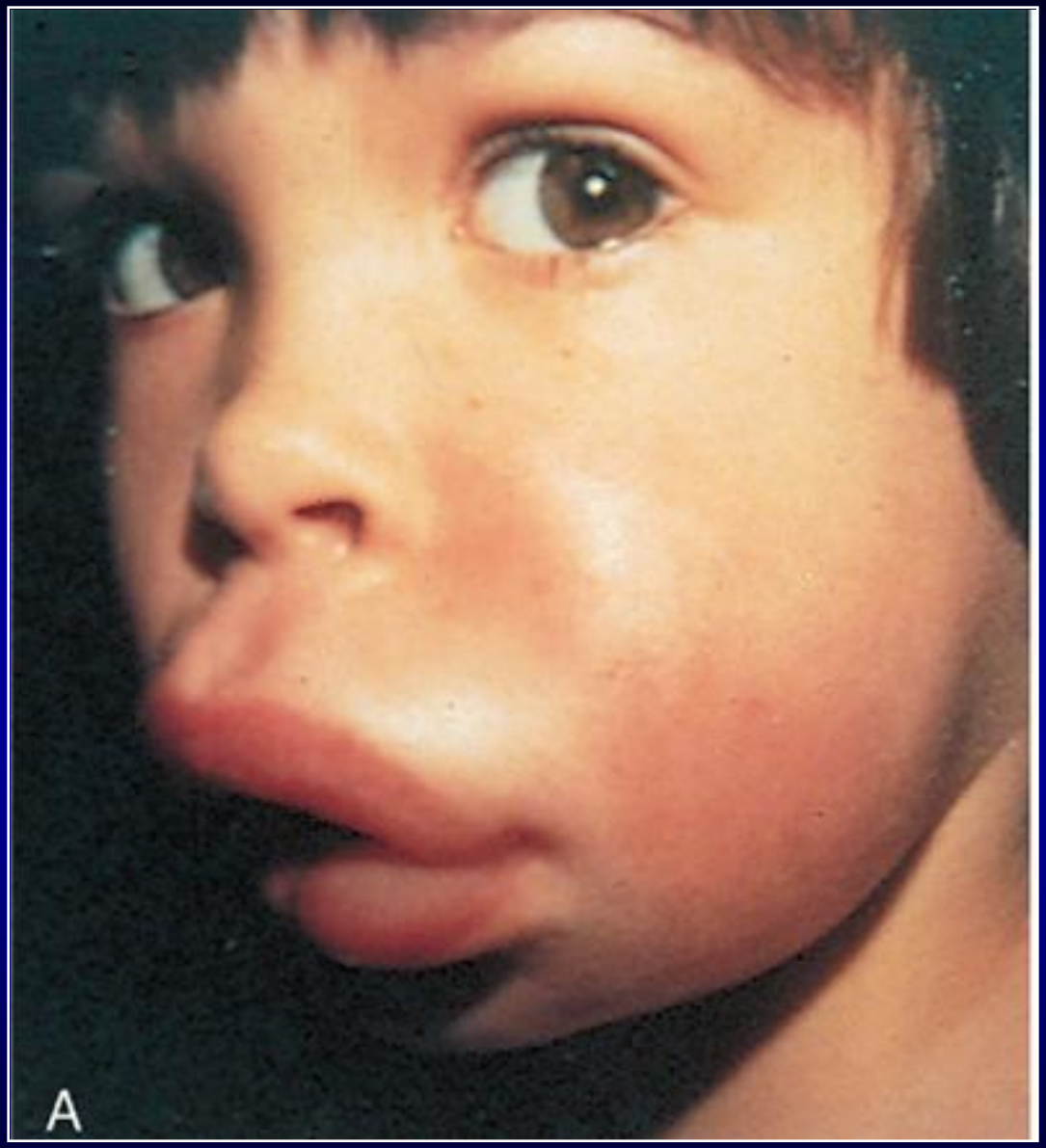
What is this called?

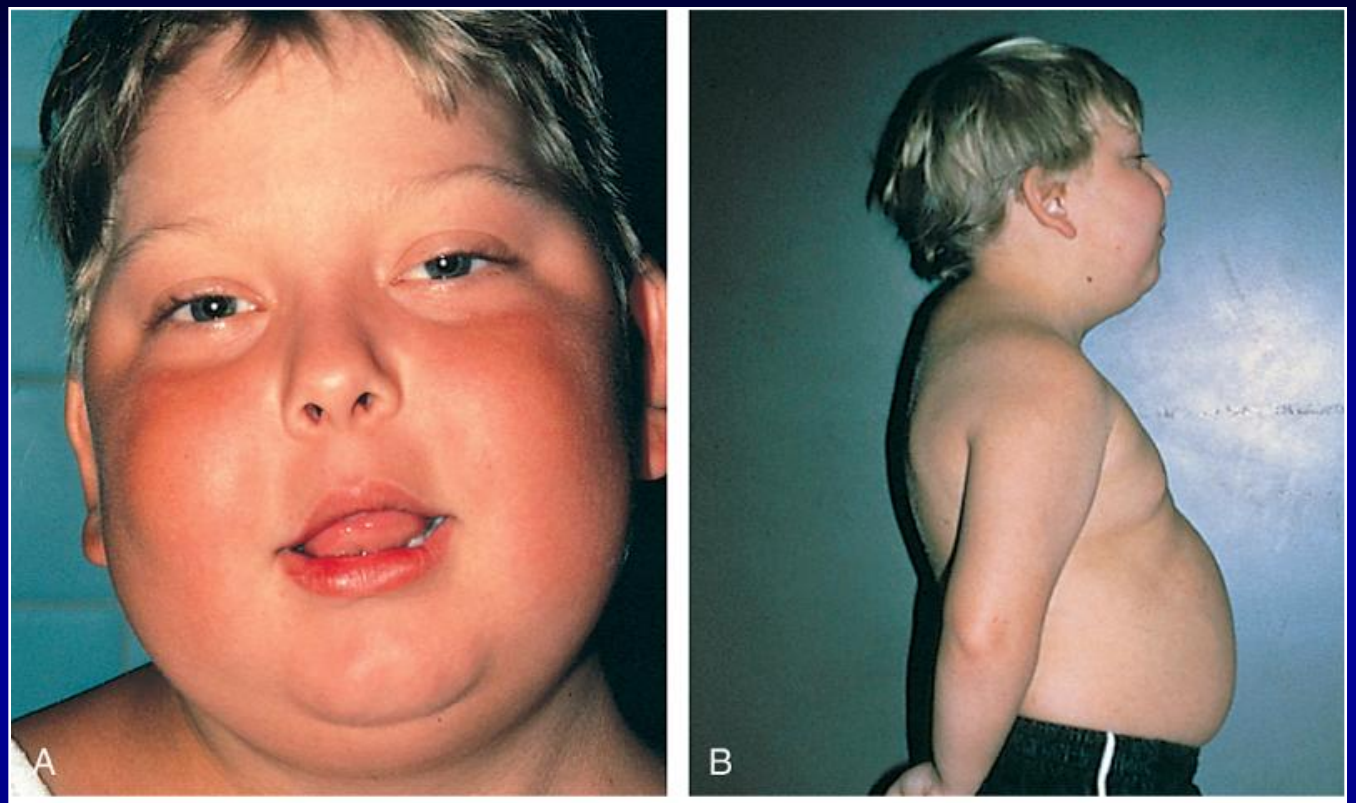
Dermatographism

This kid comes into the ER. What is the treatment you would recommend?

- **Epinephrine**
- **H2 blocker**
- **Steroids**
  to prevent what?

- **Would you send the kid home with any specific instructions or medications?**





What are the physical findings seen in this picture?
What are the diagnoses?

Cushingoid findings, long term steroid Rx

What is the treatment for the teen seen above?

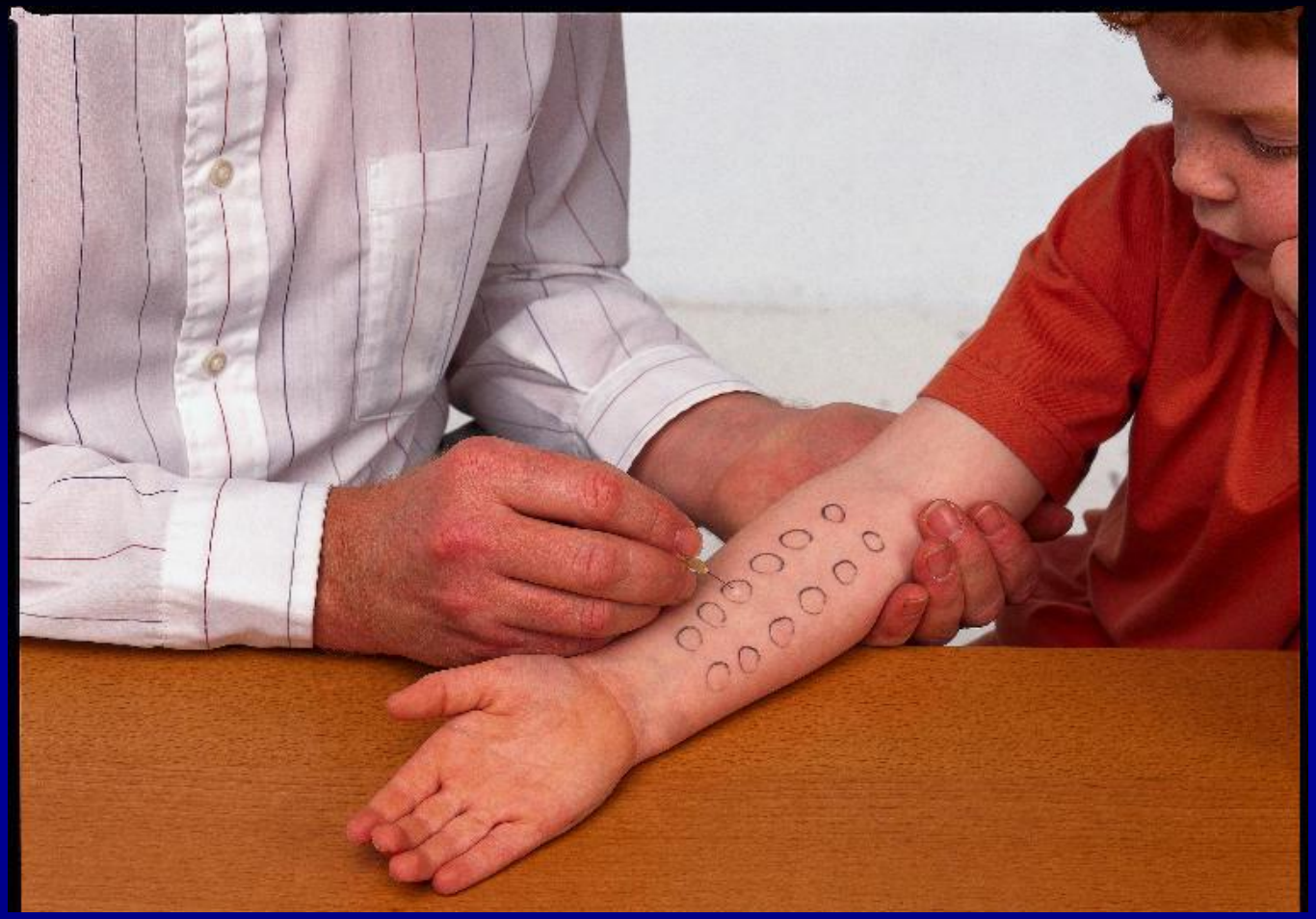
Allergen avoidance!
Intranasal steroids

A sting by this animal would be considered what type of hypersensitivity reaction?

Type I

What is the long term treatment for a child with severe allergy to hymenoptera stings?

Venom immunotherapy



These are the 4 contraindications to skin prick testing.

1. **Antihistamine use in recent past**
2. **Skin disease**
3. **Asthma exacerbation/ anaphylaxis**
4. **Use of B blocker**

Now on to the fun stuff….

- B cell or T cell ?
  - Recurrent staph abscesses?
    - B cell (antibody dysfunction)
  - Recurrent yeast infection?
    - T cell
  - Low lymphocyte count?
    - T cell- majority of circulating lymphocytes

Immunodeficiencies

- A 8 month old boy has had 4 episodes of pneumonia and 6 ear infections. Most likely diagnosis?
  A. Bruton's X-linked agammaglobulinemia
  B. Ataxia telangiectasia
  C. Hyper IgE
- Bruton's disease
- Low IgGAME levels; elevated T cell count
- Recurrent infections with pyogenic bacteria: PNA, OM, sinusitis
- IVIG

Immunodeficiencies

- A child with Crohn's disease, recurrent respiratory tract infections and recurrent herpes labialis is on IVIG for this immunodeficiency???
  A. Complement deficiency
  B. SCID
  C. CVID
  D. IgA deficiency
- Common Variable Immunodeficiency
  - B cell +/- T cell defect
  - Assoc with Autoimmune disease
  - Risk of lymphoma

Immunodeficiencies

- Meningococcal infections. Think…
  - Complement deficiency
- Tetany, Murmur, Cleft Palate, Thymic hypoplasia. Think…
  - Di George Syndrome
- Eosinophilia, eczema, recurrent skin and sinopulmonary infections and skeletal abnormalities with abnormal dentation…
  - Hyper IgE= Job syndrome

Immunodeficiencies

- An infant presents with FTT, dermatitis, diarrhea, thrush and OM. There is a complete absence of T cell function. Diagnosis?
  - SCID
  - ADA (adenosine deaminase deficiency)
- Treatment?
  - Bone Marrow Transplant

Immunodeficiencies

- You are seeing a 13 month old who has a h/o recurrent PNA and OM. He was healthy until he was 6 months old. His IgG is markedly low. IgA and IgM are normal. Diagnosis?
  - A. IgA deficiency
  - B. X linked hypogammaglobulinemia
  - C. Transient hypogammaglobulinemia of infancy
- C. Transient. Decreased T-helper function. Will outgrow by 3-6 years.

Immunodeficiencies

- Male with h/o bloody diarrhea, bruising, eczema, and is “always sick.”
  - Wiskott- Aldrich- X-linked
- Child with multiple skin abscesses and episodes of lymphadenitis and two episodes of pneumonitis.
  - Chronic Granulomatous Disease
  - Phagocytes have defective respiratory burst- NBT test

Immunodeficiencies

- You are seeing a 9 month old who has had episodes of PCP PNA and Cryptosporidium diarrhea. His immunodeficiency syndrome is?
  A. CVID
  B. SCID
  C. Hyper IgM
  D. Hyper IgG
  - Hyper IgM syndrome. Low IgG and IgA.
  - Defective CD40 ligand on T cells
  - Susceptibility to opportunistic pathogens

Immunodeficiencies

- Recurrent pyogenic infections and partial oculocutaneous albinism?
  - Chediak-Higashi syndrome
  - Abnormal microtubular function
  - Giant lysosomes on smear

Immunodeficiencies

- An infant with delayed umbilical cord separation. Think???
- Leukocyte Adhesion Deficiency
- A child with delayed wound healing, perirectal abscesses and recurrent skin infections. His boils are without much erythema or tenderness, and no fluctuance is noted. Diagnosis?
- LAD. Defect in chemotaxis. High or low WBC?
- High WBC count- cells come out of circulation but can’t adhere to tissues

Immunodeficiencies

- You are seeing a 7 month old with failure to thrive, HSM, and fever x I month. You suspect malignancy. A work up shows elevated immunoglobulins. Next step?
  - Send HIV DNA PCR.
  - Can see elevated immunoglobulins in first year of perinatal HIV. Dysfunctional and later low.