Pediatric Allergy/Immunology/Rheumatology

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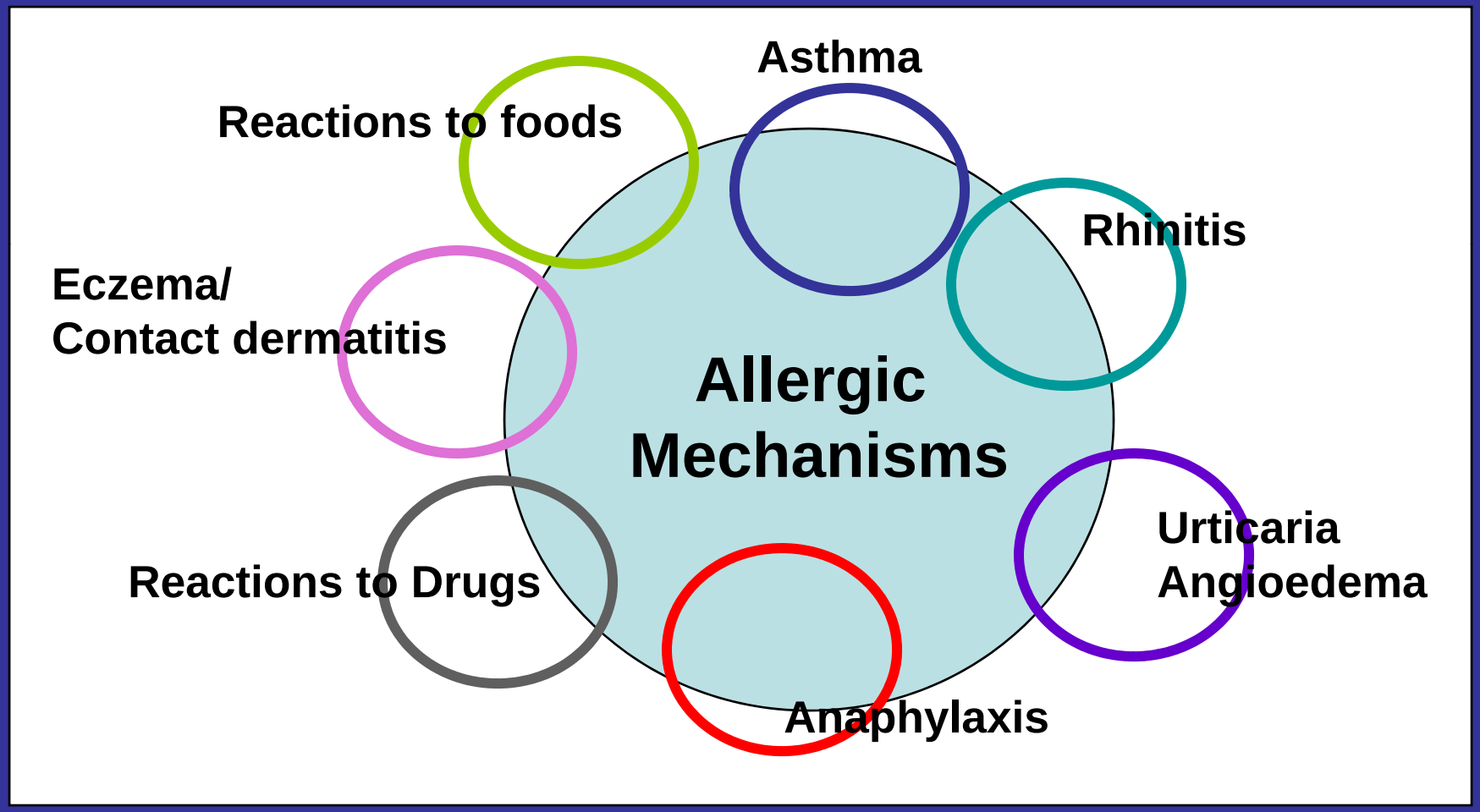
Disclosure: None

Objectives

Upon completion of this session, participants should be able to understand, recognize and manage the following conditions:

- **Common allergic diseases in children**
  - Allergic Rhinoconjunctivitis
  - Atopic dermatitis
  - Food allergy
- **Common primary Immunodeficiency**
- **Common rheumatologic diseases in children**
  - Acute arthritis: ARF, reactive arthritis, Transient toxic synovitis,
  - Chronic arthritis: JRA (JIA)

Allergic Diseases



Atopy and Atopic Diseases

- **Atopy: A genetically predisposed diathesis manifesting as exaggerated responses (eg. bronchoconstriction, IgE production, vasodilation, pruritus) to a variety of environmental stimuli (irritants, allergens, and microbes)**

- **Atopy is fundamental to the pathogenesis of atopic allergic diseases; allergic rhinoconjunctivitis, asthma, food allergy, atopic dermatitis.**

- **Not every atopic child develops atopic diseases**
- **Not every child with atopic disease is atopy.**

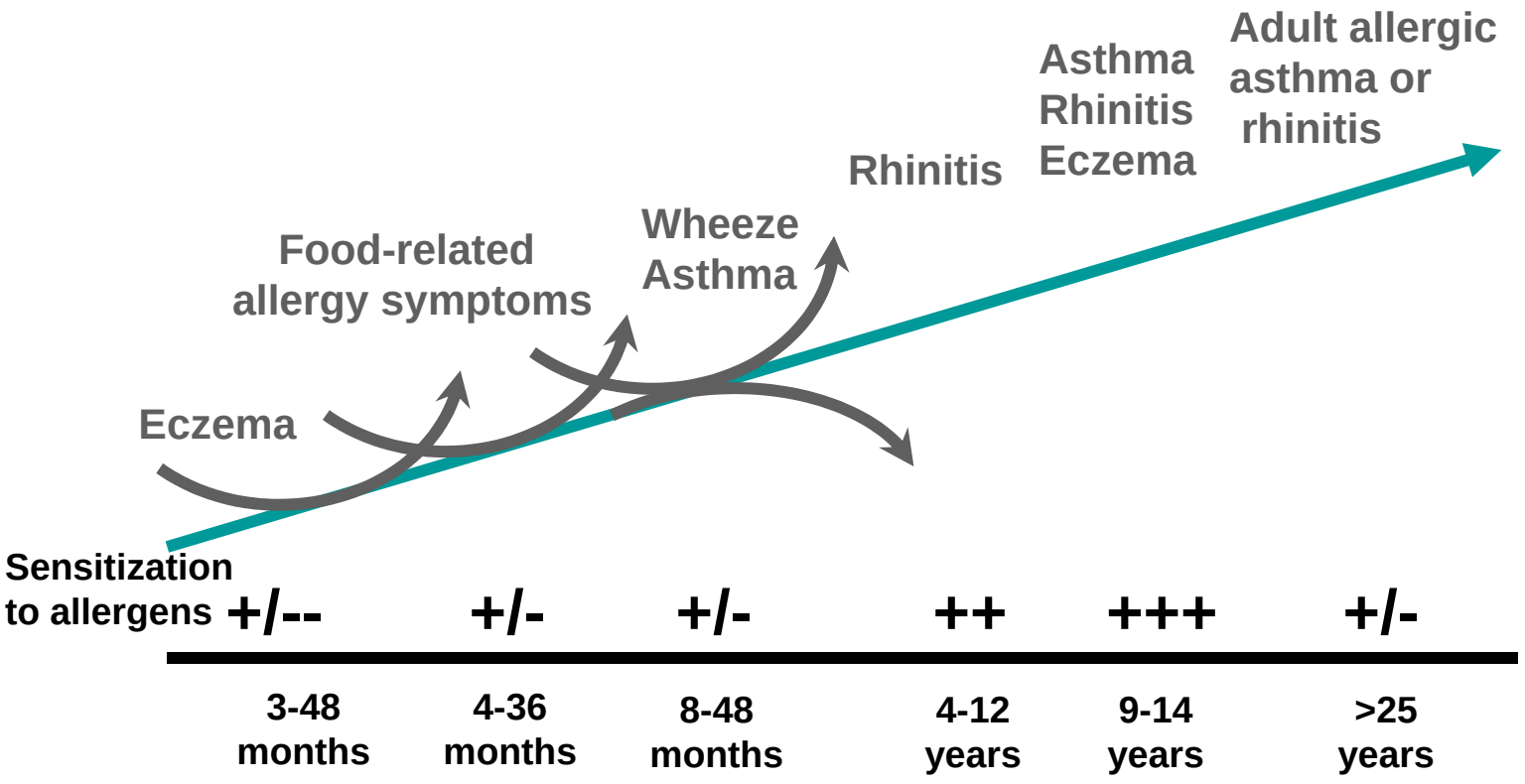
Atopy and Atopic Diseases

- **Objective evidence of being atopy:**
  - **Elevated total IgE in serum for age**
  - **Specific IgE to specific allergens:**
    - ***In vivo*: Specific IgE on mast cells (skin)**
      - **Prick skin test**
      - **Intradermal skin test**
    - ***In vitro*: Specific IgE in serum**
      - **Radioallergosorbent test (RAST)**
      - **Fluorenzymeimmunoassay (ImmunoCAP)**

Limitation of the specific IgE tests

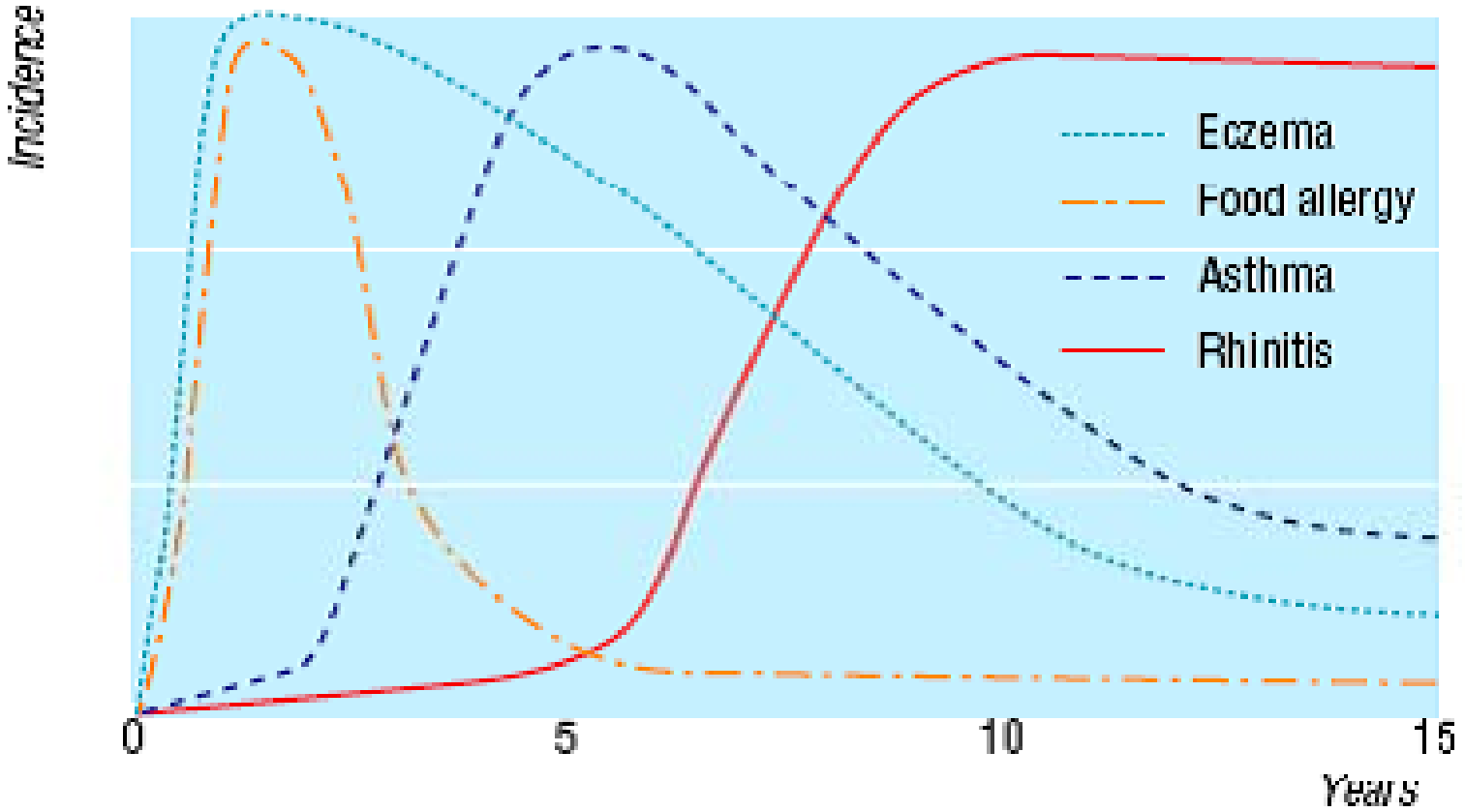
- **The positive result does not predict the severity of the reaction.**
- **The positive result does not directly inform the patient's symptoms caused by the allergen.**

Allergic March



Wickman *Allergy* 2005

Allergic March



Barnestson RS and Rogers M, *BMLJ 2002*

Key Components of Allergic Diseases

- Allergen:
  - Allergens: size 10-70kD
  - Indoor/ outdoor allergens, season, foods etc.
- Allergen exposure:
  - Major organs: Eye, upper/lower respiratory tract, GI, skin
  - Most of symptoms related to mediators from mast cell degranulation and eosinophilic inflammation.
- Family History:
  - Risk 50% if one parent is allergic
  - Risk 66% if both parents are allergic

Question 1




A 9 month old infant with on and off Itching skin rash since 3 months of age. The rash previously responded to hydrocortisone.

Which one is the most likely diagnosis?

A. Atopic dermatitis
B. Seborrheic dermatitis
C. Contact dermatitis
D. Scabies
E. Psoriasis

Atopic Dermatitis

- Chronic inflammatory pruritic skin disease characterized by a relapsing course with broad clinical presentation from minimal fleural eczema to erythroderma.
- 45% of children AD in the first 6 months
- 15% of children in US.
- 4% of all ED visit
- Often complicated by secondary skin infections

Atopic Dermatitis

Nomenclature: Neurodermatitis, atopic dermatitis, eczema

1. **Atopic eczema** is associated with IgE-mediated sensitization and typifies 70–80% of AD patients.
2. **Non-atopic eczema** is not associated with IgE-mediated sensitization seen in 20–30% of AD patients.

Both are associated with eosinophilia

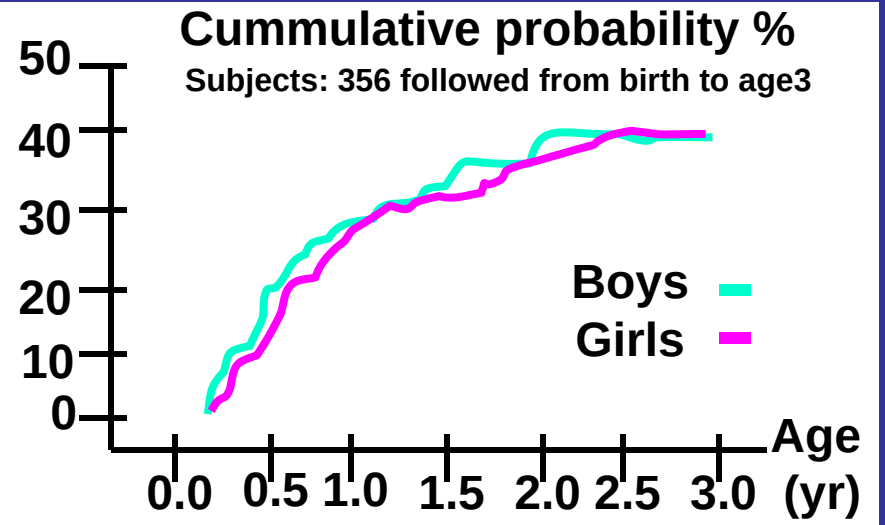
Eczema family

- **Atopic dermatitis (AD)**
- **Seborrheic dermatitis**
- **Contact dermatitis**
- **Nummular eczema**
- **Xerotic (asteatotic eczema)**
- **Ids (dermatophytids)**
- **Dyshidrotic eczema**
- **Autoeczematization**
- **Lichen simplex chronicus**
- **Prelymphomatous**

Leung, Nelson textbook of pediatric 18th ed
Simpson & Hanifin, Med Clin N Am 2006

Atopic Dermatitis

- Earliest onset at 1mo.
- Highest incidence rate in second half of 1st year.
- Peaked prevalence at age of 2 for boys, 2.5 for girls.
- Most infants presented with mild AD.
- Severity declined with age.
- Lesions begin at scalp, forehead, ear, neck, elbow, wrist, cheek, ankle, knee, nose, back etc.
- 10 most common regions cheek, knee (flex), chin, chest, upper leg (ext), perioral, upper back, lower back, abdomen, elbow (flex).



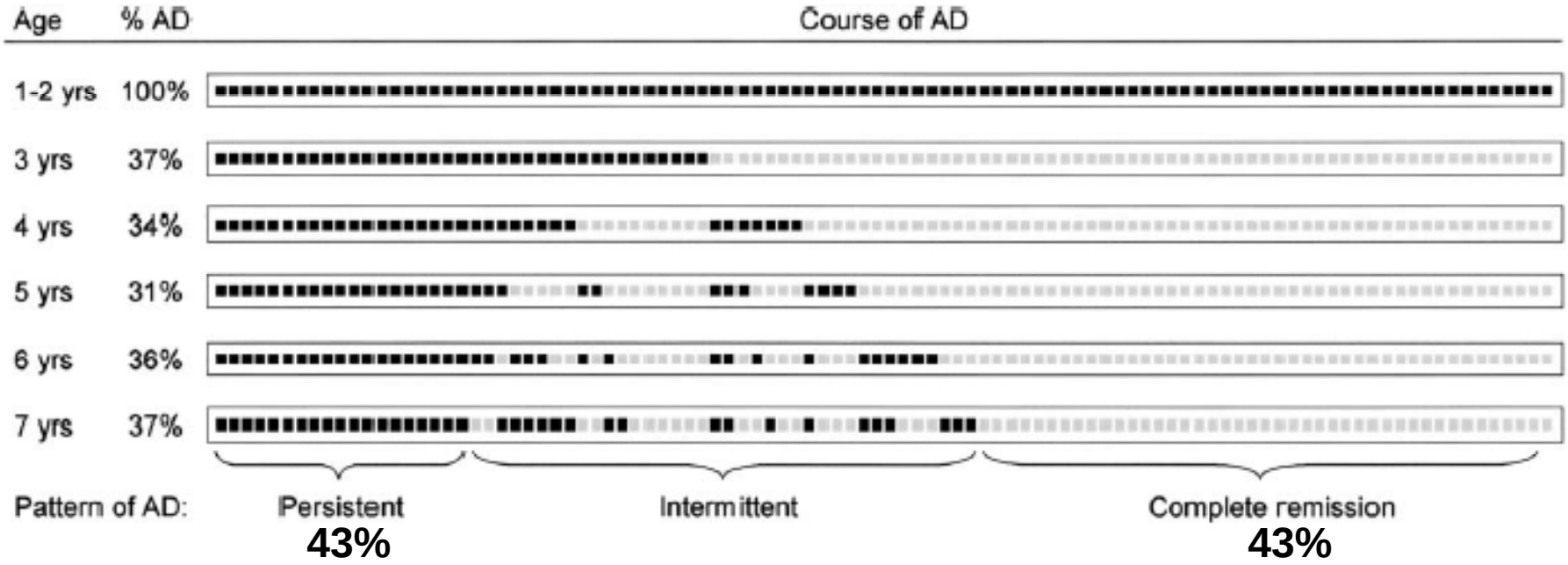
	At Half-Yearly Visits (yr)					
SCORAD	0.5	1.0	1.5	2.0	2.5	3.0
Mild*	43	52	63	68	74	81
Moderate	56	47	34	29	24	17
Severe	2	1	3	3	3	2

Data are given as mean percentage
SCORAD = Scoring Atopic Dermatitis Index

Halkjaer LB, et al. Arch Dermatol 2006

Atopic dermatitis

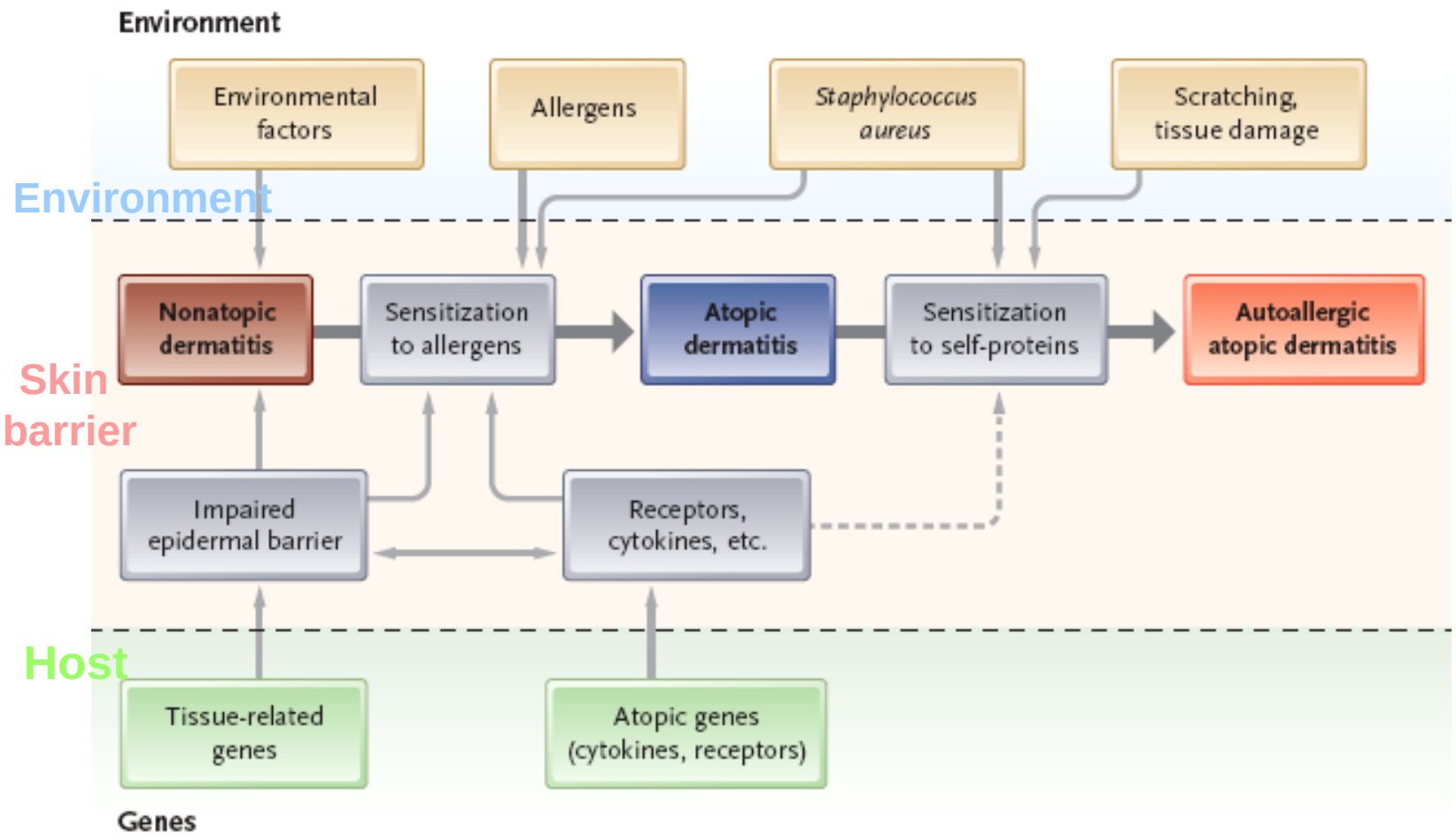
Natural course: 1123 children followed from birth to age of 7



1. **Severity of AD and early food sensitization (wheat, soy) are the strongest associations with prognosis.**
2. **Children with early AD and early wheezing have impaired lung function at age 7.**

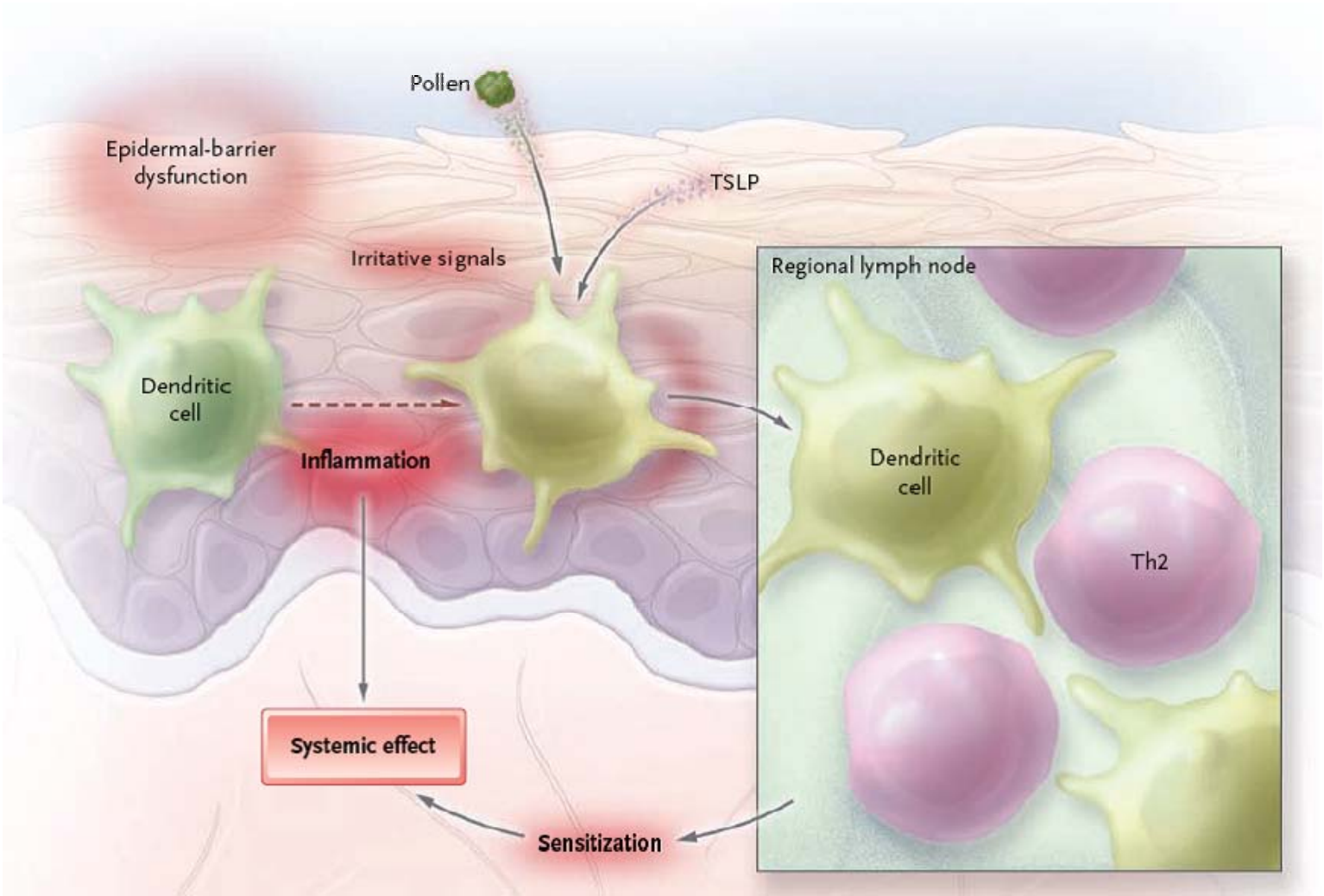
Illi S, et al JACI 2004

Atopic Dermatitis



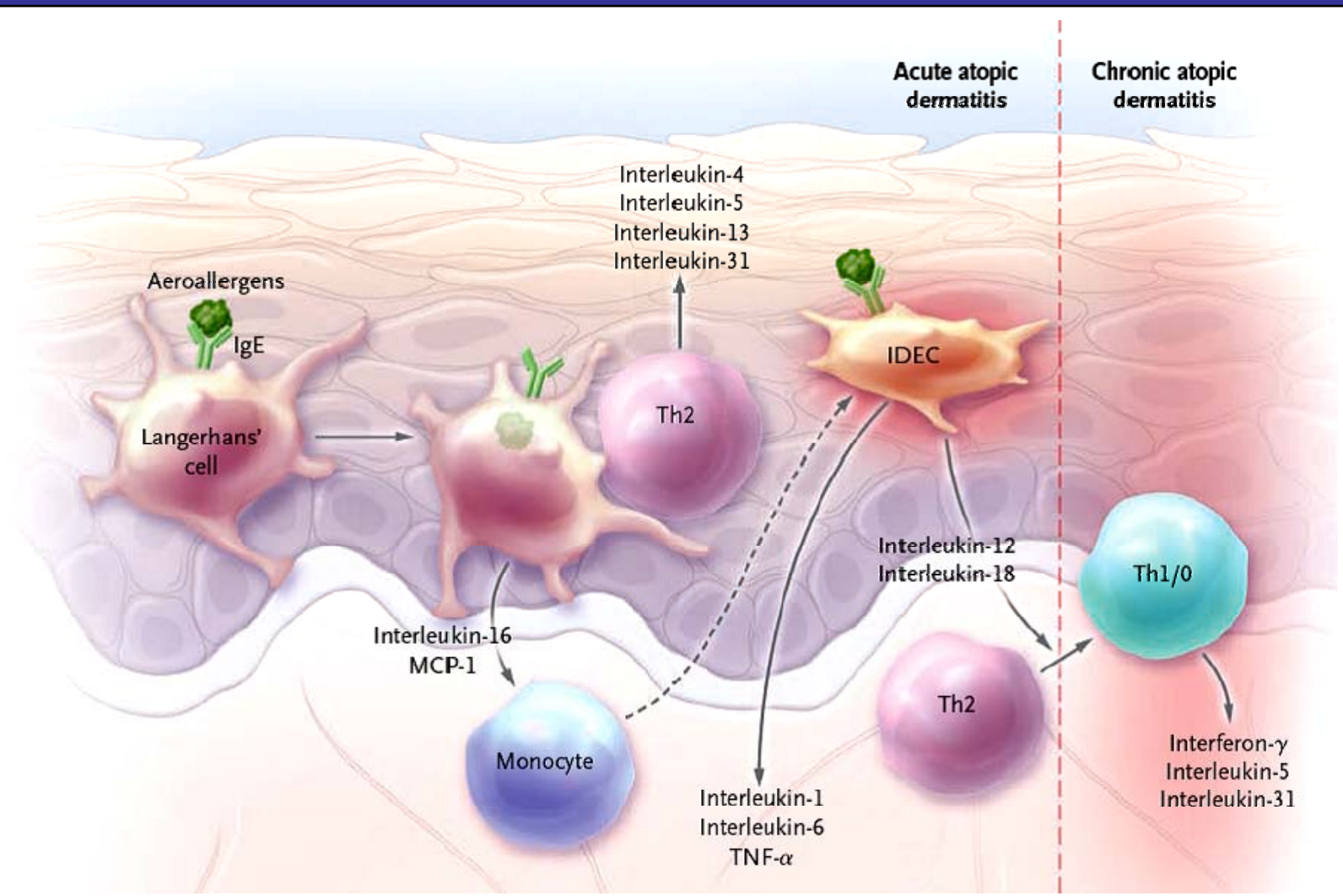
Bieber T, *NEJM 2008*

Atopic Dermatitis



Bieber T, *NEJM 2008*

Atopic Dermatitis



Bieber T, *NEJM 2008*

Atopic Dermatitis

Universal criteria for the diagnosis

A. Essential features; must be present and if complete are sufficient for Dx:

1. Pruritus
2. Eczematous changes: acute, subacute or chronic
   - Facial and extensor eczema in infants, children
   - Flexural eczema in adults/any age
   - Sparing of groin/ axillary regions
3. Chronic or relapsing course

B. Important features supporting Dx:

1. Early age at onset
2. Atopy (IgE reactivity)
3. Xerosis

C. Associated features: help but nonspecific

1. KP, ichthyosis, palmar hyperlinearity
2. Atypical vascular responses
3. Perifollicular accentuation, lichenification, prurigo
4. Ocular/ periorbital changes
5. Perioral/ periauricular lesions

D. Exclusion: other skin diseases mimicking AD

Leung, Lancet 2003
Simpson & Hanifin, Med Clin N Am 2006

Atopic Dermatitis

Differential diagnosis

Chronic dermatoses:
Other eczema
Psoriasis
Ichtyoses

Immunological disorders:
Juvenile dermatomyositis
Graft versus host disease
Pemphigus foliaceus
Dermatitis herpetiformis

Immunodeficiencies:
Hyper-IgE syndrome
Wiskott Aldrich syndrome
SCID
DiGeorge syndrome

Infections and infestations:
HIV associated dermatitis
Scabies

Congenital disorders:
Netherton's syndrome
Familial keratosis pilaris

Metabolic disorders
Zinc deficiency
Pyridoxine (B6) and niacin
Multiple carboxylase def
Phenylketonuria

Malignant diseases
Cutaneous T cell lymphoma
Letter-Siwe disease

Leung, Lancet 2003

Atopic Dermatitis

Triggers

- Viral infections
- Foods
  - 40% of moderate to severe cases
  - T cells specific to food allergens are cloned from skin lesions
- Staphylococcus aureus
  - Superantigens activate T cells & macrophages, augment synthesis of allergen specific IgE and induce glucocorticoid resistance.
  - Inflammation and scratching related to S. aureus binds to skin.
- Stress
- Aeroallergens
  - 30-50% +Atopic patch skin test (dust mites, animal dander, molds)
  - Severity associated with degree of IgE sensitization
- Autoallergens
  - IgE against human intracellular proteins
  - Autoallergens released from damaged tissues trigger responses mediated by IgE or T cells.

Atopic Dermatitis

Management

Skin care:

Skin hydration & emollients

Avoid irritants

Elimination of triggers

Foods/aeroallergens

Infections

Topical antiinflammatory:

Topical corticosteroids

Topical calcineurin inhibitors

Antihistamines

Antibiotics:

Topical: Mupirocin, fusidic acid

Systemic antibiotic

Education

Systemic corticosteroids

Immunomodulators

Cyclosporin A

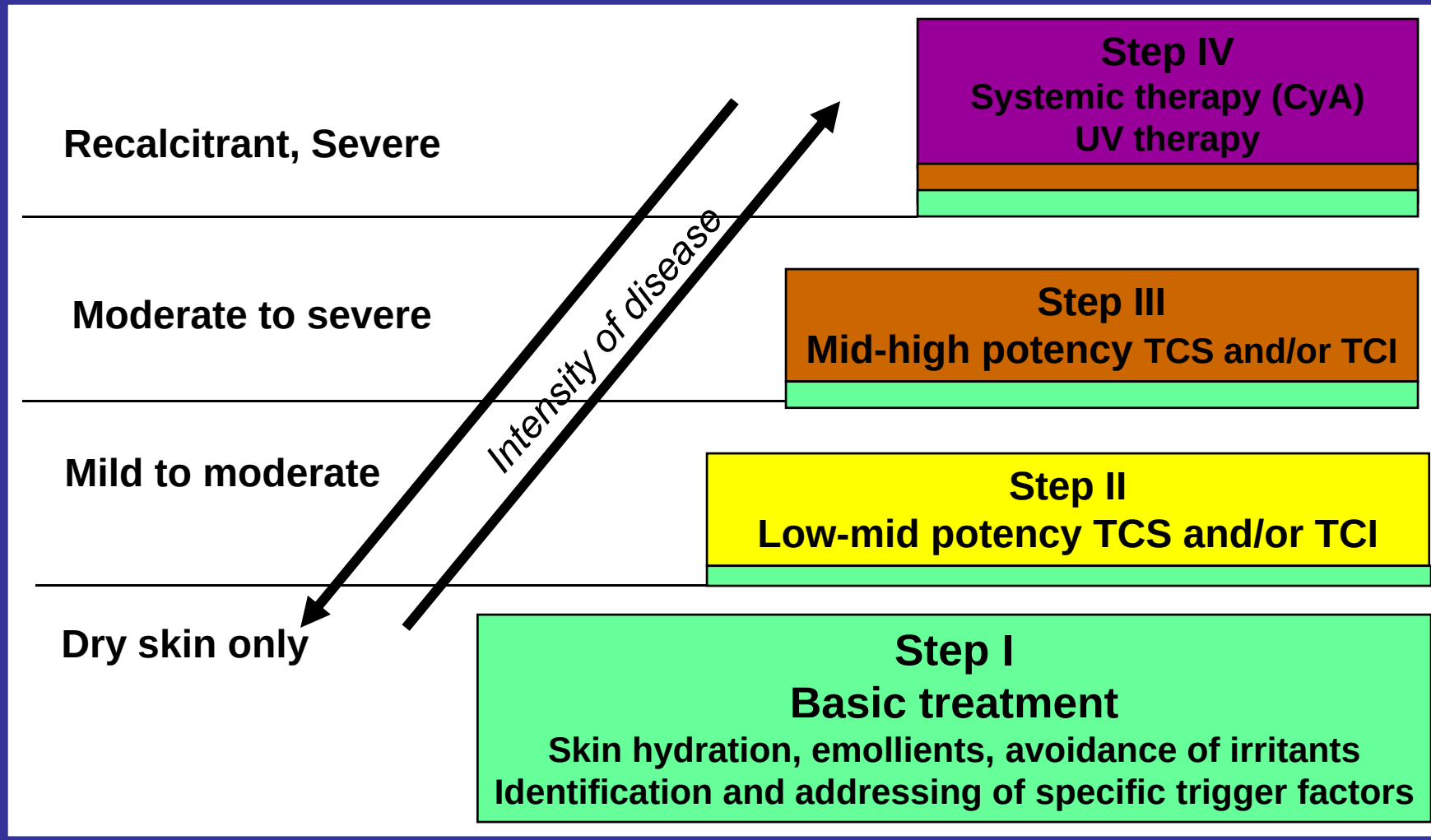
Azathioprine

Phototherapy

Immunotherapy

Atopic Dermatitis

Management



Topical Glucocorticosteroids

- **Class 1: Superpotent**
  - 0.05% Betamethasone dipropionate gel, ointment
  - 0.05% Clobetasol propionate cream, ointment
- **Class 2: Potent**
  - 0.05% Betamethasone dipropionate cream
  - 0.05%Desoximethasone cream, ointment (Topicort)
  - 0.05% Fluocinonide (Lidex)
  - 0.1% Mometasone ointment
- **Class 3: Upper midstrength**
  - 0.1% Betamethasone valerate
  - 0.005% Fluticasone propionate ointment (Cultivate)
  - 0.1% Mometasone furoate ointment
  - 0.5%Trimacinolone acetonide
- **Class 4: Midstrength**
  - 0.1% TA ointment/cream
  - 0.025% Fluocinolone acetonide oint
  - 0.05% Desoximetasone cream
- **Class 5: Lower mid-strength**
  - 0.1% TA cream/lotion
  - 0.05% Fluticasone propionate cream
  - 0.025% Fluocinolone acetonide cream
  - 0.1% Betamethasone Valerate cream
- **Class 6: Mild strength**
  - 0.05% Desonide cream
  - 0.01% Fluocinolone (Synalar) cream, lot
  - 0.05% Alclometasone oint
- **Class 7: Least potent**
  - 1, 2.5% hydrocortisone cream, oint
  - Topical with dexamethasone, flumethasone, methylprednisolone and prednisolone

Ong & Boguniewicz, Prim Care Clin Office Pract 2008

Question 1

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Question 1

Question 2

2. A 3 yo girl developed swelling lips right after her first bite with fish (tilapia). Father immediately gave a dose of Benadryl and took her to your office. She developed wheezing in the car before arrived your office.

Which one is the most immediate treatment needed?

A. Give second dose of Benadryl

B. Give albuterol neubulizer treatment

C. Give methylprednisolone injection

D. Epinephrine subcutaneous injection

E. Epinephrine intramuscular injection

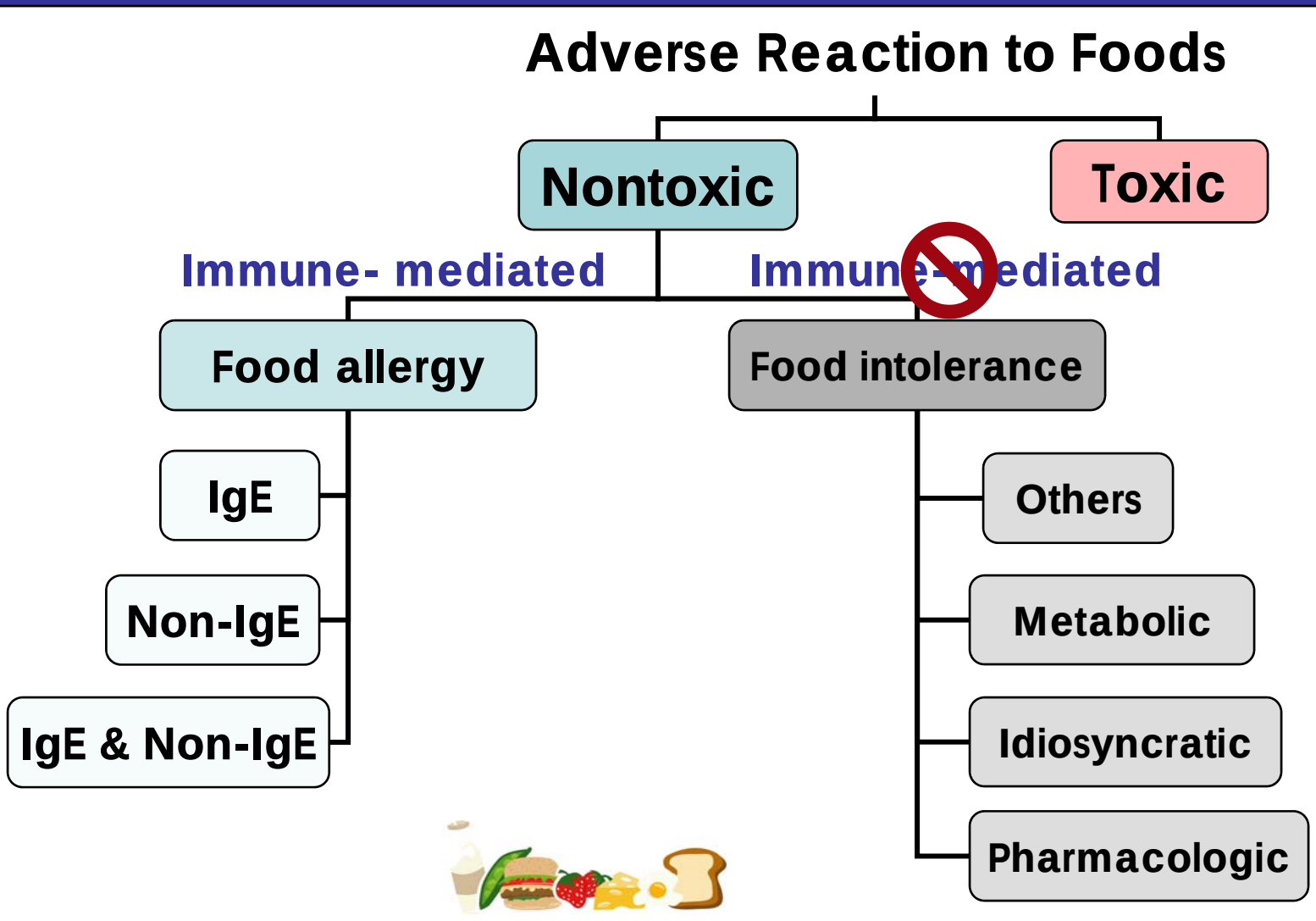
Question 3

3. A 4 yo old boy with asthma and allergic rhinitis was tested with positive specific IgE antibodies for pollens and peanut in your office. He had been eating peanut for years without any problems.

   Which one is the best recommendation?

   A. Peanut avoidance
   B. Epipen injection with accidental peanut exposure
   C. Take Benadryl before eating peanut
   D. No peanut in his class room
   E. Keep eating peanut

Food Adverse Reactions

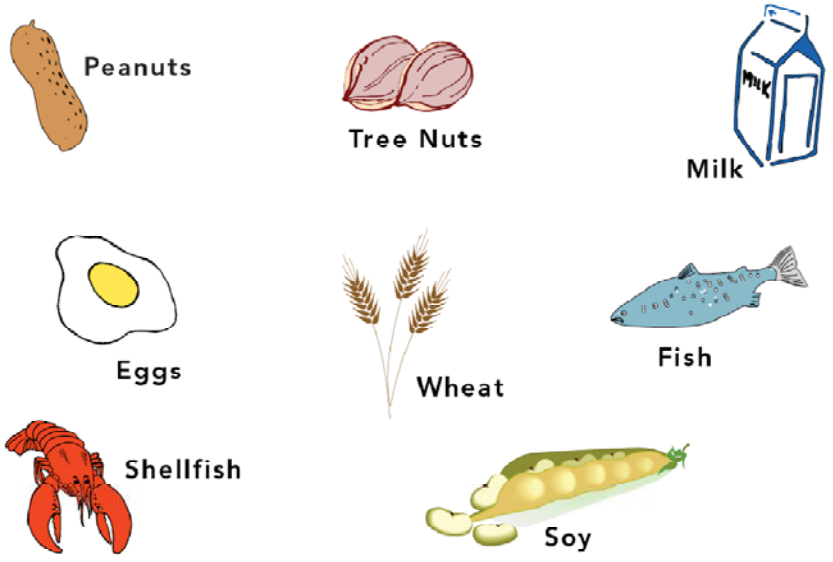


Food Allergy

- True food allergy: Prevalence
  - 6 to 8 % of children under 5 years
  - 3 to 4 % of adults

Food Allergy

- **Culprit foods**
  - **8 common foods (90%): cow milk, egg, wheat, soy, peanut, tree nuts, shelfish,fish**



  - **Others: fruits, sesame seed**

Food Allergy

Disorders	IgE-mediated	Mixed mechanism: IgE- and cell-mediated	Non-IgE mediated
Generalized	Anaphylaxis, food-dependent exercise-induced anaphylaxis		
Cutaneous	Urticaria, angioedema, flushing, acute morbilliform rash, acute contact urticaria	Atopic dermatitis, contact dermatitis	Contact dermatitis,dermatitis herpetiformis
Gastrointestinal	Oral allergy syndrome, gastrointestinal anaphylaxis	Allergic eosinophilic esophagitis, allergic eosinophilic gastroenteritis	Allergic proctocolitis, food protein-induced enterocolitis syndrome, celiac disease, infantile colic
Respiratory	Acute rhinoconjunctivitis, acute bronchospasm	Asthma	Pulmonary hemosiderosis (Heiner's syndrome)

Food Allergy

Organ	IgE-Mediated Food allergy Clinical Manifestation
Skin	Pruritus, flushing, urticaria/angioedema, diaphoresis
Eyes	Conjunctival injection, lacrimation, periorbital edema, pruritus
Resp	Nose/oropharynx: Sneezing, rhinorrhea, nasal congestion, metallic taste Upper airway: Hoarseness, stridor, sense of choking, laryngeal edema Lower airway: Dyspnea, tachypnea, wheezing, cough, cyanosis
CVS	Conduction disturbances, tachycardia, bradycardia (if severe), arrhythmias, hypotension, cardiac arrest
GI	Nausea/vomiting, abdominal cramping, bloating, diarrhea
Neuro	Sense of impending doom, syncope, dizziness, seizures

Food Allergy

Key History of IgE Mediated Food Allergy

- Symptoms: Involved organs
- Timing: Second to minutes upto 2 hours
- Culprit foods
  - Ask main dish or foods or others: sauces, dressings, breads, beverages, and side dishes eaten before the reactions.
  - Ask potential contaminant or ingredients that are uncommon in the patient's diet.
  - Processed foods also may be mislabeled or contain undeclared allergens.

Food Allergy

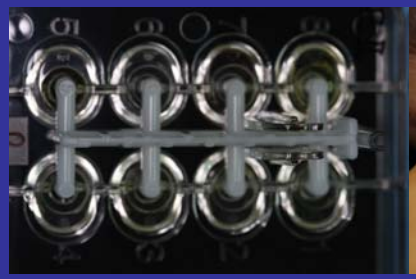
Key History of IgE Mediated Food Allergy

- Amount of food eaten
- Hx of avoiding or refusing to eat the suspected food in a young child
- Reproducible or not
- Activity before the reaction: exercise, exertion
- Most recent and most severe reactions
- Treatment required
- Related allergic diseases: AR, asthma, AD

Food Allergy

Diagnostic Tests

- **Prick skin test**
  - **Sensitivity > 90% and specificity = 50%**
  - **Low positive predictive value, High negative predictive value (>95%).**
  - **The larger the wheal, the greater the likelihood of clinical allergy: cow milk, egg, peanut (> 8mm or 4mm in < 2yrs).**
  - **Should not perform in the first 4 weeks after anaphylaxis.**
  - **If anaphylaxis, skin test increases risk of systemic reactions**



Food Allergy

Diagnostic Tests

- **Prick-Prick skin test**
  - **Heat-labile allergens, “Profilin” as an allergens for oral allergy syndrome or pollen-food syndrome**

Food Allergy

Diagnostic Tests

- **Intradermal skin test**
  - **Not adding diagnostic value**
  - **Increased risk of systemic reaction.**

Food Allergy

Diagnostic Tests

- **Specific IgE antibodies:**
  - **Unaffected if taking antihistamines or other medications.**
  - **Useful in patients with severe anaphylaxis in whom skin testing may carry an unacceptable degree of risk.**
  - **Useful in patients with dermatologic conditions that may preclude skin testing, such as severe atopic dermatitis and dermatographism.**

Food Allergy

Diagnostic Tests

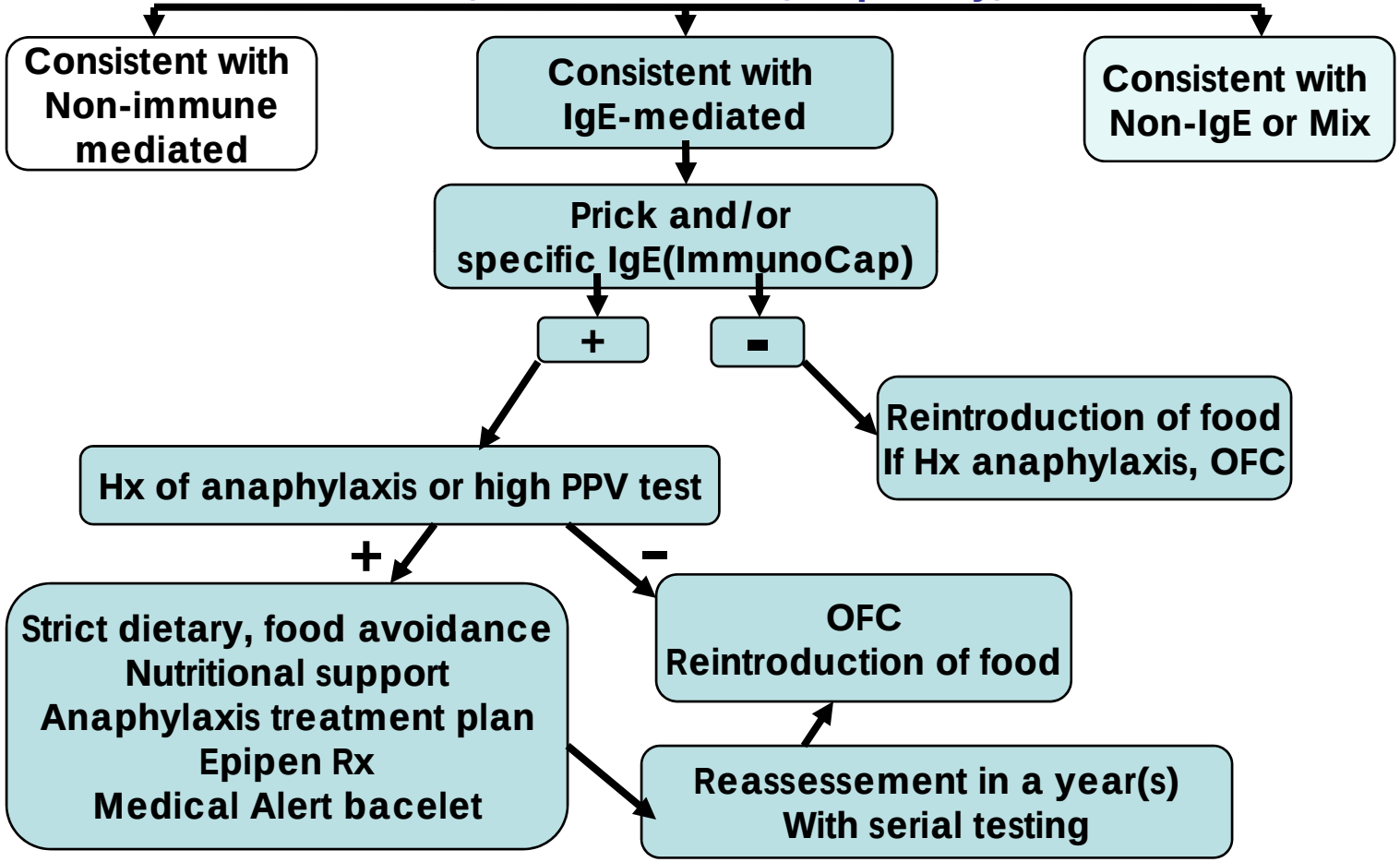
- **Specific IgE antibodies:**
  - **Radioallergosorbent test (RAST)**
  - **ImmunoCap FEIA (Fluorescent enzyme immunoassay)**
    - **The 95% predictive levels for egg, milk, peanut, tree nuts, and fish.**
    - **Egg: 7 kUA/L. If < 2 yo, the level is 2 kUA/L.**
    - **Milk: 15 kUA/L.If <2 yo, the level is 5 kUA/L.**
    - **Peanut: 14 kUA/L.**
    - **Tree nuts: 15 kUA/L.**
    - **Fish: 20 kUA/L.**

Food Allergy

Diagnostic Tests

- **Oral food challenge:**
  - **Gold standard diagnostic tool to confirm diagnosis**
  - **To determine if an identified allergy persists or has resolved.**


Hx: Symptoms & signs, amount of food ingested, timing of reaction to ingestion
Most recent reaction, most severe reaction, treatment
Personal & Fx Hx of atopy: Asthma, AR, AD
PE: V/S, mucocutaneous, respiratory, GI



Food Allergy

Anaphylaxis

Food Allergy

Food induced anaphylaxis

When any 1 of the 3 criteria are fulfilled:

1. **Acute onset of an illness (minutes to hours) with involvement of**
   - **Skin/mucosal tissue (eg, hives, generalized itch/flush, swollen lips/tongue/uvula) AND Airway compromise (eg, dyspnea, wheeze/bronchospasm, stridor, reduced PEF)**
   - **Reduced BP or associated symptoms (eg, hypotonia, syncope)**

     1 month to 1 yr: Ps <70
     1 to 10 yrs: less than (70 mm Hg + [2 × age])
     11 to 17 yrs: <90 mm Hg.

Food Allergy

Food induced anaphylaxis

When any 1 of the 3 criteria are fulfilled:

2. Two or more of the following after exposure to known allergen for that patient (minutes to hours)

- **History of severe allergic reaction**
- **Skin/mucosal tissue (eg, hives, generalized itch/flush, swollen lips/tongue/uvula)**
- **Airway compromise (eg, dyspnea, wheeze/bronchospasm, stridor, reduced PEF)**
- **Reduced BP or associated symptoms (eg, hypotonia, syncope)**
- **In suspected food allergy: gastrointestinal symptoms (eg, crampy abdominal pain, vomiting)**

Food Allergy

Food induced anaphylaxis

When any 1 of the 3 criteria are fulfilled:

3. **Hypotension after exposure to known allergen for that patient (minutes to hours)**
   - **Infants and children:**
     - **low systolic BP (age-specific) or**
     - **>30% drop in systolic BP**
   - **Adults:**
     - **systolic BP <100 mm Hg or**
     - **>30% drop from their baseline**

Food Allergy

Treatment

- Avoidance
  - Reading labels on commercial food products
  - Ask about ingredients when eating outside the home.
  - Preparation for children at schools or camps
- Being prepare for acute reactions
  - Antihistamine, epinephrine

Food Allergy

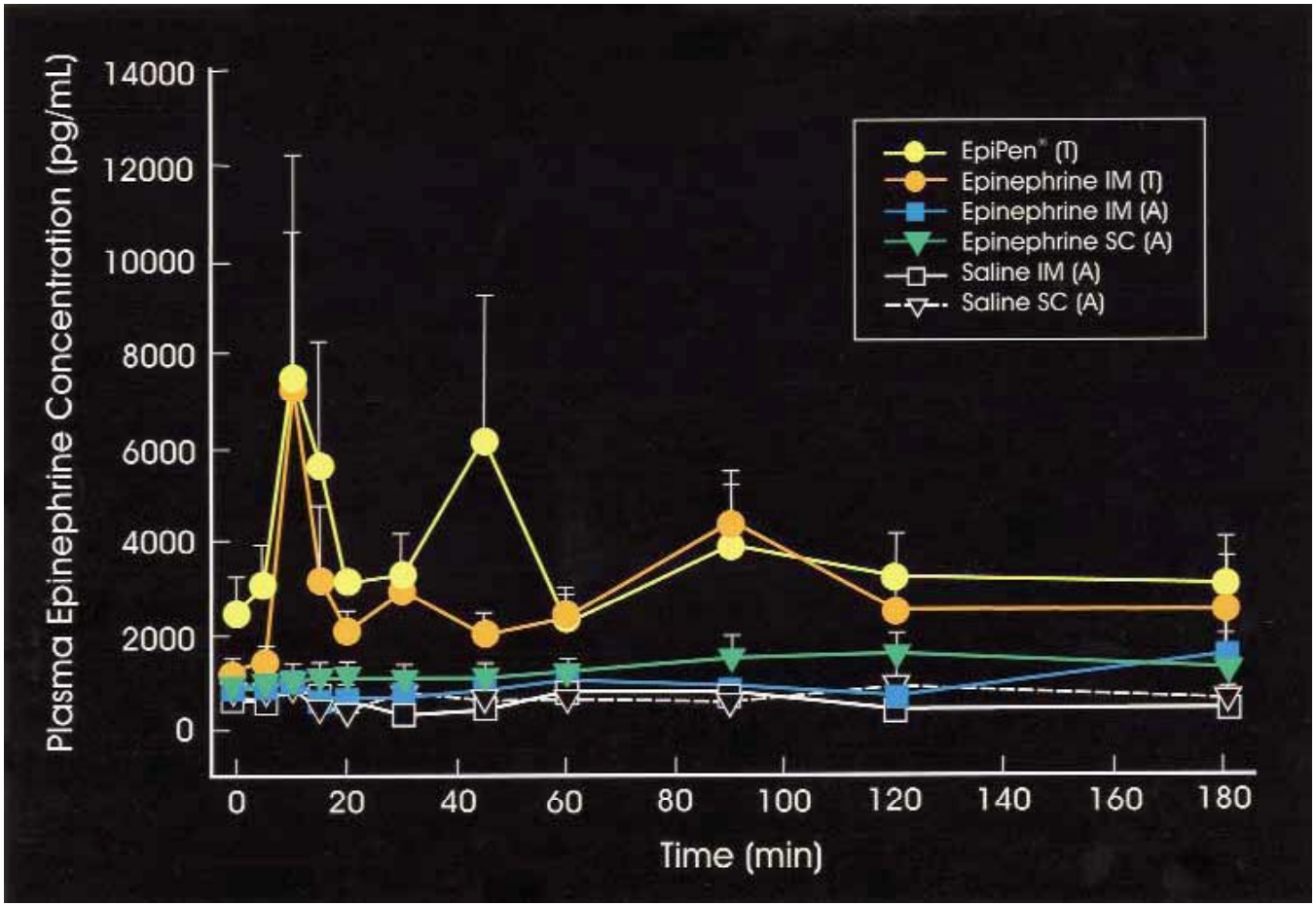
Epinephrine

- Who are at risk of food induced Anaphylaxis
  - Prior food allergic reactions involving respiratory and cardiovascular system
  - Generalized urticaria/angioedema
  - Food allergy and asthma or hx of wheezing with any severity
  - Allergy to peanut, nut or seafood
  - Family history with severe food allergic reactions
- How many doses needed
  - Ideally 2 doses

Sicherer SH, JACI 2004

Food Allergy

Route of epinephrine injection



Simons FE, JACI 2001

Peanut in School: To ban or not to ban	
Pro	**Con**
“Loaded gun” argument: reducing chance of exposure to potentially lethal allergen	**“No peanut detectors” to enforce ban: very difficult to guarantee “peanut-free school”**
Young children cannot bear responsibility, school staff might be inadequate	**Might cause undue burden on children without peanut allergy**
Food contamination of shared sports equipment and other sources of skin contact	**“Slippery slope argument”: ban other foods for other allergies, ban all foods**
Food sharing a common behavior in children	**“False sense of security” argument**
School bullying difficult to control	**Schools should be preparing students for the “real world”**
A community approach to safety	**Feelings of divisiveness**

Young MC, JACI2009

Food Allergy

Natural history

Food	Onset	Resolution
Cow's milk	6-12 months	76 percent resolve by 5 years
Hen's egg	6-24 months	75 percent resolve by 7 years
Wheat	6-24 months	80 percent resolve by 5 years
Soybean	6-24 months	67 percent resolve by 2 years
Peanut	6-24 months	Persistent (20 percent resolve by 5 years)
Tree nuts	1-7 years	Persistent (9 percent resolve after 5 years)
Sesame seed	6-36 months	Persistent (20 percent resolve by 7 years)

Food Allergy

Indications for Referral to the Allergist

- Diagnosis & assessment of the patient with
  - Severe or persistent disease
  - Multiple food sensitivity
  - Complications
  - Coexisting allergic disease (asthma, atopic dermatitis)
- Test interpretation
- Identification of offending foods
- Performance of food challenges
- Development of targeted elimination diets
- Comprehensive patient education

Question 2

2. A 3 yo girl developed swelling lips right after her first bite with fish (tilapia). Father immediately gave a dose of Benadryl and took her to your office. She developed wheezing in the car before arrived your office.

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   C. Take Benadryl before eating peanut
   D. No peanut in his class room
   E. Keep eating peanut

Question 4

4. A 7 years-old male complaints of year-round nasal stuffiness with itching and sneezing.

   Which one is the most likely cause of his symptoms?

   A. Grasses

   B. Trees

   C. Weeds

   D. House dust mites

   E. Molds

Question 5

5. A 7 years-old male complaints of year-round nasal stuffiness with itching and sneezing.
   Which one is the most effective medication for his symptoms?
   A. Second generation of H1 Antihistamines
   B. Intranasal antihistamine
   C. Ipratropium nasal spray
   D. Intranasal corticosteroid
   E. Montelukast

Allergic Rhinoconjunctivitis

Clinical definition

- **Symptomatic disorder of the nose/ eyes after allergen exposure by an IgE-mediated inflammation.**
- Rhinorrhea, waterry eyes, nasal obstruction, itching nose/ eyes, sneezing
- Postnasal drip occurs with profuse ant. rhinorrhea or without ant. rhinorrhea; esp. in chronic cases.
- Preschool children may just have nasal obstruction.
- Spontaneously reversible or with treatment
- Non allergic rhinitis may have similar symptoms

Bousquet J, et al. *Allergy 2008*

Allergic Rhinoconjunctivitis

TABLE 2

Most Common Chronic Conditions, by Age, Gender and Race

	MALE		FEMALE	
	BLACK	WHITE	BLACK	WHITE
ALL AGES	Hypertension Orthopedic impairments Sinusitis Arthritis Hay Fever	Orthopedic impairments Sinusitis Hearing impairments Hay Fever Hypertension	Sinusitis Hypertension Arthritis Orthopedic impairments Hay Fever	Sinusitis Arthritis Orthopedic impairments Hypertension Hay Fever
0–17	Asthma Sinusitis Hay Fever Anemia Orthopedic impairments	Asthma Hay Fever Bronchitis Sinusitis Dermatitis	Sinusitis Asthma Hay Fever Dermatitis Anemia	Sinusitis Hay Fever Asthma Bronchitis Dermatitis
18–44	Orthopedic impairments Sinusitis Hypertension Hay Fever Arthritis	Orthopedic impairments Sinusitis Hay Fever Hearing impairments Hypertension	Sinusitis Hay Fever Orthopedic impairments Migraine Hypertension	Sinusitis Orthopedic impairments Hay Fever Migraine Asthma

Data from 3 national surveys of the community-dewelling population living within the US (1994)

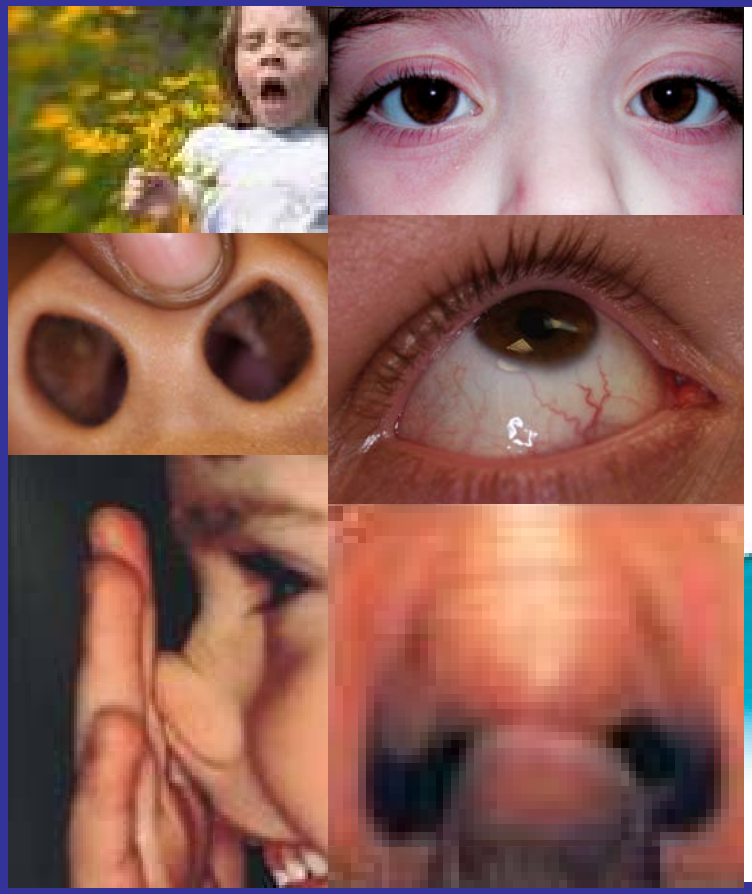
National Academy on an Aging Society, 2000

Allergic Rhinoconjunctivitis

Classification

- **Seasonal allergic rhinoconjunctivitis (20%)**
- **Perennial allergic rhinoconjunctivitis (40%)**
- **Mixed-Perennial allergic rhinoconjunctivitis with seasonal exacerbations (40%)**

Allergic Rhinoconjunctivitis



http://www.mountnittany.org/assets/images/krames/97649.jpg

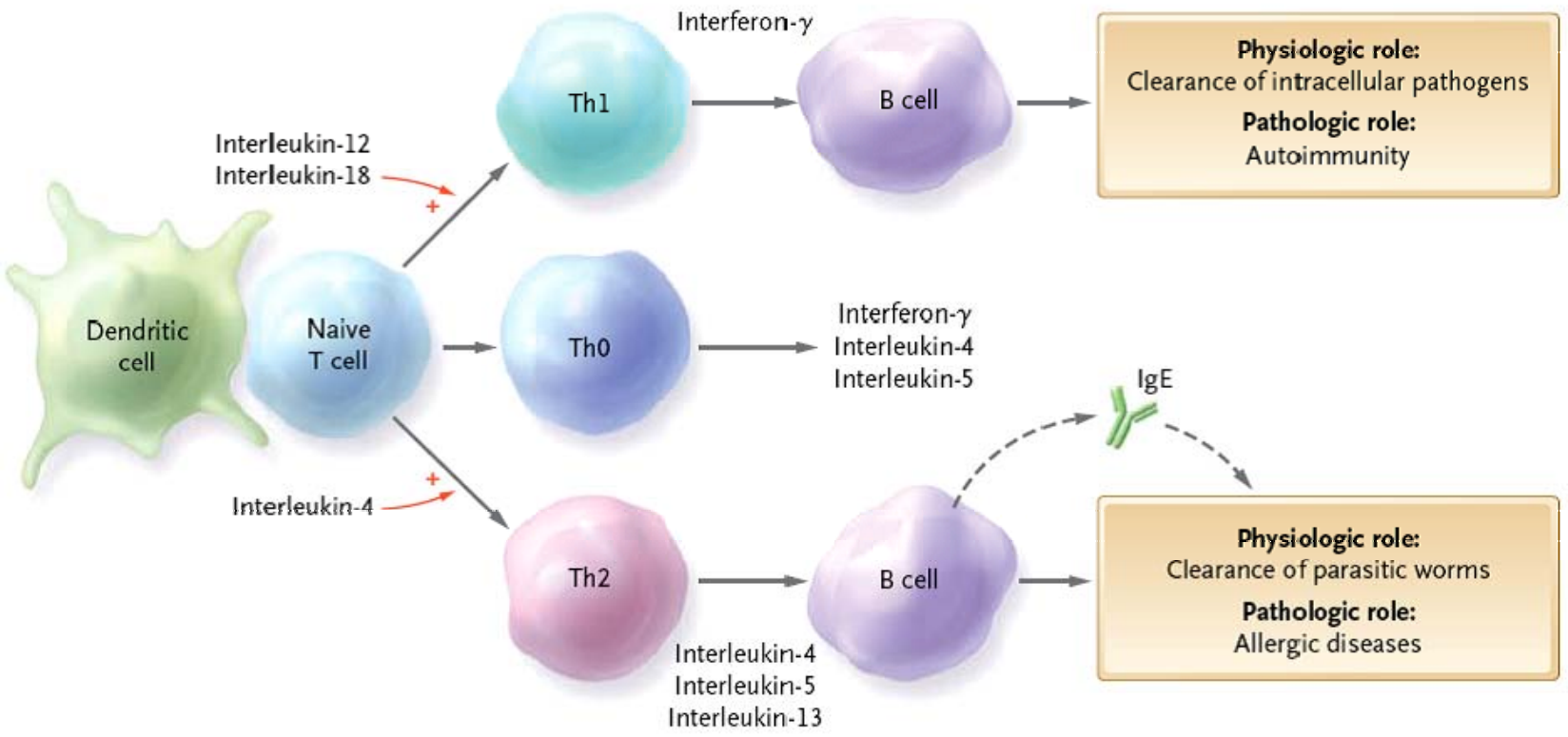
Allergic Salute

Causes of Rhinitis

- Allergic rhinitis
- Infectious rhinitis (acute, chronic)
- Perennial nonallergic rhinitis (Vasomotor rhinitis)
- Nonallergic rhinitis
  - Structural/mechanical factors
  - Hypertrophic turbinates
  - Adenoidal hypertrophy
  - Foreign bodies
  - Nasal tumors
  - Choanal atresia
  - Emotional factors
  - Enviromental factors
    - Odors, Temperature
    - Weather/barometric pressure
  - Hormonally induced
    - Hypothyroid, pregnancy
    - Contraceptive pills, menses
  - Drug induced
    - Antihypertensive therapy
    - Rhinitis medicamentosa
    - NSAID, Contraceptive pills
  - Reflex induced
    - Gustatory rhinitis,
    - Chemical/irritant induced
    - Nasal cycle
  - Inflammatory/immunologic
    - Wegener granulomatosis
    - Sarcoidosis
    - Mildline granuloma
    - SLE, Sjogren syndrome

Leung DYM, Sampson HA, Geha RS, et al: *Pediatric Allergy Principles and Practice.* St. Louis, Mosby, 2003, p 290

Allergic Rhinoconjunctivitis

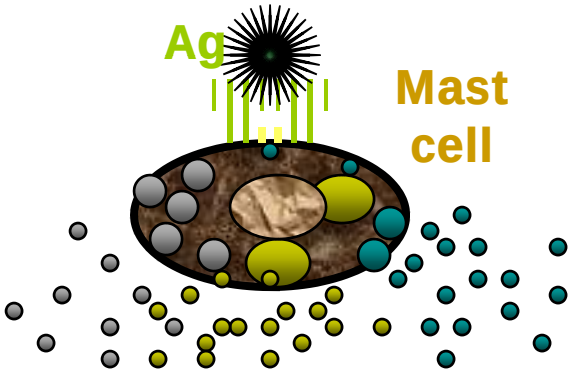


Bieber T, *NEJM 2008*

Allergic Rhinoconjunctivitis

Early phase: Mediator

(minutes)



50 %

Late phase: Cellular

(hours -> days)

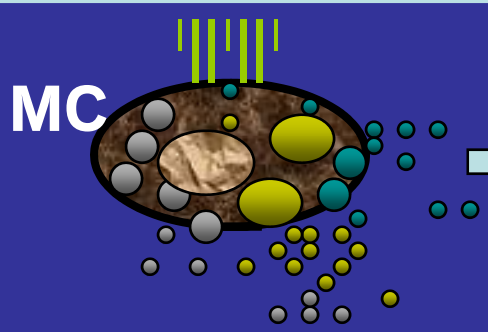
Nerve: Sneezing & itching
Gland: Rhinorrhea
Blood Vessels: Congestion

“Sneezer”

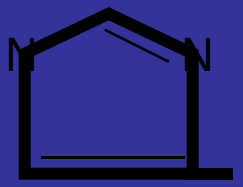
Priming effect
Hyperreactivity
Acute & Chronic inflammation
Tissue remodeling

“Blocker”

Histamine

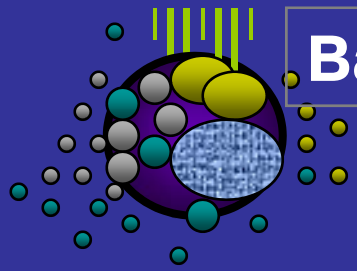


MC



$CH_2CH_2NH_2$

Histamine



Baso

H1-Receptor

Degradation

Nociceptive Nerves
(Axon Response?)

Endothelium
(Vascular Permeability)

CNS

Itch

Syetemic Reflexes

Sneeze

Allergic Salute

Parasympathetic Reflexes

Glandular Exocytosis

Mucus Secretion

Adapted from Baraniuk JN. Pathogenesis of allergic rhinitis. *JACI* 1997; 99.2

Allergic Rhinoconjunctivitis

Allergens

Perennial

- Dust mites
- Animals (Cat/dog)
- Cockroaches
- Molds
- Occupational or Hobby-Related

Seasonal

- Trees (Spring)
- Grasses (Summer)
- Weeds (Fall)

Nonspecific

- Cigarette Smoke
- Odors, Fumes
- Change in Temperature

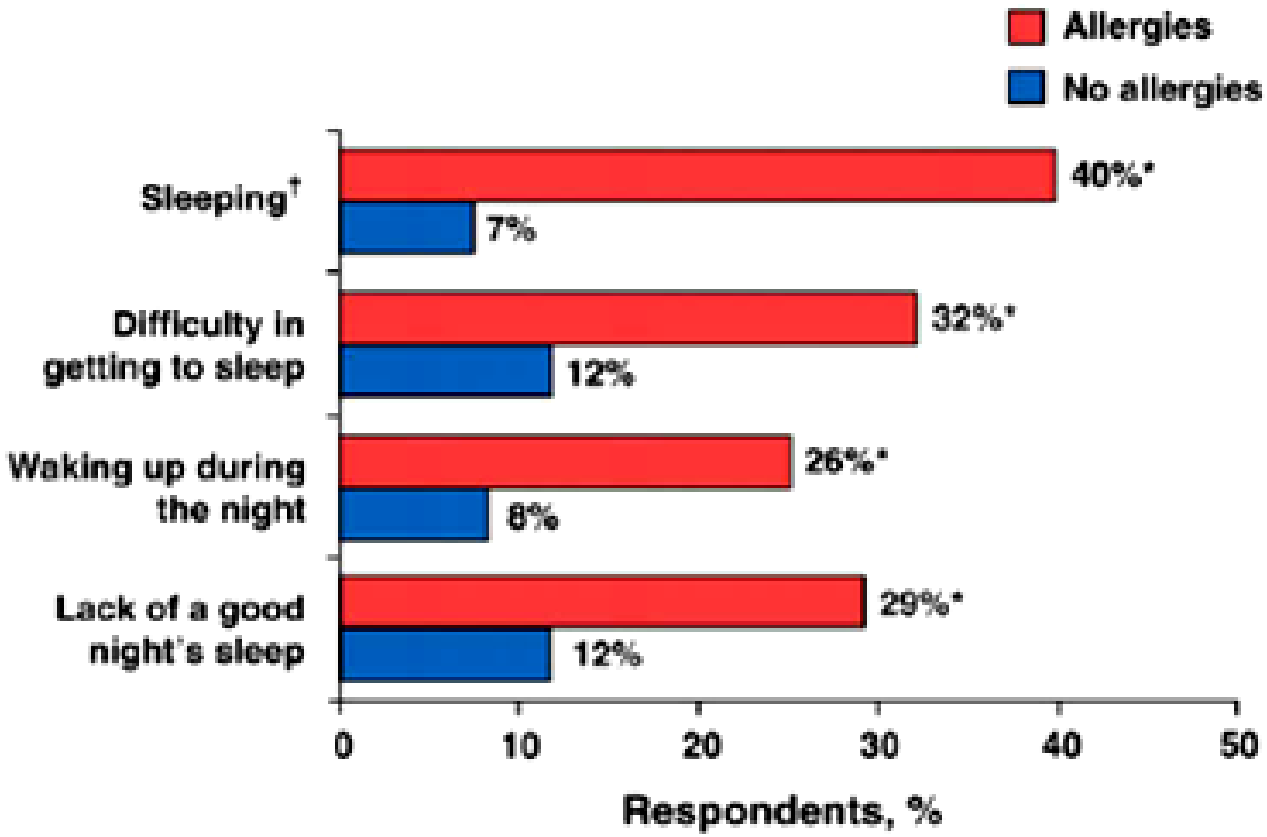
Allergic Rhinoconjunctivitis

Impact in children

- Quality of life
  - Cough
  - Fatique, malaise
  - Emotional Limitation
  - Activity Limitation
  - Sleep disturbance, sleep apnea?
- Learning problems
- School/ work performance impairment
- Contributing to other illnesses
- Healthcare costs

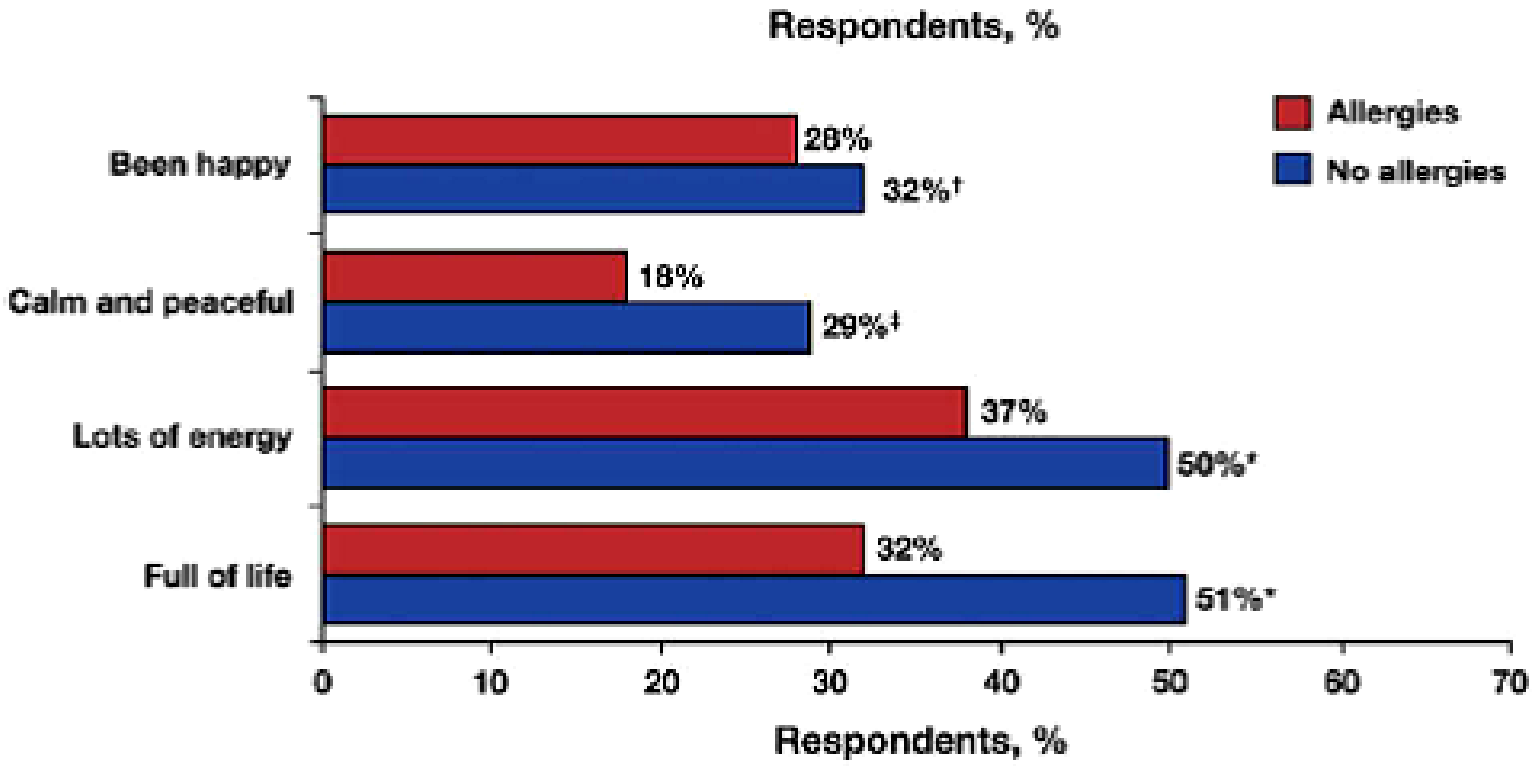
Bousquet J, et al. *Allergy 2008*

Allergic Rhinoconjunctivitis



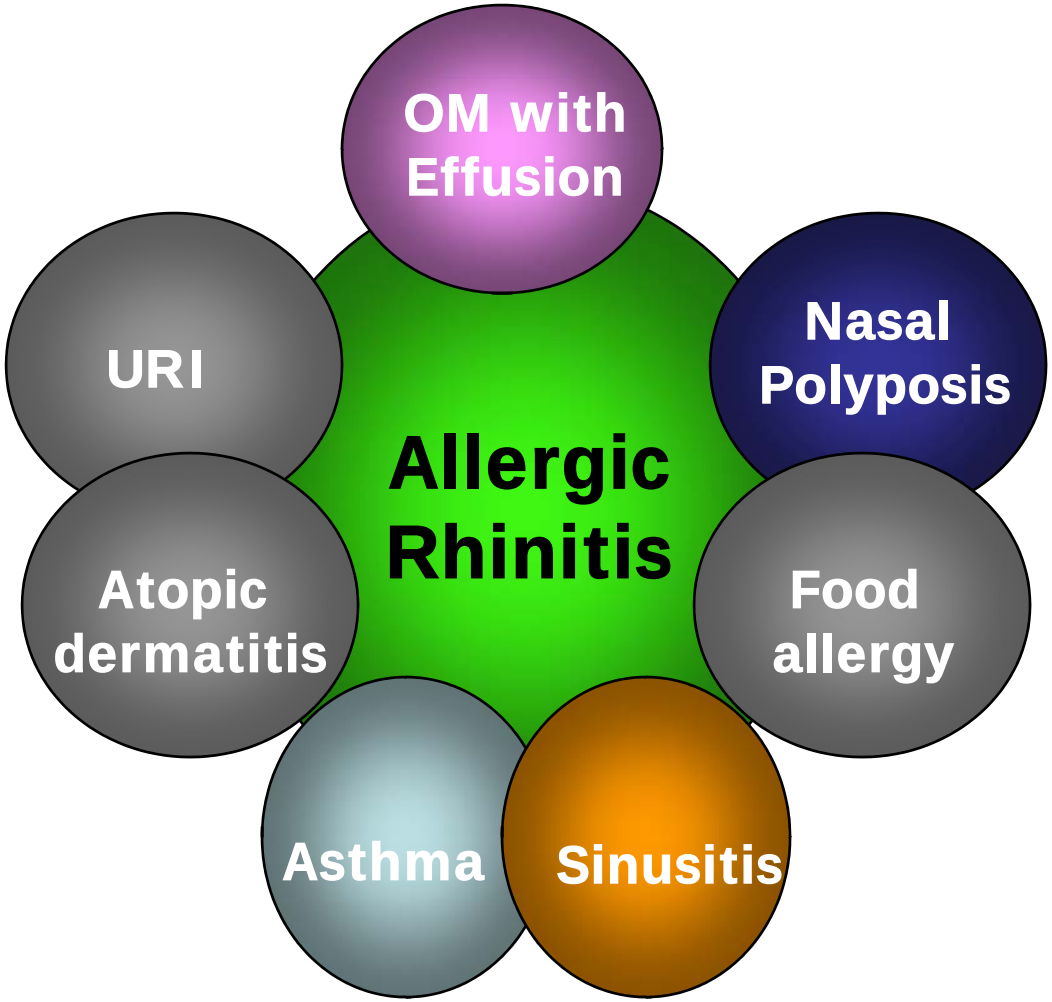
Meltzer et al. *JACI 2009*

Allergic Rhinoconjunctivitis



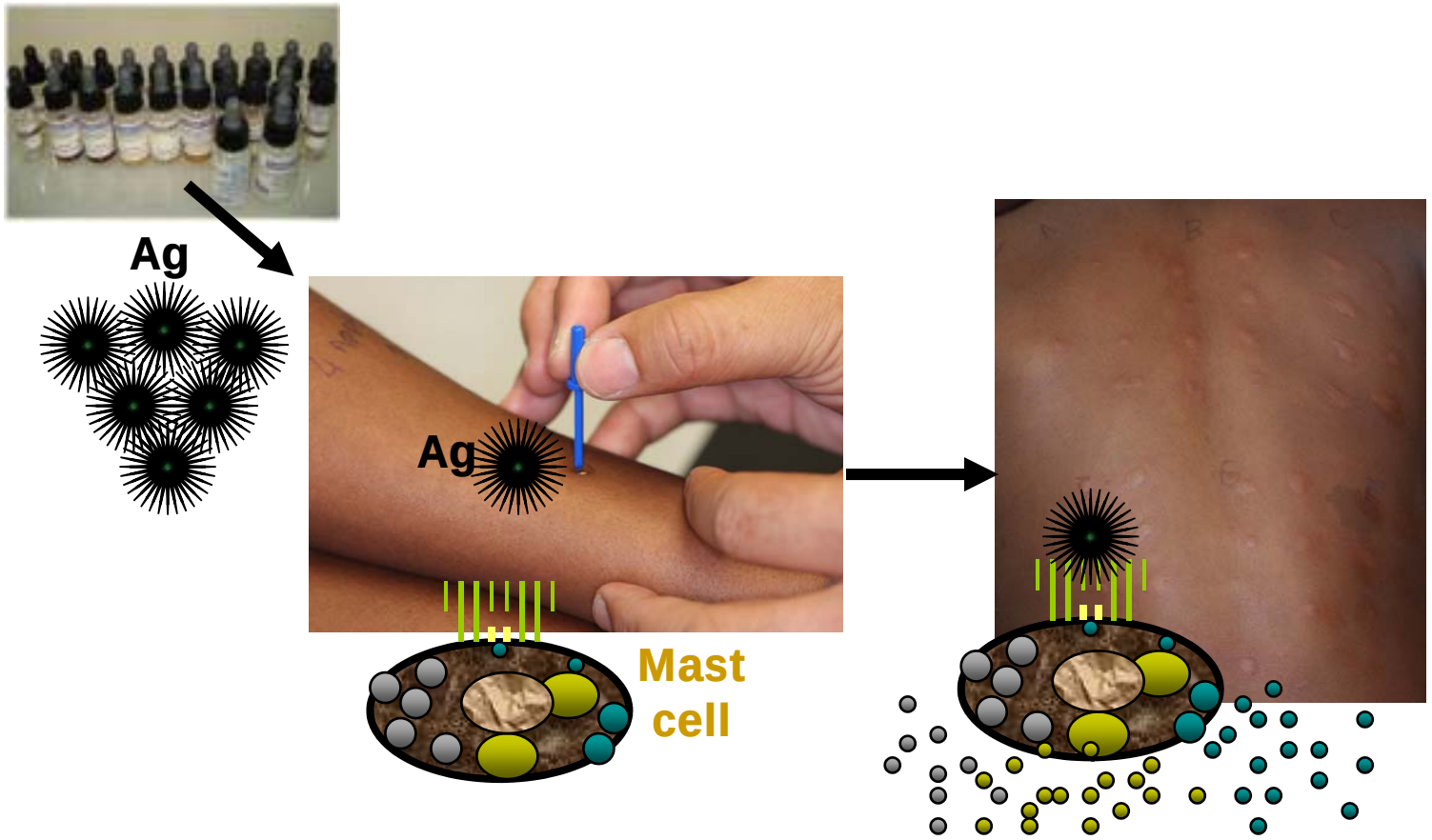
Meltzer et al. *JACI 2009*

Allergic Rhinoconjunctivitis



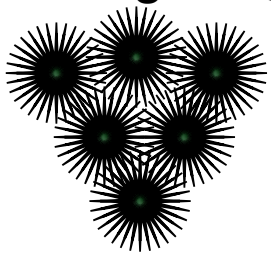
Adapted from Meltzer EO, et al. *Ann Allergy Asthma Immunol* 1999; 83: 455-463

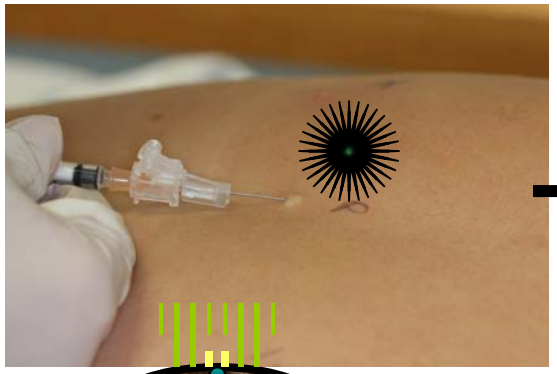
Prick Skin Test



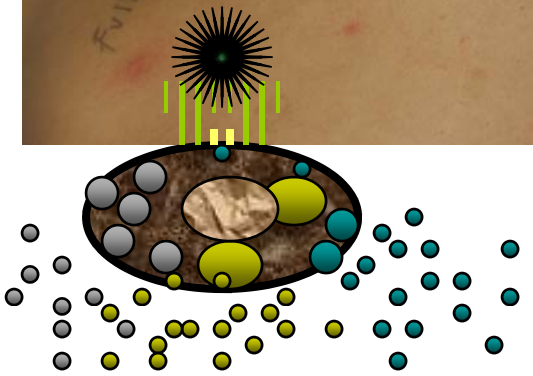
Intradermal Skin Test

Ag





Mast cell



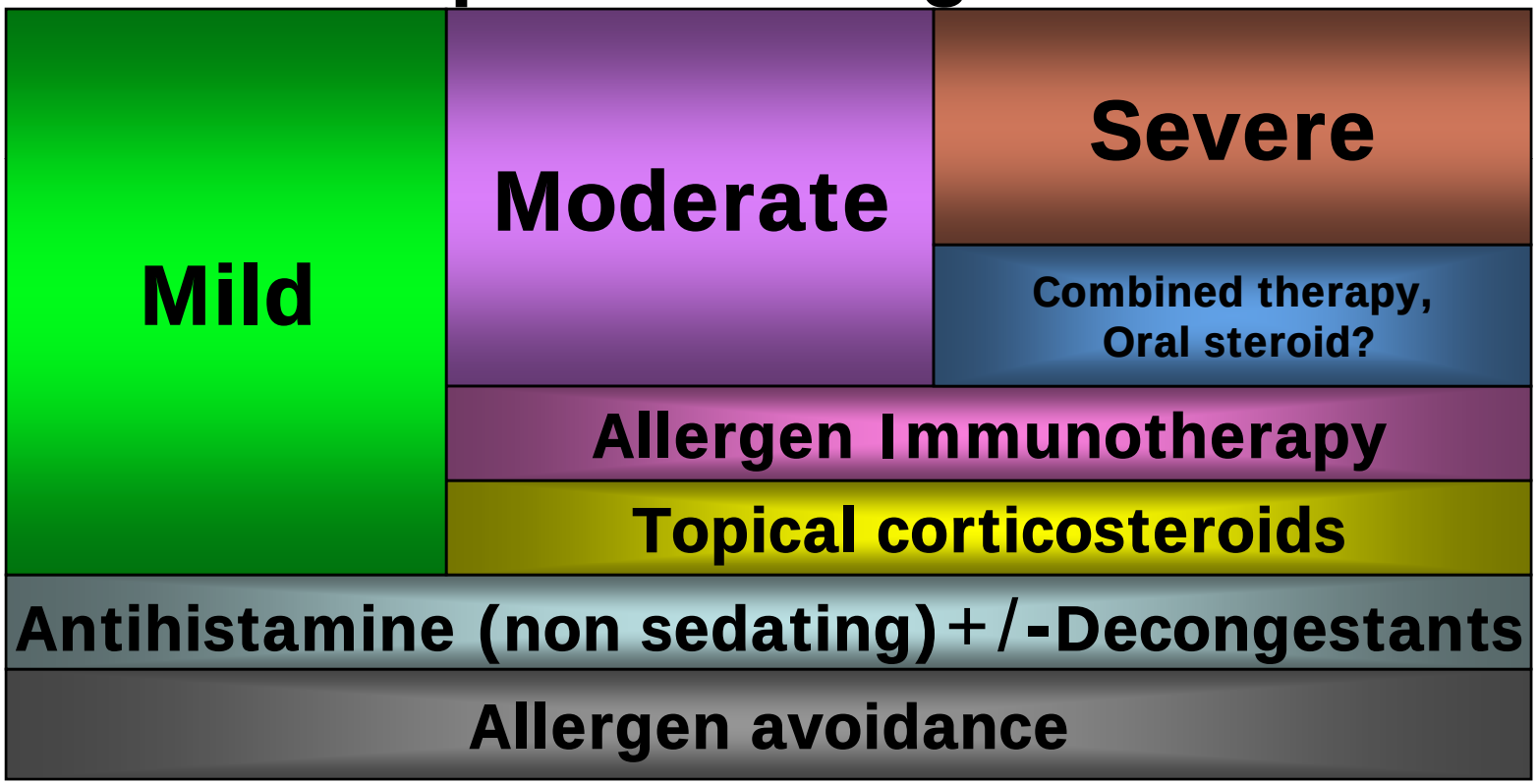
Prick Test vs Intradermal Test

	Prick test	Intradermal test
Detection of specific IgE	Yes	Yes
Sensitivity	+++	++++
Specificity	++++	+++
Reproducibility	+++	++++
False positive	Rare	Possible
False negative	Possible	Rare
Simplicity	+++	++
Speed	++++	++
Easiness of Interpretation	++++	++
Safety	++++	++
Discomfort	+	+++
Testing of infants	Yes	Difficult
Clinical use	All allergic disease	Insect, drug, some aeroallergens

Modified from Middleton's Allergy 7th ed

Allergic Rhinoconjunctivitis

Stepwise Management



Modified from Casale T, Respiratory Digest Vol1, Issue 3

Patient Name
DOB
Phone number
Pharmacy Phone number

Sample Rhinitis Action Plan

Date Completed: _____

Physician Name
Address
Phone number

Signature MD/Physician Extender

These are Your Rhinitis and Allergic Conjunctivitis Medications

Antihistamines

- ❑ Allegra (fexofenadine) ❑ D ____mg tab ❑ Syrup
- ❑ Claritin (loratadine) ❑ D ____ mg tab ❑ Syrup
- ❑ Clarinex (desloratadine) ❑ D ____ mg tab ❑ Syrup
- ❑ Xyzal (levocetirizine) ❑ D ____mg tab ❑ Syrup
- ❑ Zyrtec (cetirizine) ____ mg tab
- ❑ Benadryl ____ mg tab ❑ Syrup
- ❑ _____ ____ mg tab ❑ Syrup

Nasal Antihistamines

- ❑ Astelin ___ sp./nostril

Combinations

- ❑ _____ _____mg tab ❑ Syrup
- ❑ _____ _____mg tab ❑ Syrup

Nasal Corticosteroids

- ❑ Flonase (fluticasone propionate)
- ❑ Nasacort AQ (triamcinolone acetonide)
- ❑ Nasonex (mometasone)
- ❑ Rhinocort (budesonide)
- ❑ Veramyst (fluticasone furoate)

Leukotriene Modifiers

- ❑ Singulair_____mg tab ❑ Syrup

Mast Cell Inhibitors

- ❑ NasalCrom (cromolyn)

Anti-cholinergics

- ❑Atrovent Nasal (ipratropium) ❑0.03% ❑0.06%

Nasal Saline/moisturizer

- ❑ _____

Oral Decongestants

- ❑ Sudafed ____mg tab ❑ Syrup
- ❑ Phenylephrine

Nasal Decongestants

- ❑ Oxymetazoline (Afrin, Equate, …)
- ❑ Phenylephrine

Eye Drops

- ❑Alamast (pemirolast)
- ❑ Alocril (nedocromil)
- ❑ Crolom (cromolyn)
- ❑ Elestat (epinastine)
- ❑ Emadine (emedastine)
- ❑ Optivar (azelastine)
- ❑ Pataday ❑ Patanol (olopatadine)

Rhinitis Steps / What to do

Rhinitis Steps	What to do			
Prophylaxis before allergen exposure	❑ NasalCrom	____ dose(s)	____ times a day as needed	____ before exposure
Step 1: Episodic	❑ Decongestant ❑ Nasal ❑ Oral	____ dose(s)	____ times a day as needed	❑ AM ❑ PM
	❑ Antihistamine ❑ Oral ❑ Nasal	____ dose(s)	____ times a day as needed	❑ AM ❑ PM
	❑ Eye Drops	____ dose(s)	____ times a day as needed	❑ AM ❑ PM
	❑ NasalCrom			
	❑ Nasal Corticosteroid			
	❑ Atrovent	____ dose(s)	____ times a day as needed	❑ AM ❑ PM
Step 2: Mild (eg: 1 medication)	❑ Nasal Corticosteroid	____ dose(s)	____ times a day regularly	❑ AM ❑ PM
	❑ Oral antihistamine ❑ D	____ dose(s)	____ times a day regularly	❑ AM ❑ PM
	❑ Nasal antihistamine	____ dose(s)	____ times a day regularly	❑ AM ❑ PM
	❑ Singulair	____ dose(s)	____ times a day regularly	❑ AM ❑ PM
	❑ Atrovent	____ dose(s)	____ times a day regularly	❑ AM ❑ PM
	❑ _____	____ dose(s)	____ times a day regularly	❑ AM ❑ PM
Step 3: Mild to Moderate (eg: 2 medications or change to another medication)	❑ Nasal Corticosteroid	____ dose(s)	____ times a day regularly	❑ AM ❑ PM
	❑ Oral antihistamine ❑ D	____ dose(s)	____ times a day regularly	❑ AM ❑ PM
	❑ Nasal antihistamine	____ dose(s)	____ times a day regularly	❑ AM ❑ PM
	❑ Singulair	____ dose(s)	____ times a day regularly	❑ AM ❑ PM
	❑ Atrovent	____ dose(s)	____ times a day regularly	❑ AM ❑ PM
	❑ _____	____ dose(s)	____ times a day regularly	❑ AM ❑ PM
Step 4: Moderate to Severe (eg:2-3 medications and/or change of 1or more medications)	❑ Nasal Corticosteroid	____ dose(s)	____ times a day regularly	❑ AM ❑ PM
	❑ Oral antihistamine ❑ D	____ dose(s)	____ times a day regularly	❑ AM ❑ PM
	❑ Nasal antihistamine	____ dose(s)	____ times a day regularly	❑ AM ❑ PM
	❑ Singulair	____ dose(s)	____ times a day regularly	❑ AM ❑ PM
	❑ Atrovent	____ dose(s)	____ times a day regularly	❑ AM ❑ PM
	❑ _____	____ dose(s)	____ times a day regularly	❑ AM ❑ PM
Step 5: Severe (Oral Corticosteroid)	❑ Orapred 15mg/5mL	____ mL	____ times a day regularly for 3-5 days	
	❑ Orapred 15mg ODT	____ tab(s)	____ times a day regularly for 3-5 days	
	❑ Prednisone/Medrol ___ mg	____ tab(s)	____ times a day regularly for 3-5 days	

What to do for Increased Nasal Symptoms

- You have a cold •It is your allergy season •You are exposed to your triggers
- **First**, take your step 1 or step 2 medicine

Green Zone	Yellow Zone	Red Zone
Mild Episode	Moderate Episode	Severe Episode
• Complete response to medicine • No Nasal Symptoms **Step up 1 level**	• Fair response to medicine • Mild Nasal Symptoms **Step up 2 levels**	• Poor response to reliever medicine • Moderate to severe Nasal Symptoms **Step up 3 levels**

Long-Term Management of Nasal Symptoms

Controlled	Fair Control	Not Controlled
• No interference with activities • < 2 days per week sneezing, itching, congestion, eye symptoms **Stay at the same step or consider stepping down**	• Mild interference with activities • 2 – 6 days per week sneezing, itching, congestion, eye symptoms Increase treatment by one step	• Severe interference with activities • Daily sneezing, itching, congestion, eye symptoms Increase treatment by 2 steps

Dust Mite Control

- **Bed room:**
  - **Dust mite proof covers for mattress, pillows**
  - **Wash sheets, pillowcases, and blankets in warm water with detergent or dry in an electric dryer on the hot setting weekly**
  - **Remove comforter, clutter, soft toys, books and upholstered furniture**
  - **Use washable, vinyl, or roll-type window covers**
  - **If possible, remove carpet and use washable area rugs**
- **Rest of the house:**
  - **Reduce upholstered furniture, particularly old sofas.**
  - **Replace carpets with polished flooring where possible**
  - **Vacuum weekly using a cleaner with a HEPA filtration system.**
  - **Window coverings should be washable, vinyl, or roll type.**
  - **Use humidifier to control humidity to <50% relative humidity.**
- No role: Acaricides, denaturants, airfilters

Animal Dander Control

- Removing animal from the house
- Controlling allergen with an animal in the house
  - Reduce reservoirs: remove carpets, reduce upholstered furniture to a minimum, replace drapes with blinds, or/and vacuum clean weekly using a vacuum with good filtration (Double thickness bags and/or HEPA filtration).
  - Room air filters: HEPA or electrostatic.
  - Washing dogs x 2/week
  - Washing cats does not reduce allergen levels

Pollen Avoidance

- Keep window and door shut.
- Use air conditioning in the home.
- Avoid early morning outdoor exposure.
- Shower and change clothes after outdoor activities.
- Avoid using towels and bedding dried outside.
- Avoid having indoor plants.
- Keep animal outside, since pollens can be transported on animal furs.

OTC Drug Therapies

Saline drops/spray

- Remove mucus, reduce inflammation
- 2-6 spray as needed

Intranasal Cromolyn Sodium

- Mild to moderate
- Prophylactic agent before allergen exposure, onset of season
- Need 1 spray qid

Oral and Intranasal Antihistamine

Second generation	Trade name	Age limit	Pediatric dose	Adut dose
Cetirizine	Zyrtec	6 mo	2.5mg (6m-5yr) qd 5-10mg (6y-11yr) qd	5-10mg qd
Levocetirizine	Xyzal	6 mo	1.25mg qd (6m-5yr) 2.5mg qd (6y-11yr)	5mgqd
Loratadine	Claritin	2yr	5mg qd (2y-5yr) 2.5mg qd (6y-11yr)	10mg qd
Desloratadine	Clarinex	6 mo	2ml (1mg) qd(6m-11m) 2.5ml (1.25mg) qd (12m-5yr) 5ml (2.5mg) qd (6-11yr)	5mg qd
Fexofenadine	Allergra	6 mo	2.5 ml (15mg) bid (6m-2yr) 30mg bid (2-11yr)	180mg bid 60mg bid
Azelastine	Astelin, Astepro	5yr 12yr	1-2sp/nose bid	2 sp/nose bid
Otoptadine	Patanase	12 yr	2sp/nase bid	2 sp/ nose bid

Intranasal Antihistamine

Azelastine (Astelin® 137mcg or Astepro ® 205.5mcg)

- **Bioavailability of about 40%.**
  - Seasonal (Astelin & Astepro) perennial AR (Astepro)
  - Vasomotor rhinitis (2 sprays BID)
  - Rapid onset of action (15mins-45mins)
  - Prolonged duration (12 to 24 hours)
- **Side effects :**
  - Bitter tase (75%)
  - Somnolence (11.5% vs 5.4% placebo)
  - Headache
  - Nasal burn
  - Rhinitis

Lieberman P, Management of allergic rhinitis with a combination antihistamine/anti-inflammatory agent *JACI* 1999

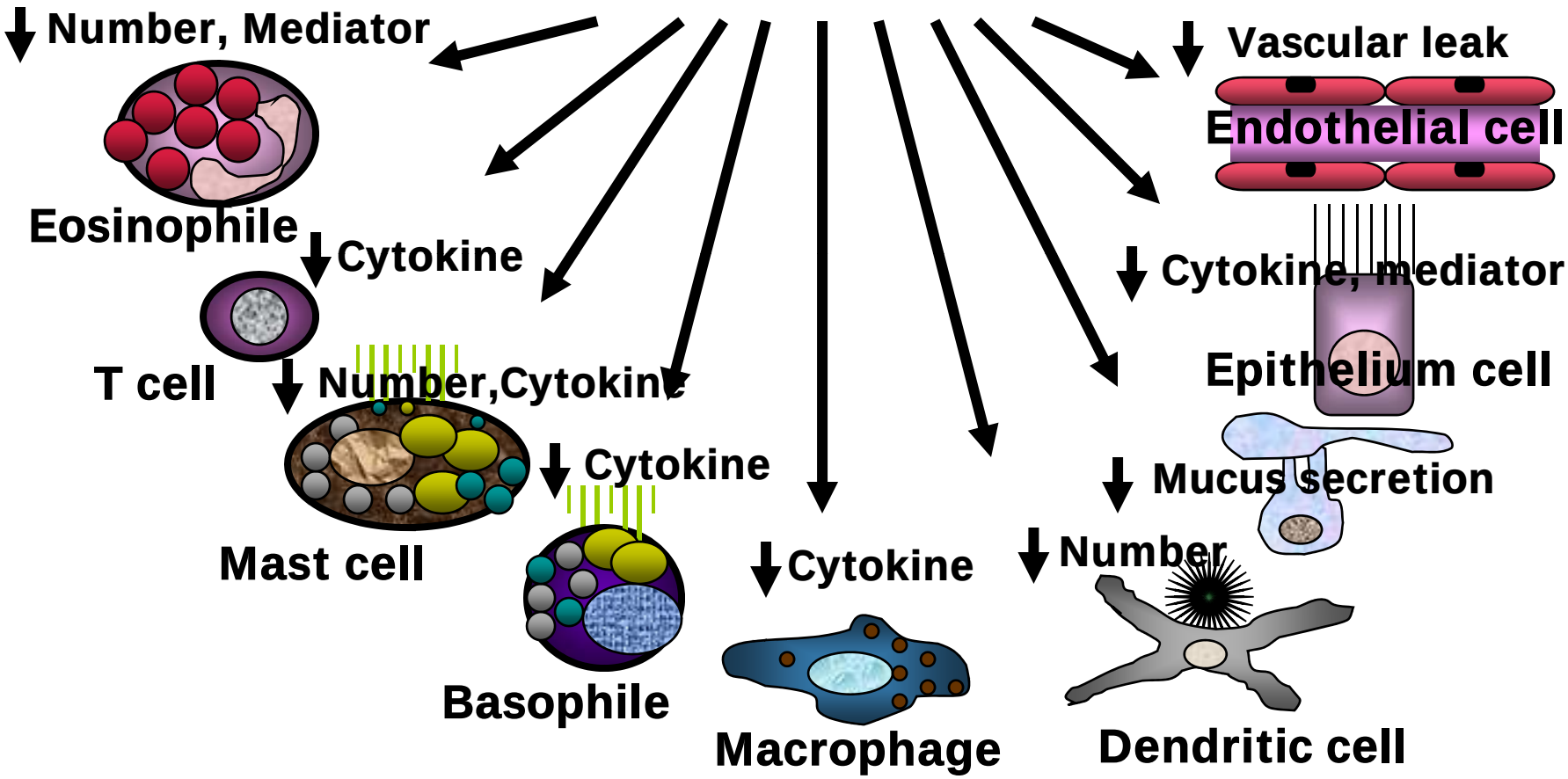
Antihistamine

Diseases/Conditions	Level
Allergic rhinoconjunctivitis	1A
Urticaria	1A
Atopic dermatitis	1B
Asthma	1C
URI infection (Colds)	3D
Otitis media	3D
Others (mosquito bite, eosinophilic cellulitis, etc)	1B

Level 1 = Randomized controlled, clinical trial
Level 2 = Case-control cohort study
Level 3 = Consensus of expert group

A = good evidence for use
B = Some evidence for use
C = evidence neither for nor against use
D = some evidence against use
E = Strong evidence against use

Effects of Intranasal Corticosteroids



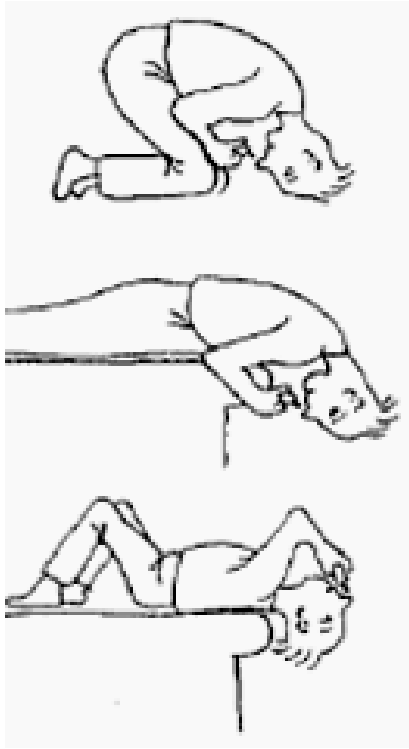
Adapted from Barnes PJ. Current issues for the establishing inhaled corticosteroids as the antiinflammatory agents of choice in asthmaDay J Allergy Clin Immunol 1998 Mar;101: S427-S433

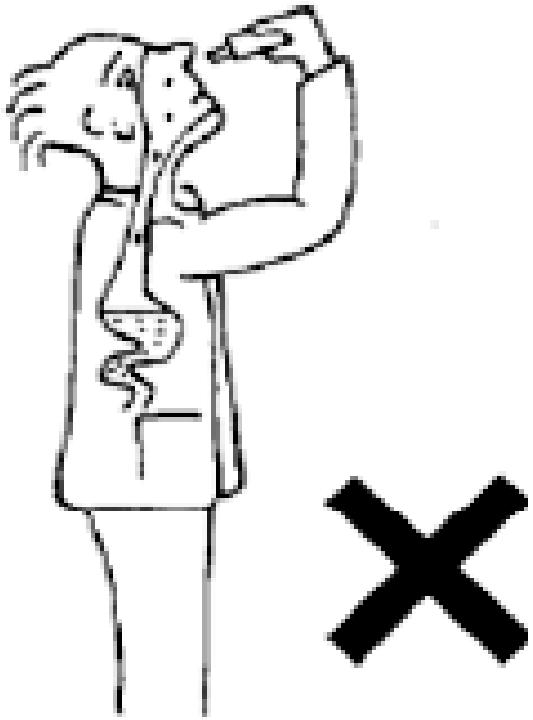
Intranasal Corticosteroid

Drug	Age limit (Y)	Usual child dose	Alcohol	BKC
Bedesonide (Rhinocort)	6	1-2 sp/nose qd	None	None
Beclomethasone (Beconase)	6	1-2 sp/nose bid	Yes	Yes
Fluticasone propionate (Flonase)	4	1-2 sp/nose qd	Yes	Yes
Flunisolide (Nasarel)	6	2 sp/nose bid	Propylene glycol	Yes
Momentasone (Nasonex)	2	1 sp/nose qd	None	Yes
Triamcinolone (Nasocort)	6	1-2 sp/nose qd	None	Yes
Ciclesonide (Omnaris)	12	NA	None	None
Fluticasone furoate (Veramyst)	2	1 sp/nose qd	None	Yes

Intranasal Corticosteroid

Technique of Nasal spray use





Scadding, et al. Clin Exp Allergy 2008

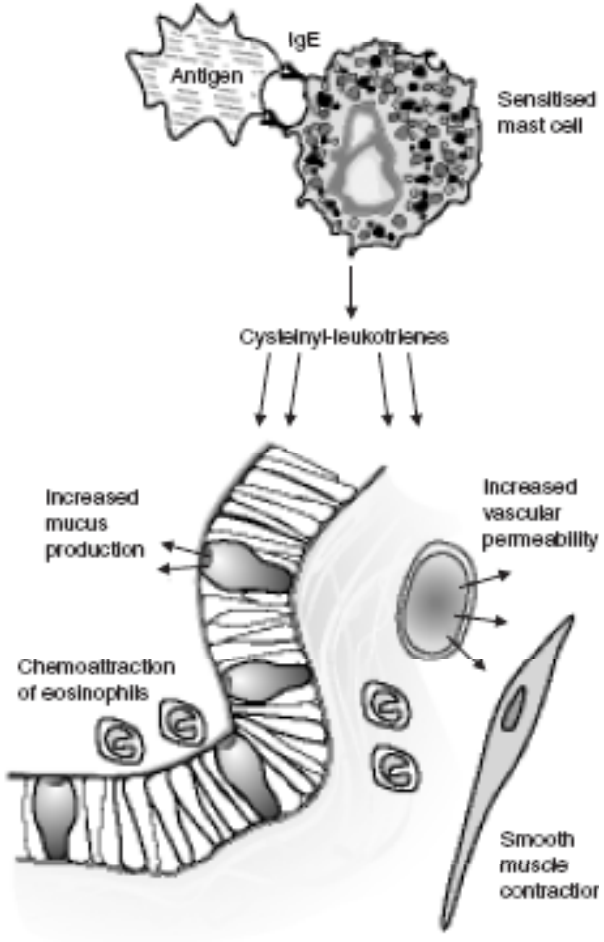
Efficacy of Intranasal corticosteroids

- Nasal blockage
- Nasal discharge
- Sneezing
- Nasal itch
- Postnasal drip
- Total nasal symptoms
- Quality of life

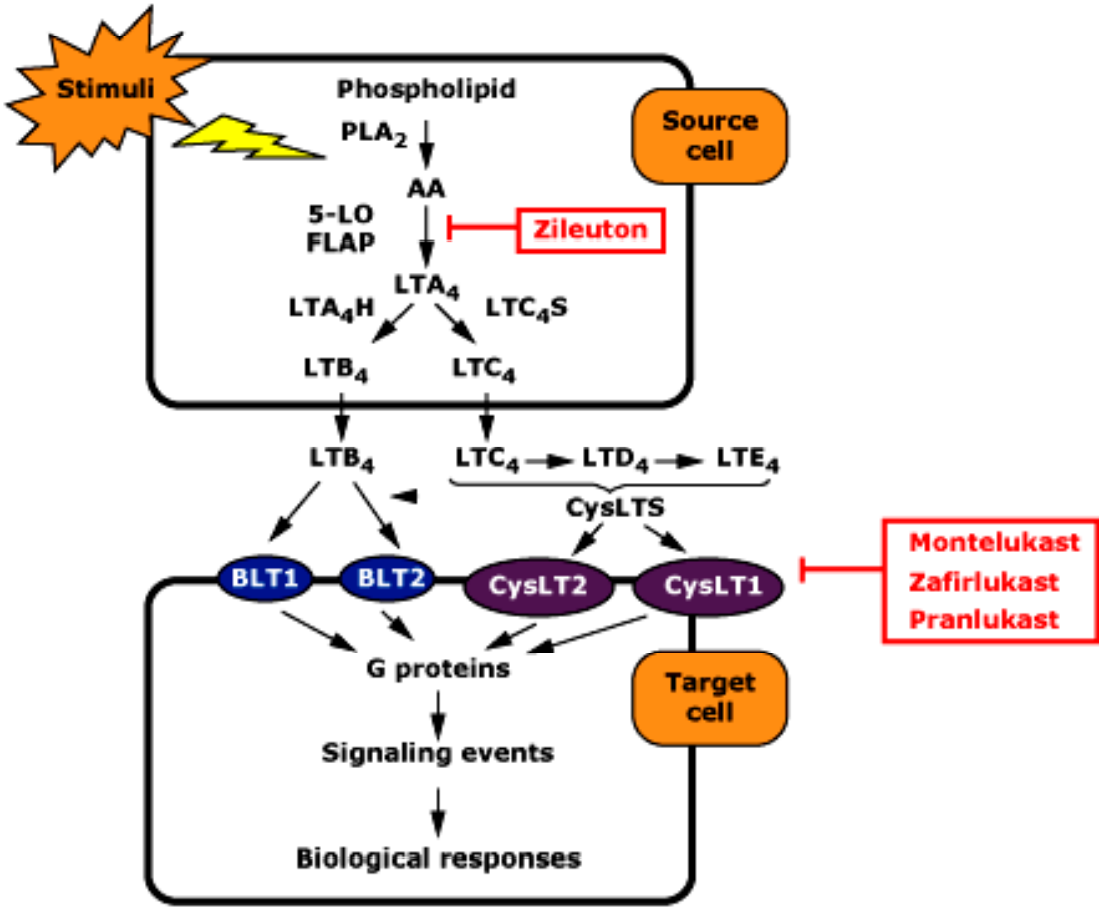
Intranasal corticosteroids produced significantly greater relief than oral antihistamines.

Weiner JM. et al. Intranasal corticosteroids versus oral H1 receptor antagonists in allergic rhinitis: systematic review of randomised controlled trials. *BMJ*, 1998 Dec, 317:7173, 1624-9

Anti-Leukotriene Agents



Nayak and Langdon, Drugs 2007



UpToDate.

Intranasal Anticholinergic

Ipratropium Bromide (0.06%, 0.03% Atrovent)

- Mechanism of action:
  - Blockage of muscarinic receptors of seromucinous glands
  - Effective only in controlling watery nasal discharge
    - Seasonal, perennial AR
    - Non allergic rhinitis
    - Common cold
  - Need 3-4 time of administration
    - Seasonal, perennial AR
    - Common cold
- Local side effects: dryness, irritation, burning

Adapted from Cauwenberge PV, et al. Position paper: Consensus statement on the treatment of allergic rhinitis *Allergy*. 2000; 55: 116-134

Herbal Medicines

Butterbur leaf extract Ze 339

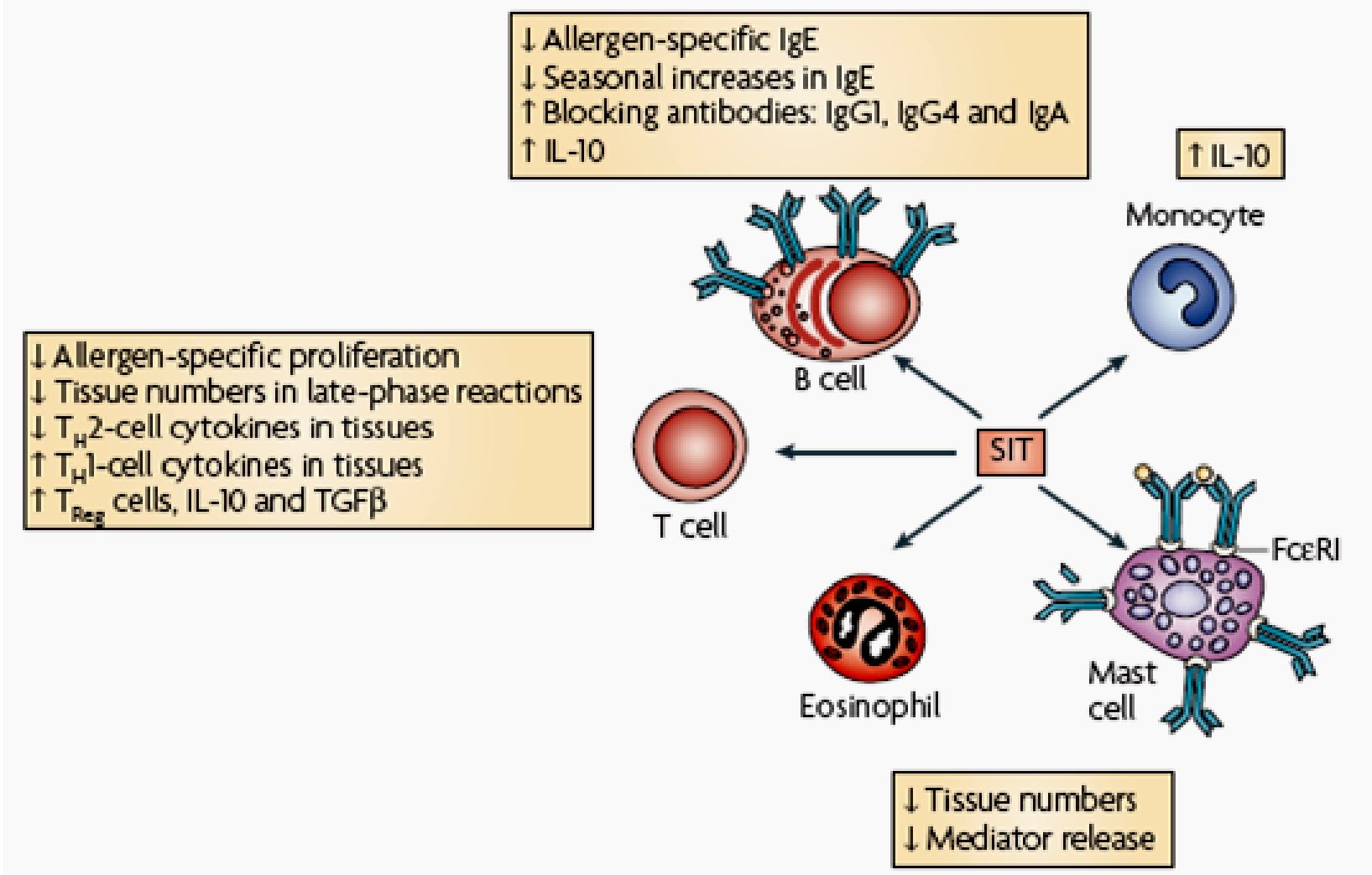
(CO2 extract from the leaves of Petasites hybridus L., 8 mg petasines/tab)

Kaufeler R et al. Adv Ther 2006

An open postmarketing surveillance study: 2 tabs/day for 2wks

- 580 subjects treated & evaluated on a visual analogue scale for rhinorrhea, sneezing, nasal congestion, itchy eyes/nose, red eyes, and skin irritation.
- 90% improvement. Differences observed before & after therapy were significant and clinically relevant for all symptoms.
- The improvement was inversely related to symptom severity.
- 80% Efficacy, 92% tolerability, and 80% improvement in quality of life.
- 44% of patients given an antiallergic comedication and Ze 339 did not result in a better effect than was attained with Ze 339 monotherapy.
- 3.8% adverse events (GI complaints predominantly)

Allergen-Specific Immunotherapy



Consultation with an allergist/immunologist

1. Prolonged manifestation of rhinitis
2. Complications of rhinitis, such as OM, sinusitis, and/or nasal polyposis
3. Comorbid condition such as asthma
4. Required systemic corticosteroid for the treatment of rhinitis
5. Symptoms or medication side effects interfere with his/her ability to function such as causing sleep disturbance or impairing school/work performance.
6. Symptoms significantly decrease QOL such as a decrease in comfort and well being, sleep disturbance, anosmia, ageusia

Consultation with an allergist/immunologist

7. Medications for rhinitis is ineffective or produces adverse events
8. Rhinitis medicamentosa
9. Allergic/environmental triggers symptoms need further identification and clarification.
10. Need for more complete education.
11. Requiring multiple and/or costly medications over a prolong period.
12. Allergy immunotherapy is a treatment consideration.

Question 6

6. A 2 year-old boy presents with recurrent sinus infections, low IgG, normal CBC, normal IgM, IgA, IgE, normal tetanus, HIB, pneumococcal titers and normal lymphocyte subpoppulations (CD3, CD4, CD19, CD56).

   Which one is the best recommendation?

   A. Antibiotic prophylaxis

   B. IVIG replacement therapy

   C. Bone marrow transplantation

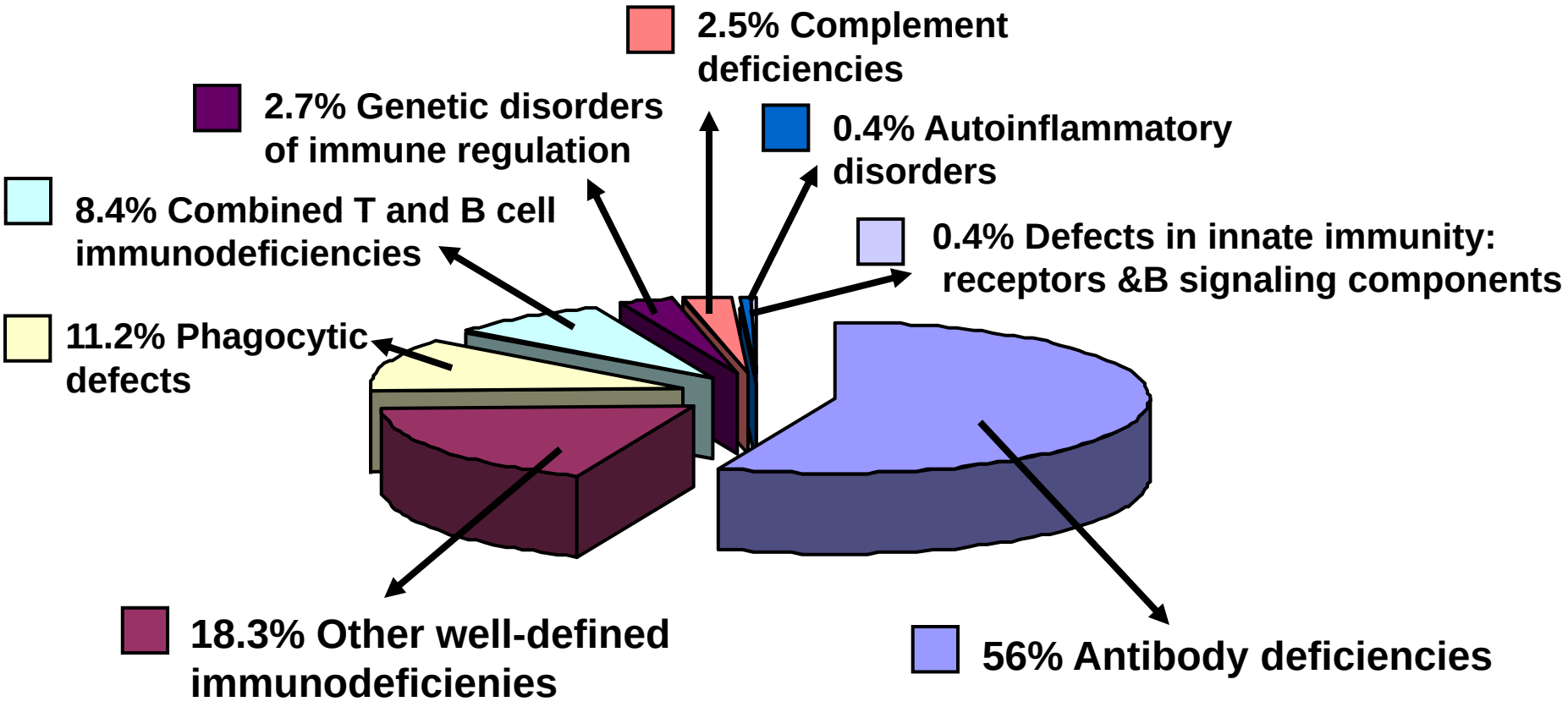
   D. Gene therapy

   E. Good hygiene, observation, recheck IgG in a couple years

Primary Immunodeficiencies (PID)

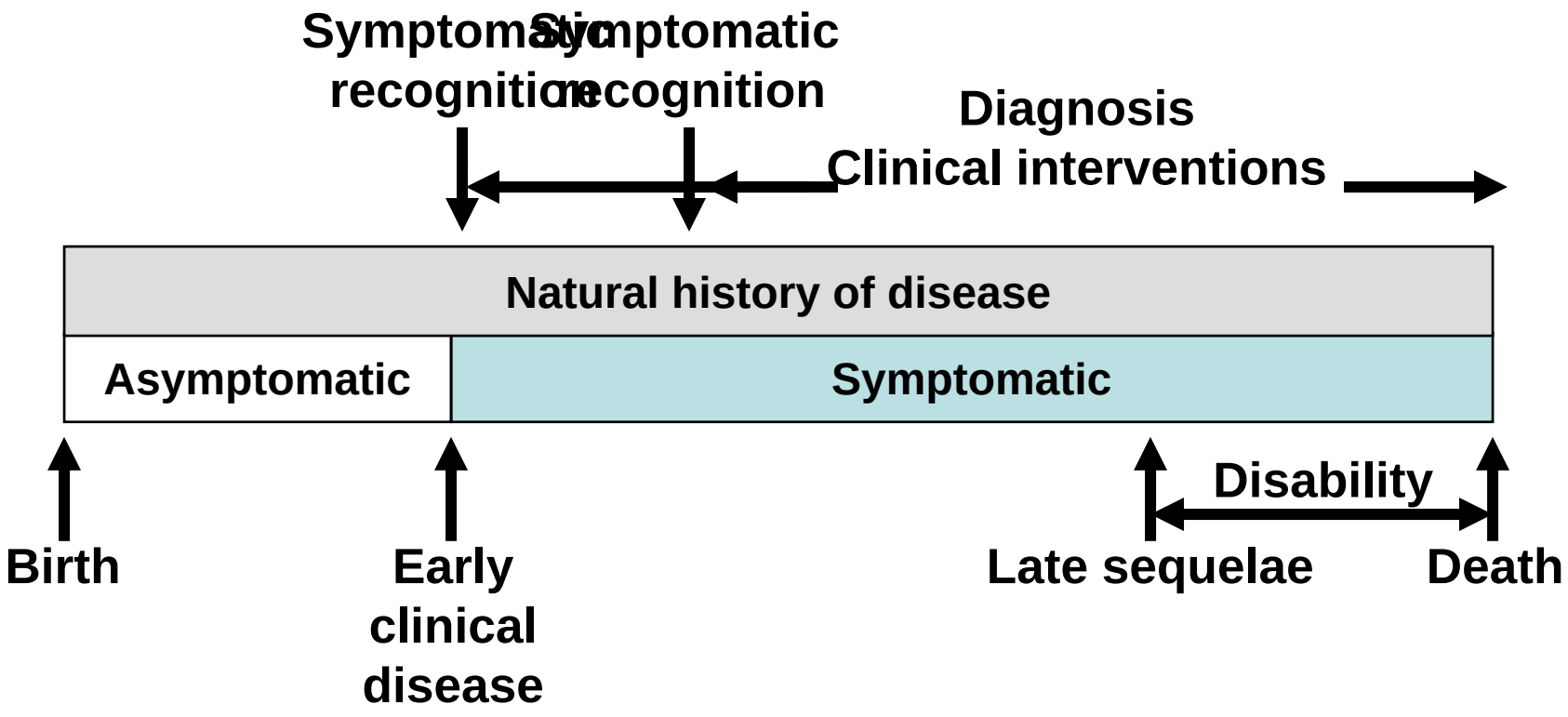
Orange JS. *Immunol Allergy Clin N Am* 2008

Primary Immunodeficiencies



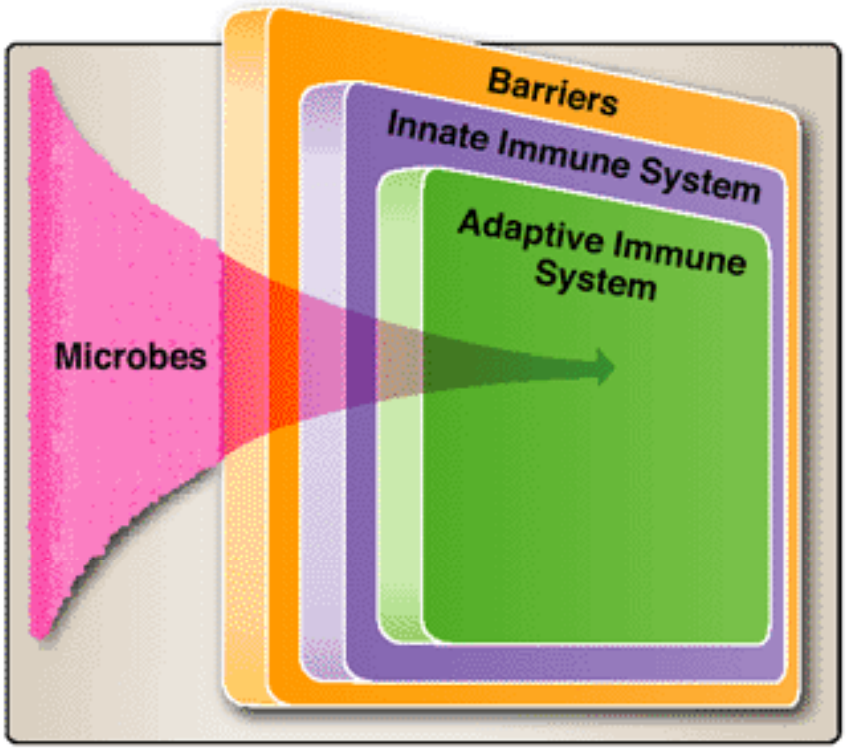
Rezaei N et al. Primary Immunodeficiency Diseases 2008

Primary Immunodeficiencies



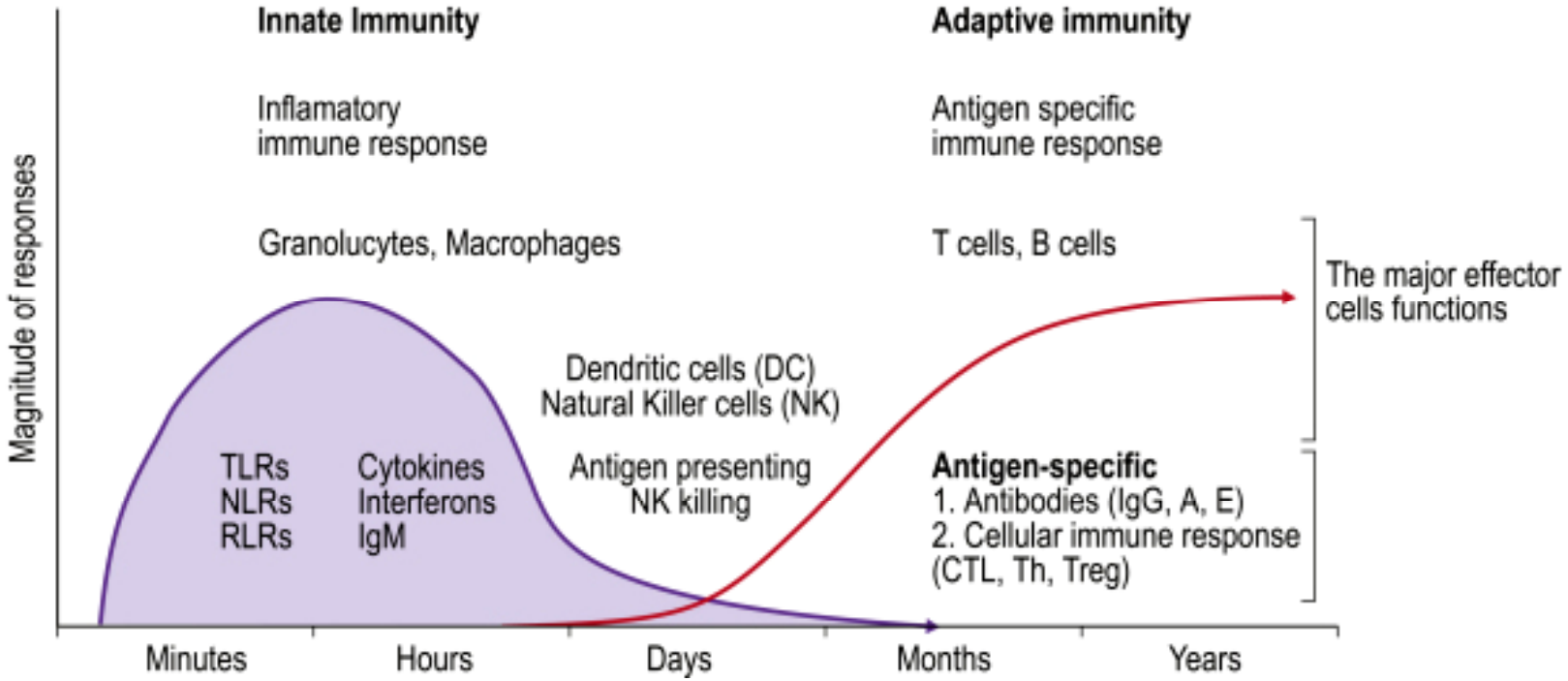
Modifed from *MMWR* 2004

Immune System



Doan et al. *Immunology*

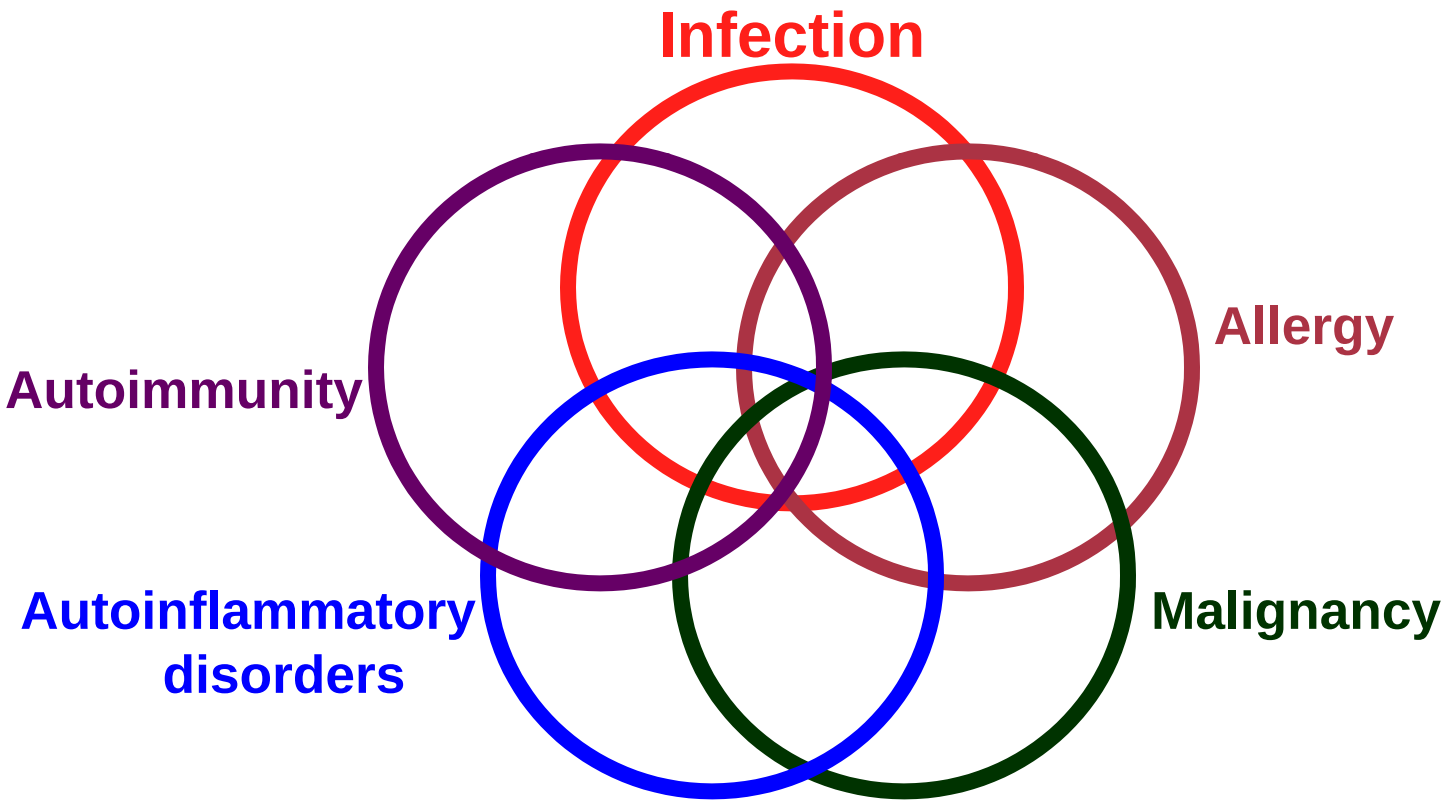
Innate Immunity



Rich. *Clinical Immunology* 2007

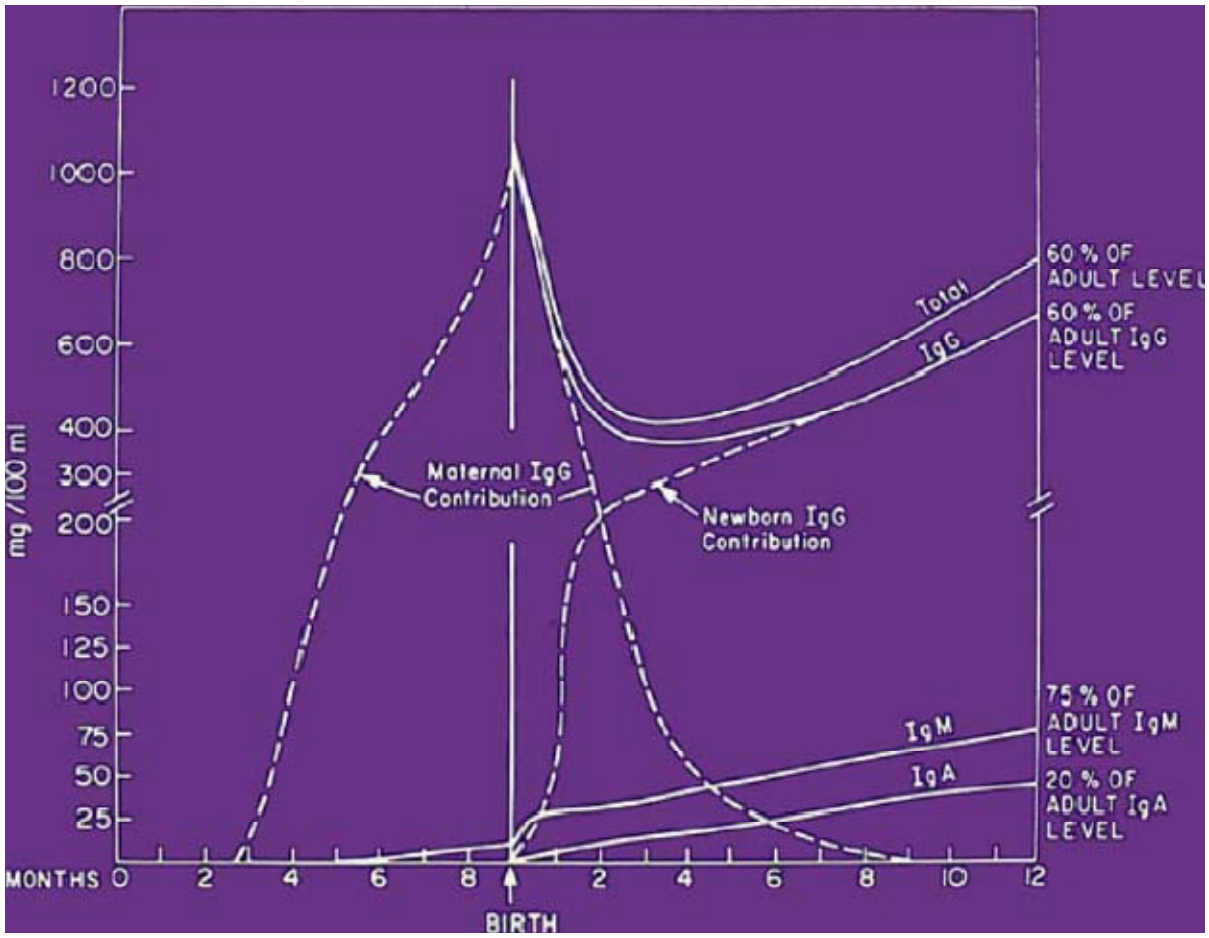
Features of Immune System Failure

Self VS Non-self Recognition



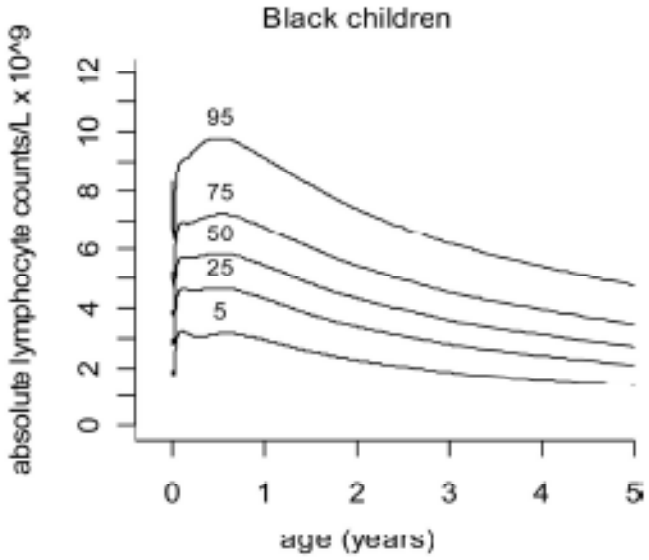
Gennery AR, Cant AJ. Adv Exp Med Biol. 2009

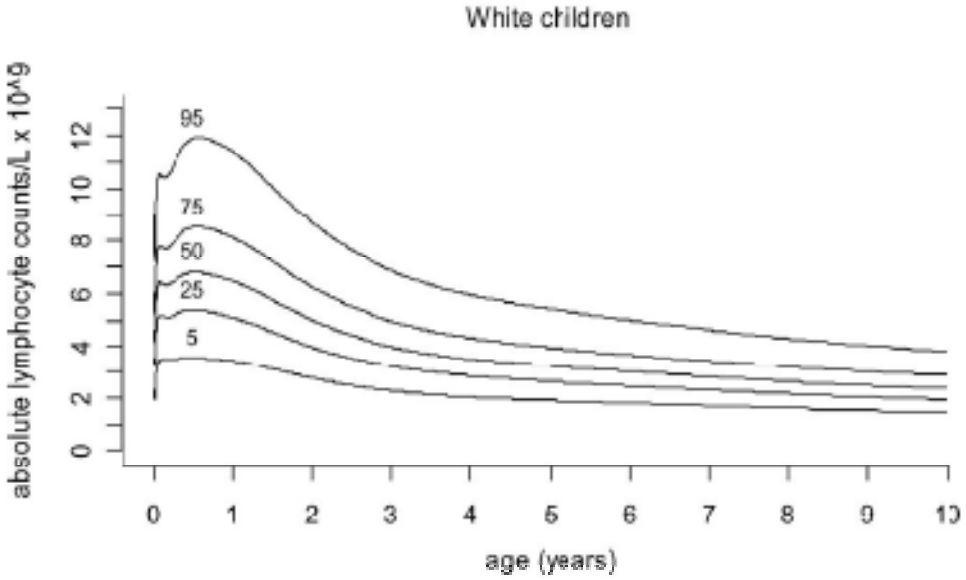
Adaptive Immunity



Stiehm et al. *Immunology disorders in Infants & Children 2004*

Lymphocyte





Absolute lymphocyte count < 2,800 in infants needs further work up

Pediatr Infect Dis J 2005;24:595-600

Lymphocyte Subsets

Marker name	Cell type
CD3	T cell
CD4	T cell subset
CD8	T cell subset
CD19, CD20	B cell
CD16	NK cell (may not present in some NKs)
CD56	NK cell (majority)

Lymphocyte Functions

Cell	Test
B cells	•Immunoglobulins (IgG,A,M,E) •Specific antibodies (HIB, Pneumo, Tetanus)
T cells	•Delayed type hypersensitivity •Lymphocyte mitogen stimulation (PHA, ConA, Pookweed, PMI/Io) •Lymphoctye antigen stimulation (Candida, Tetanus, Diptheria)
NK cells	•NK cell function

Non-Immunologic Causes

Recurrent infections

- **Abnormal mucous membranes and integuments:**
  - **Burns, severe eczema, bullous diseases, ectodermal dysplasia, percutaneous catheters.**
- **Obstruction of hollow viscus:**
  - **Allergic rhinitis, adenoid hypertropy with Eustachian tube dysfunction, asthma, cystic fibrosis, inhaled foreign body, posterior urethral valves, ureteropelvic junction obstruction.**
- **Foreign body:**
  - **Ventriculoperitoneal shunt, prosthetic cardiac valves, orthopedic devices, catheters.**
- **Vascular abnormalities:**
  - **Large left to right intracardiac shunt, diabetes mellitus.**

Non-Immunologic Causes

Recurrent infections

- **Congenital:**
  - **Cysts and sinus tracts, tracheoesophageal fistula, abnormal ciliary function.**
- **Neurologic:**
  - **Incoordinate swallowing, recurrent aspiration, poor respiratory effort.**
- **Metabolic disorders:**
  - **Galactosemia, certain amino acid and organic acid disorders.**
- **Unusual microbiologic factors:**
  - **Antibiotic overgrowth, resistant organism, continuous reinfection.**

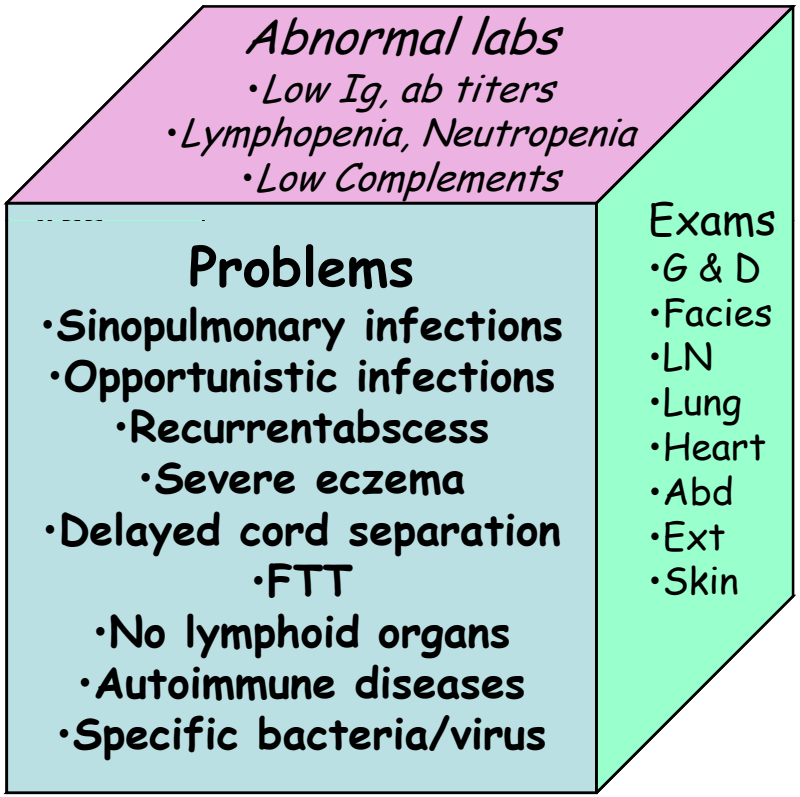
Secondary Immunodeficiency

- **Premature and Newborn**
- **Hereditary & Metabolic Diseases:**
  - **Chromosal abnomalities (Down syndrome, etc)**
  - **Uremia, DM, NS, myotonic dystrophy**
  - **Malnutrition,vitamine & mineral deficiency**
  - **Protein-losing enteropathies,**
- **Immunosuppressive agents & Radiation**
- **Infectious diseases:**
  - **Congenital rubella, viral examthem (measles, varicella, etc)**
  - **HIV, CMV, EBV**
  - **Bacterial infections, mycobacterial, fungal, parasite.**

Secondary Immunodeficiency

- **Infiltrative & Hematologic diseases**
  - **Histiocytosis, lymphoma, leukemia, myeloma**
  - **Agranulocytosis, aplastic anemia, cyclic neutropenia**
  - **Transplant recipiens**
- **Surgery & Trauma**
  - **Burns, head injury, hypothemia**
  - **Splenectomy, anesthesia**
- **Miscellaneous**
  - **SLE, alcoholic hepatitis, chronic active hepatitis, etc.**
  - **Aging**

Clinical Features of PID

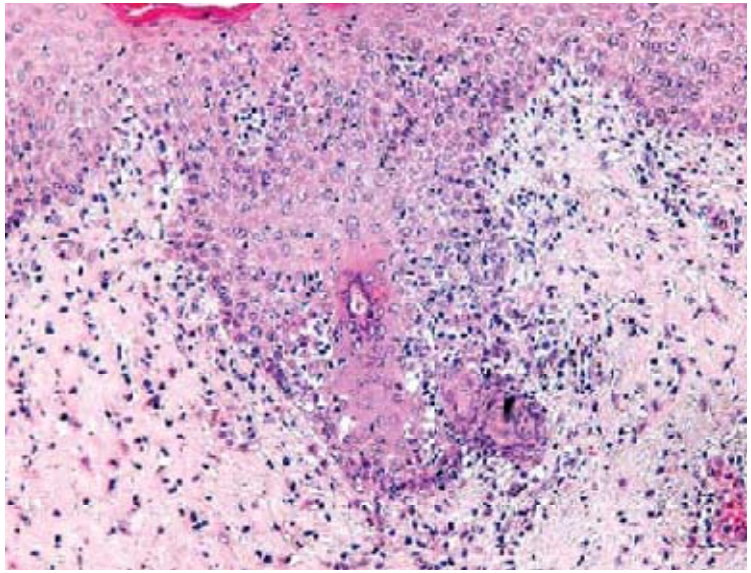


Clinical Features of PID

Age at presentation	PID
Neonatal period	•Omenn syndrome •Severe congenital neutropenia •DiGeorge syndrome •LAD •Reticular dysgenesis
First 6 months	•SCID •Other T cell deficiency •CD40 ligand deficiency

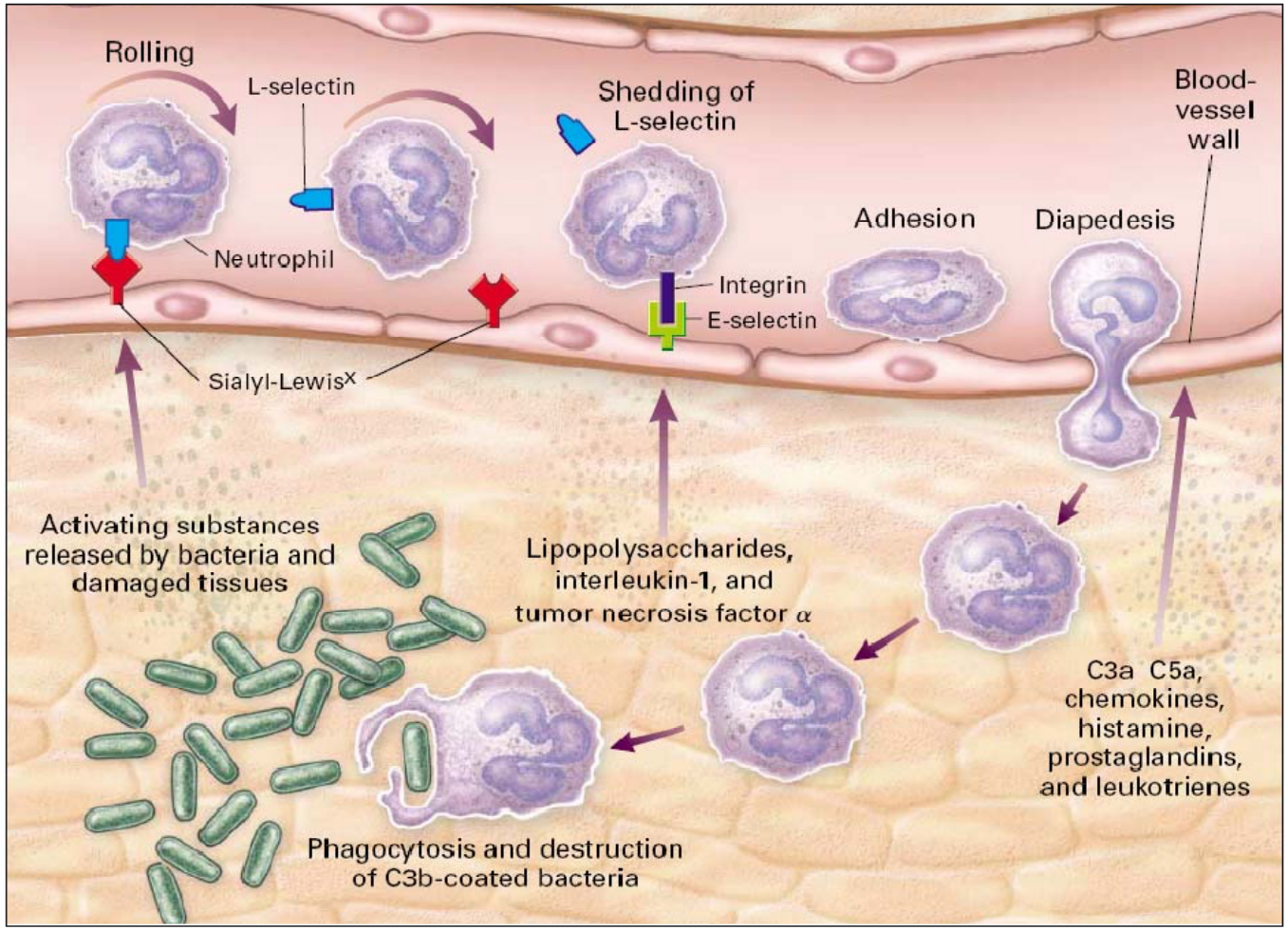
Omenn’s Syndrome

Generalized scaly exudative erythroderma, enlarged lymphoid tissues
Protracted diarrhea, FTT, eosinophilia, hypogammaglobulinemia
Genetic defects: RAG1, ARG2, Artemis, ADA deficiency, IL7Ra



Abundant lymphocytic infiltrate in superficial dermis with keratinocytes damage and eosinophil infiltrate

Leukocyte Adhesion Defect (LAD)



Delves PJ. *N Engl J Med* 2000

Leukocyte Adhesion Defect (LAD)

Hallmarks: Gingivitis, severe periodontitis, failure to form pus, limited inability to demarcate the fibrotic skin debris, and limited inflammation.

Clinical Immunology, Principles and Practice 3rd, 2007

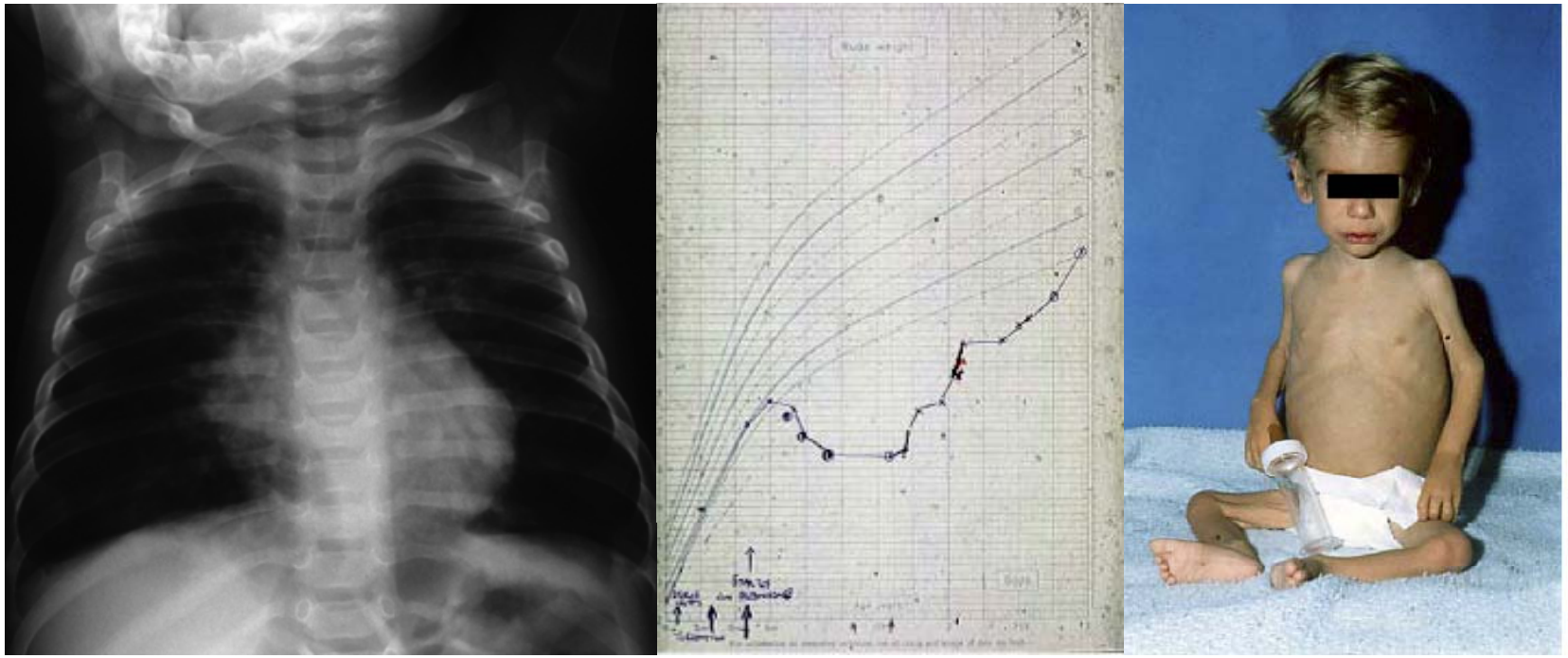
When an umbilical cord separates

Cord care regimen and days to umbilical cord separation

Cord Care Regimen	Author	Mean Time to Separate (d)	Standard Deviation	Range (d)	Number of Infants Studied
Dry care	Dore et al 1998 (15)	8.16	±3.1	1 to 24	907
Dry care	Mugford et al 1986 (16)	7.27	±2.09		
Dry Care	Oudesluys-Murphy et al 1990 (26)	7.4	±3.3 days	1 to 29	911
Dry care	Pezzati et al 2002 (20)	7.5	±3.1 days		177
Triple dye	Pezzati et al 2002 (20)	11.6	±6.6 days		195
70% alcohol	Dore et al 1998 (15)	9.8	±4.6	2 to 49	900
70% alcohol	Golombek et al 2002 (27)	10			
70% alcohol	Mugford et al 1986 (16)	7.14	±2.09		
70% alcohol	Pezzati et al 2002 (20)	16.9	±7.5 days		178
70% alcohol	Rais-Bahrami et al 1993 (28)	10.9		3 to 43	293
Salicylic acid powder	Pezzati et al 2002 (20)	5.6	±2.3 days		167

JoDee M, et al. *NeoReviews* 2004

SCID

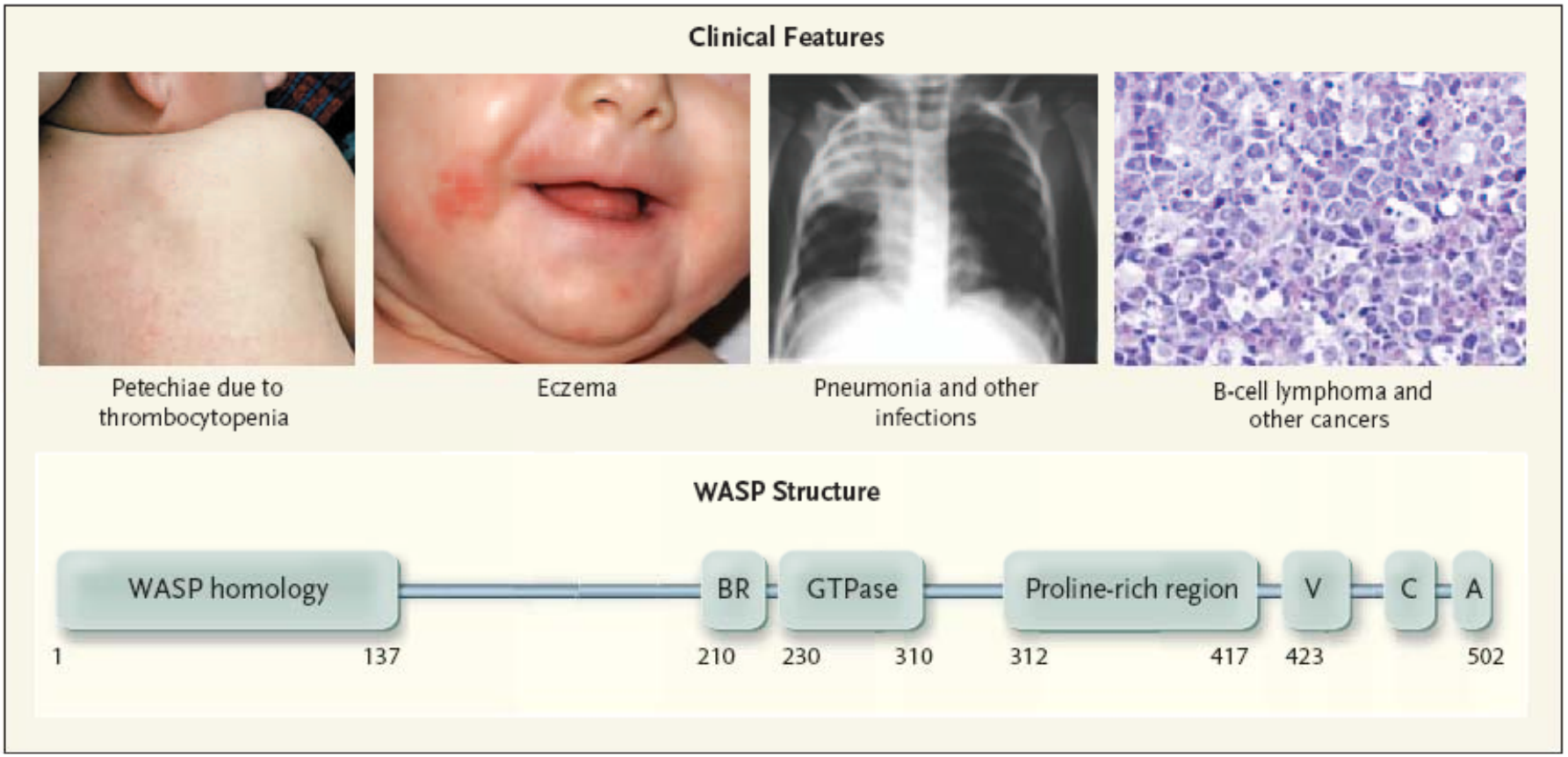


Wang HC, et al. *Allergy Asthma Proc* 2006

Clinical Features of PID

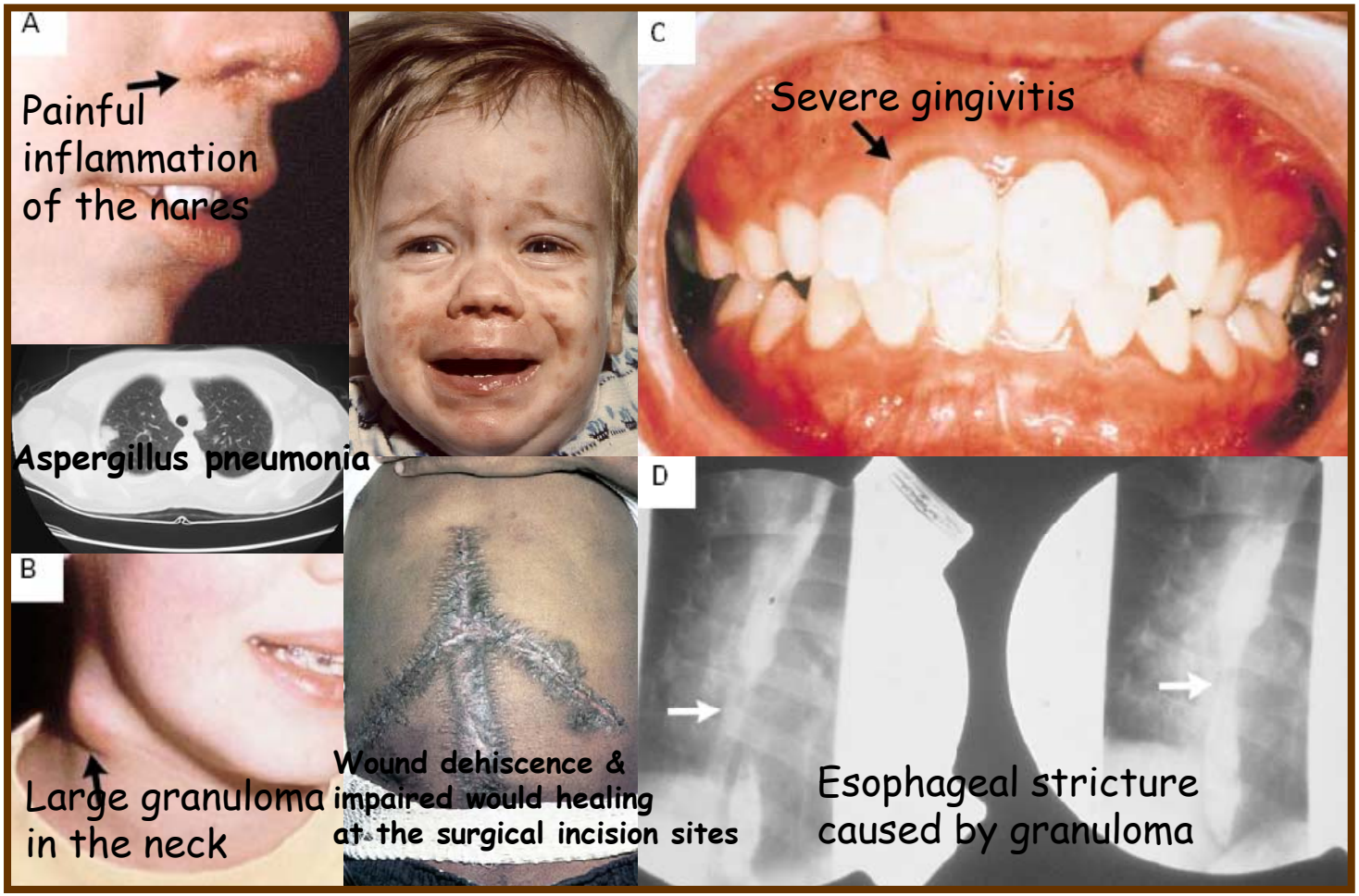
Age at presentation	PID
After 6 months- 5 years	•Hypogammaglobulinemia •Wiskott-Aldrich syndrome •Phagocytic defects •DiGeorge syndrome •Chronic mucocutaneous candidiasis
After 5 years	•Late presentation of the above •AT, other DNA repair disorder •CVID •Specific antibody deficiency •Complement disorder

Wiskott-Aldrich syndrome (WAS)



Puck JM. *N Engl J Med* 2006

Chronic Granulomatous Disease (CGD)



Lekstrom-Himes. *N Engl J Med* 2000

Clinical Features of PID

Organism	Candidate immune defect
Pneumococcus, HIB	• B cell/ Antibody • Complement
Staphylococcus	• Neutrophil
Meningococcus	• Complement (Late C5-C9)
Gram negative bacteria	• Neutrophil
Salmonella	• Cell–mediated • Type 1 cytokine defects
Giardia lamblia	• B cell/antibody • Cell mediated
Crytosporidium	• Cell mediated

Adapted from Slatter MA. *Clin Exp Immunol* 2008

Clinical Features of PID

Organism	Candidate immune defect
Mycoplasma	• B cell/ Antibody
Candida albicans	• Cell mediated • Neutrophil • Monocyte
Aspergillus spp	• Neutrophil
Herpes viruses (eg CMV)	• Cell-mediated
Enteroviruses	• Antibody • Cell–mediated
Other viruses (eg measles)	• Cell mediated

Adapted from Slatter MA. *Clin Exp Immunol* 2008

Clinical Features of PID

Organism	Candidate immune defect
BCG	• **Cell-mediated** • **Type 1 cytokine defects** **IFN-gR1** **IFN-gR2** **STAT1,** **IL-12RB1** **IL-12B**
Mycobacteria (typical & atypical)	• **Type 1 cytokine defects** • **NFkBsignalling pathway defects (NEMO)**

Adapted from Slatter MA. *Clin Exp Immunol* 2008

Clinical Features of PID

Features	Primary Immunodeficiency
Respiratory tract infections Persistent sinopulmonary infections	• SCID • Hypogammaglobulinemia • Specific antibody def • Complement deficiency • Cyclic neutropenia • NEMO • IRAK4 deficiency
Recurrent skin infection, periodontitis, gingivostomatitis	• CGD • HIE • LAD • XLA • Neutropenia

Clinical Features of PID

Features	Primary Immunodeficiency
Eczema	• **HIE** • **WAS** • **Omenn's syndrome** • **Netherton syndrome** • **CGD** • **IPEX** • **Hypogammaglobulinemia (CVID, HIM, IGAD, XLA)**
Recurrent mucosal candidiasis	• **SCID** • **Chronic mucocutaneous candidiasis** • **HIE**

Clinical Features of PID

Features	Primary Immunodeficiency
Respiratory tract infections Persistent sinopulmonary infections	• SCID • Hypogammaglobulinemia • Specific antibody def • Complement deficiency • Cyclic neutropenia • NEMO • IRAK4 deficiency
Recurrent skin infection, periodontitis, gingivostomatitis	• CGD • HIE • LAD • XLA • Neutropenia

Clinical Features of PID

Features	Primary Immunodeficiency
Neutropenia	• XLA • CVID • HIM • IGAD • WHIM • Cartilage-hair hypoplasia • Reticular dysgenesis • Dubowitz syndrome • Griscelli syndrome
Thrombocytopenia	• WAS • DiGeorge syndrome • CVID • CGD

Clinical Features of PID

Features	Primary Immunodeficiency
Telangiectasia	• Ataxia telangiectasia
Absence or scanty lymphoid tissues	• XLA • SCID • Complete DiGeorge anomaly
Delayed cord separation	• LAD
Lymphoma	• AT • WAS • XLP • CVID
Hepatoma	• HIM (CD40 ligand def)

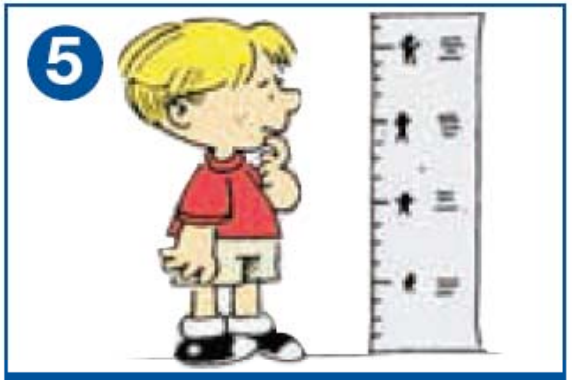
Warning Signs

Eight or more new ear infections within 1 year.

Two or more serious sinus infections within 1 year.

Two or more months on antibiotics with little effect.

Two or more pneumonias within 1 year.



Failure of an infant to gain weight or grow normally.

2 or more of the warning sings

Presented as a public service by:
Jeffrey Modell Foundation

History of respiratory infections in the first 12 yr among children from a birth cohort

1314 German children born in 1990 tracked until age 12 yr (760 children)

Age	Normal number of respiratory tract infection episodes per year
Infant (0-2 Yr)	11
Pre-school age (3-5 Yr)	8
School age (6-12 Yr)	4

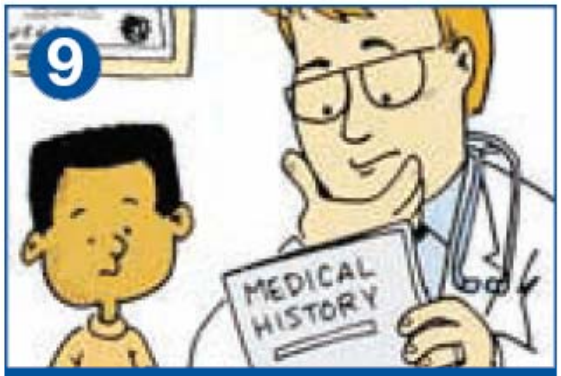
Gruber C, et al. Pediatr Allergy Immunol 2008

Warning Signs

Recurrent, deep skin or organ abscesses.

Persistent thrush in mouth or elsewhere on skin, after age 1.

Need for intravenous antibiotics to clear infections.



Two or more deep-seated infections.

A family history of Primary Immunodeficiency.

2 or more of the warning sings

Presented as a public service by:
Jeffrey Modell Foundation

Underlying causes of recurrent pneumonia in children

238 children (2.5 mo-15.6yr)
220 (92%) with underlying causes,18 (8%) with unknown cause

Underlying illness	Mean age	Dx prior to pneumonia	Dx after 1st pneumonia	Dx after recur pneumonia	Total
Aspiration syndrome	6.3yr	109	1	4	114
Immune disorder	3.8yr	26	7	1	34
Cong heart disease	1.8yr	22	0	0	22
Asthma	4.5yr	12	0	7	19
Anomalies respiratory	4mo	9	7	2	18
GE reflux	1.4yr	0	10	3	13
Total		178 (80.9%)	25(11.4%)	17 (7.7%)	220

Owayed AF, et al. Arch Pediatr Adolesc Med 2000

Warning Signs

- **Unexplainted bronchiectasis.**
- **Unusual presentation of the infection.**
- **Dysmorphic features associated with recurrent infection.**
- **Infections worsening chronic disorders (asthma or seizure).**
- **Development of vaccine pathogen after vaccination (e.g., HiB infection despite previous HiB vaccine).**
- **Complication associated with live vaccination.**
- **Delayed umbilical cord separtation**
- **Unexplained autoimmune disease.**

Screening for PID

Recurrent sinopulmonary tract infections

Encapsulated bacteria

Diagnosis consideration:

B cell/ antibody def, Complement, phagocytic def, WAS, HIV

Initial tests: **CBC with differential count, IgG, IGA, IgM,**
Specific antibody titers (Tetanus, HIB, Pneumococcal), CH50

Referring: if abnormal, or normal but problems persist

Screening for PID

Recurrent skin infections

Recurrent pyogenic infections

Diagnosis consideration:

B cell/ antibody def, Complement, phagocytic def, LAD, HIE

Initial tests: **CBC with differential count, IgG, IGA, IgM, IgE**

CH50, nasal swab culture

Referring: if abnormal, or normal but problems persist

Screening for PID

Failure to thrive, opportunistic/ fungal infections
Unusual or severe infections

Diagnosis consideration:
B cell/ antibody def, T cells defects & SCID, STAT1 deficiency, XLP, NEMO IRAK4 def

Initial tests: **CBC with differential count, IgG, IGA, IgM, IgE**

Referring: All cases

Screening for PID

Autoimmune or chronic inflammatory disease

Lymphoproliferative diseases

Diagnosis consideration:

ALPS, XLP, IPEX, APECED, CVID, complement def

Initial tests: **CBC with differential count, IgG, IGA, IgM, CH50**
Autoantibodies, ESR, CRP

Referring: All cases, especially with infections

Transient Hypogammaglobulinemia in Infancy (THI)

- **A prolongation of physiologic hypogammaglobulinemia**
- **Low IgG with or without low IgA and/or IgM beyond 6 months of age**
- **Most infants are able to respond normally to vaccine antigens**
- **Asymptomatic VS symptomatic**
- **Hypogammaglobulinemia may persist up to the age of 5 years.**

Transient Hypogammaglobulinemia in Infancy (THI)

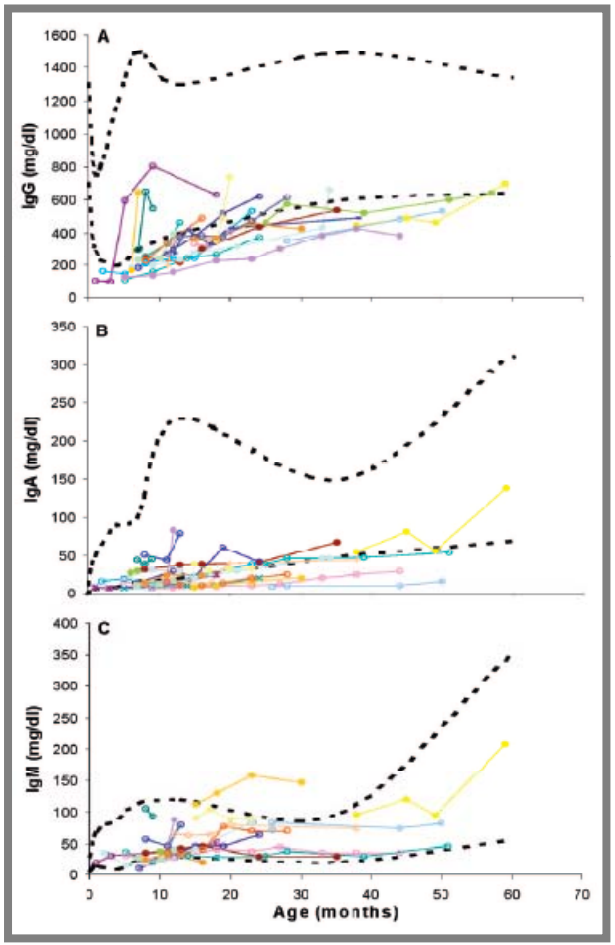
Clinical Features

- **Recurrent sinopulmonary tract infections, recurrent diarrhea, prolonged oral candidiasis.**
- **Eczema, AR, food allergy**
- **Tonsils and lymph nodes are present.**
- **Mild neutropenia or thrombocytopenia**

Transient Hypogammaglobulinemia in Infancy (THI)

Lab Features

- Low IgG beyond 6 months of age
- Normal or low IgA (1/2 of cases)
- Normal or low IgM (1/5 of cases)
- Normal protective antibody titers or non-protective or antibody titers (15% of cases) including low tetanus HIB, pneumococcal titers



Dorsey MJ, *Ann Allergy Asthma Immunol* 2006

Transient Hypogammaglobulinemia in Infancy (THI)

Diagnosis

Require follow up and retesting with normal results.

- **Typical case**

  Low IgG, not profound hypogammaglobulinemia except premature

  Normal antibody titers

  Normal B (CD19), T (CD3/4/8), NK (CD3/4/8, CD56) cells

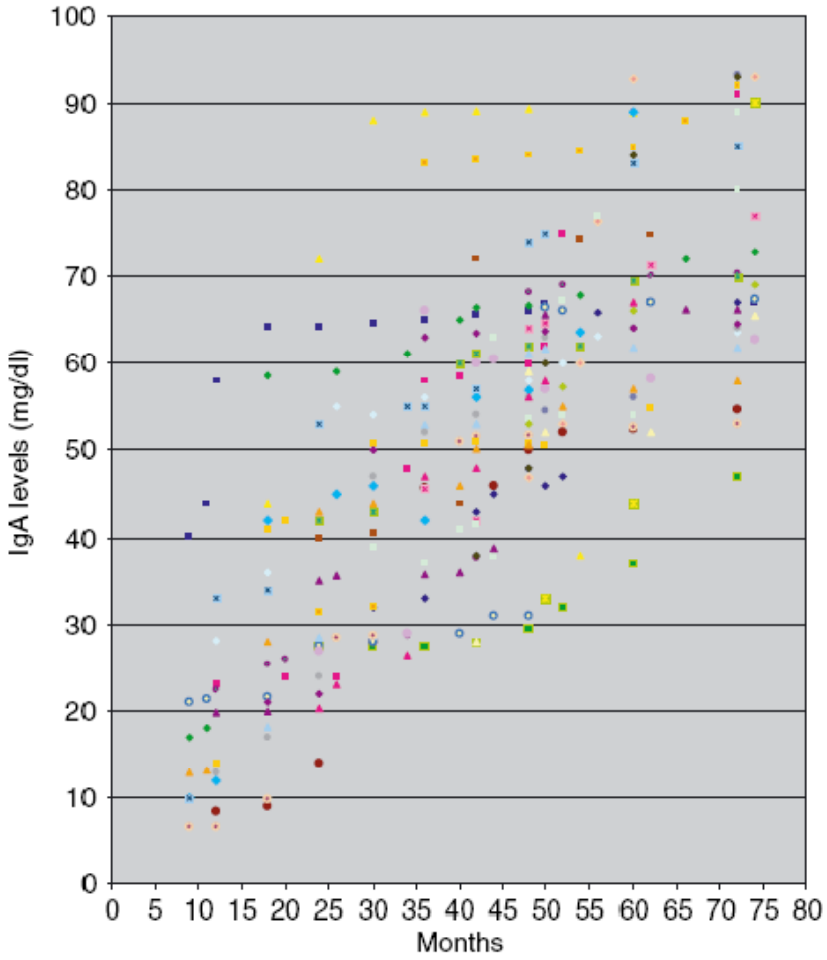
- **May have low IgG + Low IgA +/- Low IgM, +/- Low antibody titers and elevated B (CD19) cells**

Transient Hypogammaglobulinemia in Infancy (THI)

Treatment

- **Observation, F/U Immunoglobulin level yearly**
- **Most THI will spontaneously resolve by age 4.**
- **Antibiotic prophylaxis**
- **IVIG is not indicated. A period of IVIG replacement may be considered.**

Selective IgA Deficiency

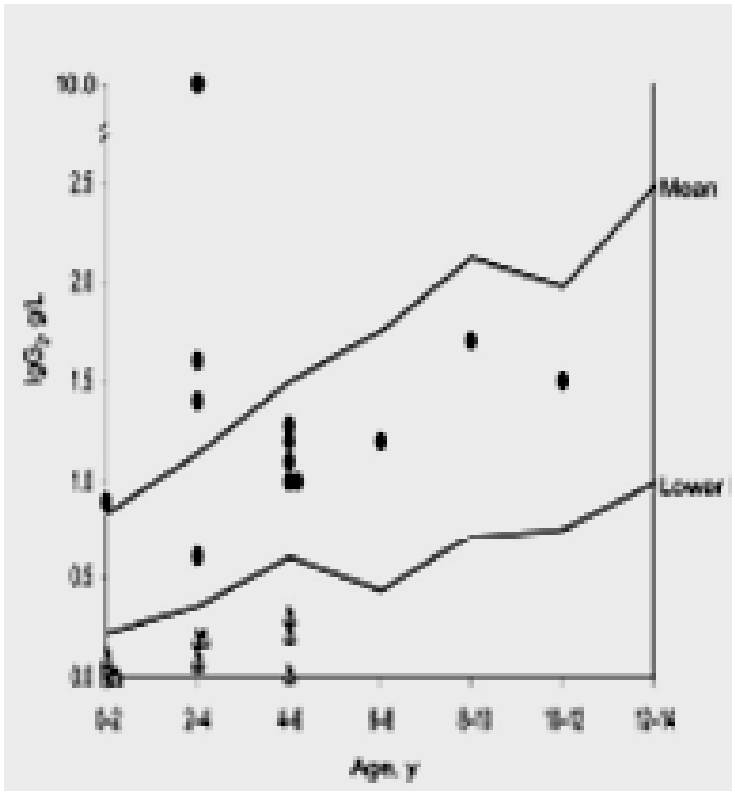


Kutukculer N *Pedriatr Allergy Immunol 2007*

IgG Subclass Deficiency

Low Serum Immunoglobulin G_2 Levels in Infancy Can Be Transient

Adelle R. Atkinson, MD, Chaim M. Rolfman, MD



PEDIATRICS
OFFICIAL JOURNAL OF THE AMERICAN ACADEMY OF PEDIATRICS

Question 6

6. A 2 year-old boy presents with recurrent sinus infections, low IgG, normal CBC, normal IgM, IgA, IgE, normal tetanus, HIB, pneumococcal titers and normal lymphocyte subpoppulations (CD3, CD4, CD19, CD56).

   Which one is the best recommendation?

   A. Antibiotic prophylaxis

   B. IVIG replacement therapy

   C. Bone marrow transplantation

   D. Gene therapy

   E. Good hygiene, observation, recheck IgG in a couple years

Question 7

7. A 6 year-old girl presents with left knee/ankle swelling and limping, no fever for 2 days. Yesterday, her mother noticed bruises on both legs. The patient had URI 2 weeks before limping. ROS is negative.

   Which one is the most likely diagnosis?

   A. Reactive arthritis

   B. Septic arthritis

   C. HSP

   D. Leukemia

   E. Hemophilia

Joint pain, not moving joint
limping, pain on extremity

↓

Is it arthritis?

Definition by ILAR* 2001

Swelling within a joint, or

Limitation in the range of joint movement with joint pain or tenderness

observed by a physician, and not due to primarily mechanical disorders or to other identifiable causes.

Acute Arthritis: Overview

- **A relatively common problem.**
- **Acute arthritis = any arthritis present < 6wks.**
- **A small proportion of children will go on to have chronic arthritis**

Acute Arthritis: Overview

- **A large proportion of acute arthritis**
  - **Self limiting**
  - **Symptomatic Rx for a short period of time.**
- **The challenge is to identify conditions requiring more than just symptomatic Rx.**

Joint pain, not moving joint

limping, pain on extremity

Is it arthritis?

What are the possible causes?

Acute Arthritis: Overview

- **The diagnosis requires**
  - **-A good history including relevant ROS**
  - **-A good knowledge of musculoskeletal exam**
  - **-A good knowledge of conditions commonly associated with joint complaints.**

Joint complaints “ARTHRITIS”

- **A** = Avascular necrosis and degenerative disorders: Perthes’ disease, Osteochondritis dissecan, Scheurermann’s disease, Slipped capital femoral epiphysis, Patellofemoral pain syndrome, Hypermobility
- **R** = Reactive arthritis: Post viral, poststreptococcal, postenteric infections
- **T** = Trauma: Accidental and non-accidental (Child abuse)
- **H** = Hematological: Leukemia,neuroblastoma, lymphoma,hemophilia,hemoglobinopathy
- **R** = Rickets: Hypophosphatemic rickets, metabolic and endocrine disorders (Diabetes, Hypothyroidism)
- **I** = Infections, Immunodeficiencies: Septic arthritis, osteomyelitis, tuberculosis, Brodie’s abscess, pediatric AIDS, common variable immunodeficiency (CVID)
- **T** = Tumors of cartilage, bone, muscle: Benign (Osteoid osteoma, hemangioma, pigmented villonodular synovitis), malignancy (Osteosarcoma)
- **I** = Inborn error metabolism, idiopathic pain syndromes
- **S** = Systemic connective tissue diseases, Syndromes: SLE, Vasculitis (including HSP, Kawasaki disease), dermatomyositis, PAN, mixed connective tissue disease, Ehlers-Danlos syndrome, Down syndrome, Stickler’s syndrome

Acute Arthritis

- **Essential history**
  - Trauma and significant symptoms in 24-48hours
  - Swelling, limited ROM
  - Morning, Nocturnal symptoms
  - Duration
  - Constitutional symptoms
  - URI, diarrhea, dysuria, rash
  - Underlying diseases
  - Medications
- **Essential physical finding**
  - Joint swelling
  - Warm
  - Tenderness of jt line
  - Limited ROM
  - Red (Don't routinely expect!!!)

Joint pain, not moving joint

limping, pain on extremity

Is it arthritis

What are the possible causes?

Work Up

Diagnostic Tests

Acute	Chronic
CBC ESR, CRP ASO, Anti-DNaseB Liver enzyme BUN, Creatinine U/A	CBC ESR, CRP ANA, RF HLA-B27 FT4, TSH U/A
Synovial fluid culture Blood culture Throat swab culture Urine culuture LDH, uric acid ANA	Anti-dsDNA, anti-smith C3,C4 ANCA IgG CPK PPD

Diagnostic Tests

- **ESR:**
  - **Highly sensitive, low specificity**
  - **Normal ESR may be seen in JRA, SLE, systemic vasculitis, inflammatory muscle disease etc.**
  - **Be considered as an adjunct to a pt's overall clinical status rather than an absolute reflection of disease activity.**

Diagnostic Tests

False negative (Low ESR)	False positive (High ESR)
Agammaglobulinemia	Hypergammaglobulinemia
Afibrinogenemia	Hyperfibrinogenemia
Hyperviscosity state	Hypercholesterolemia
Polycythemia	Anemia
Microcytosis, spherocytosis	Macrocytosis
High WBC	High ambient temperature
CHF	
Cachexia	
Delay testing (>2hrs)	

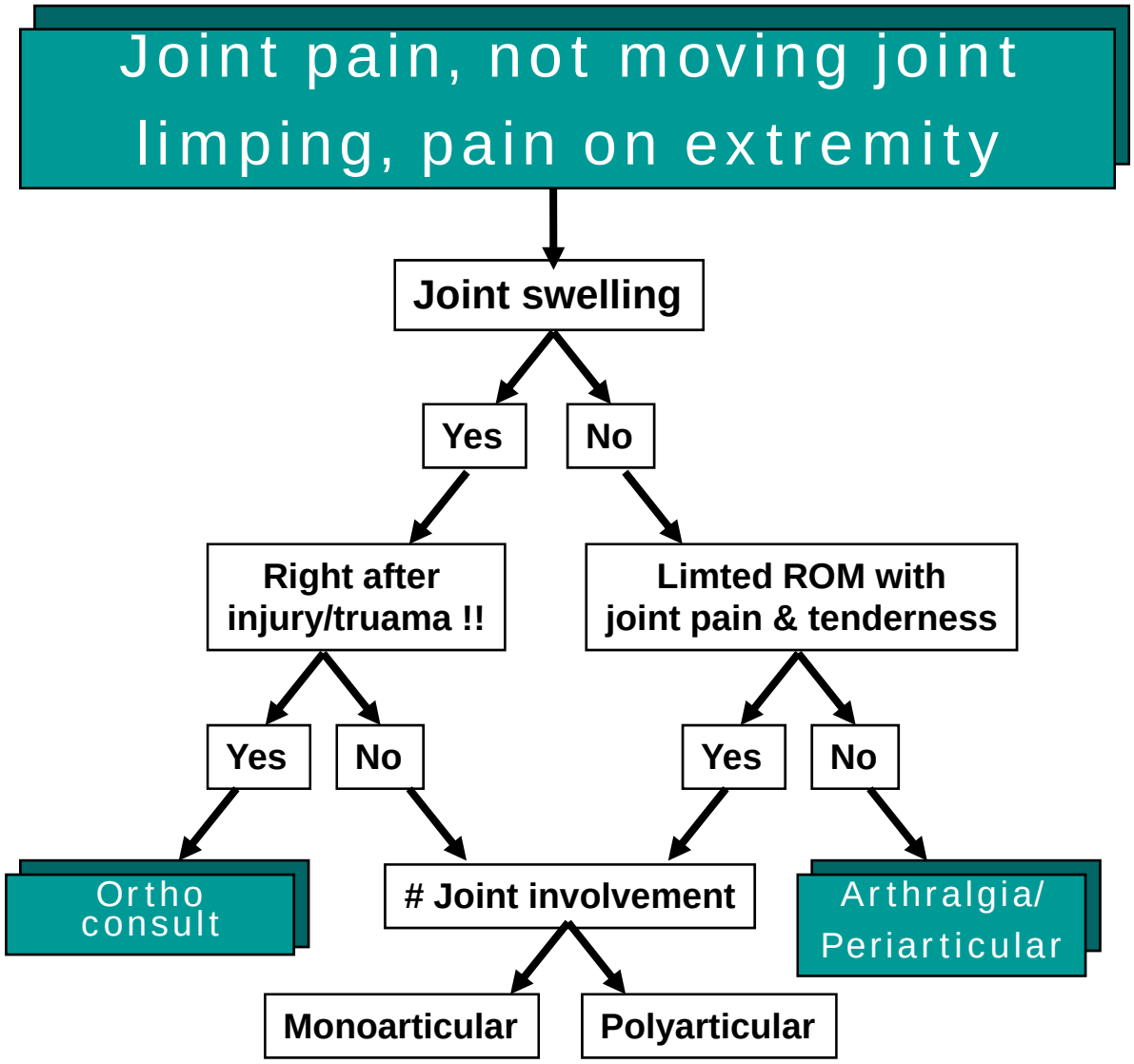
Joint pain, not moving joint
limping, pain on extremity

Is it arthritis

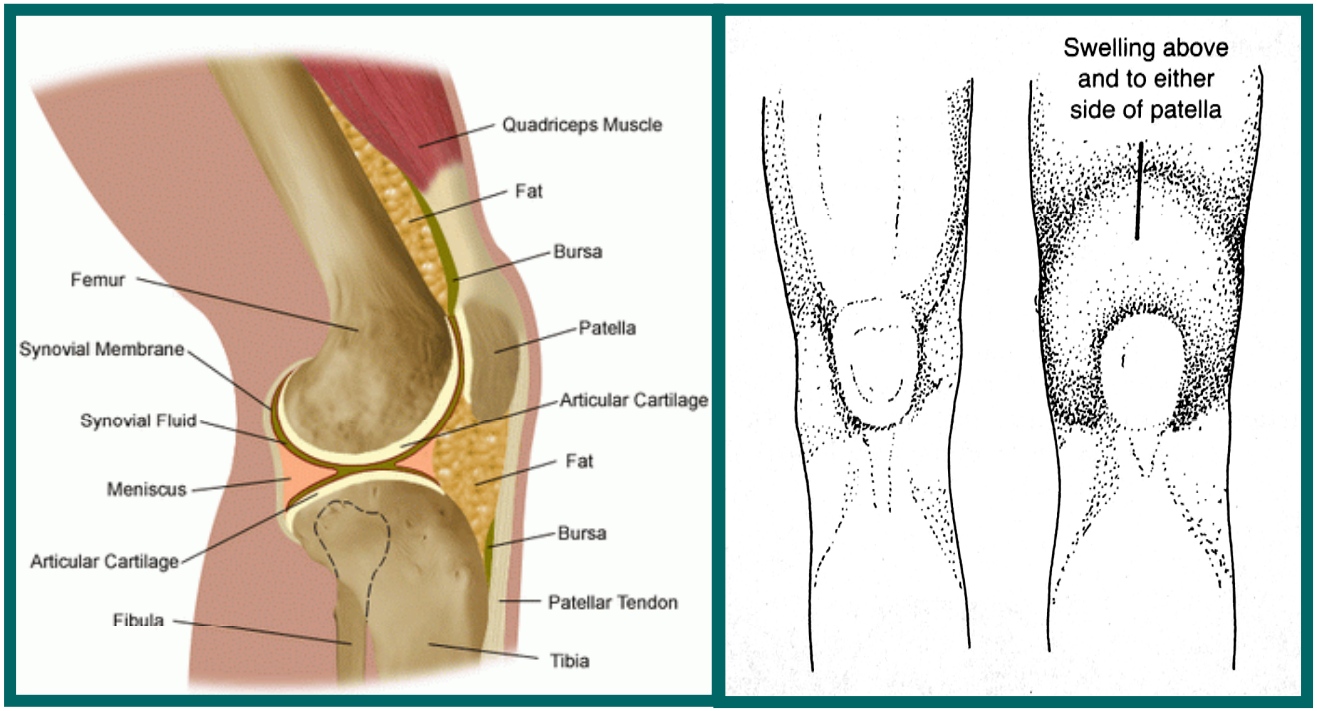
What are the possible causes?

Work Up

Treatment


Joint pain, not moving joint
limping, pain on extremity
Joint swelling
Yes
No
Right after injury/truama !!
Limted ROM with joint pain & tenderness
Yes
No
Yes
No
Ortho consult
Joint involvement
Arthralgia/ Periarticular
Monoarticular
Polyarticular

Joint Swelling

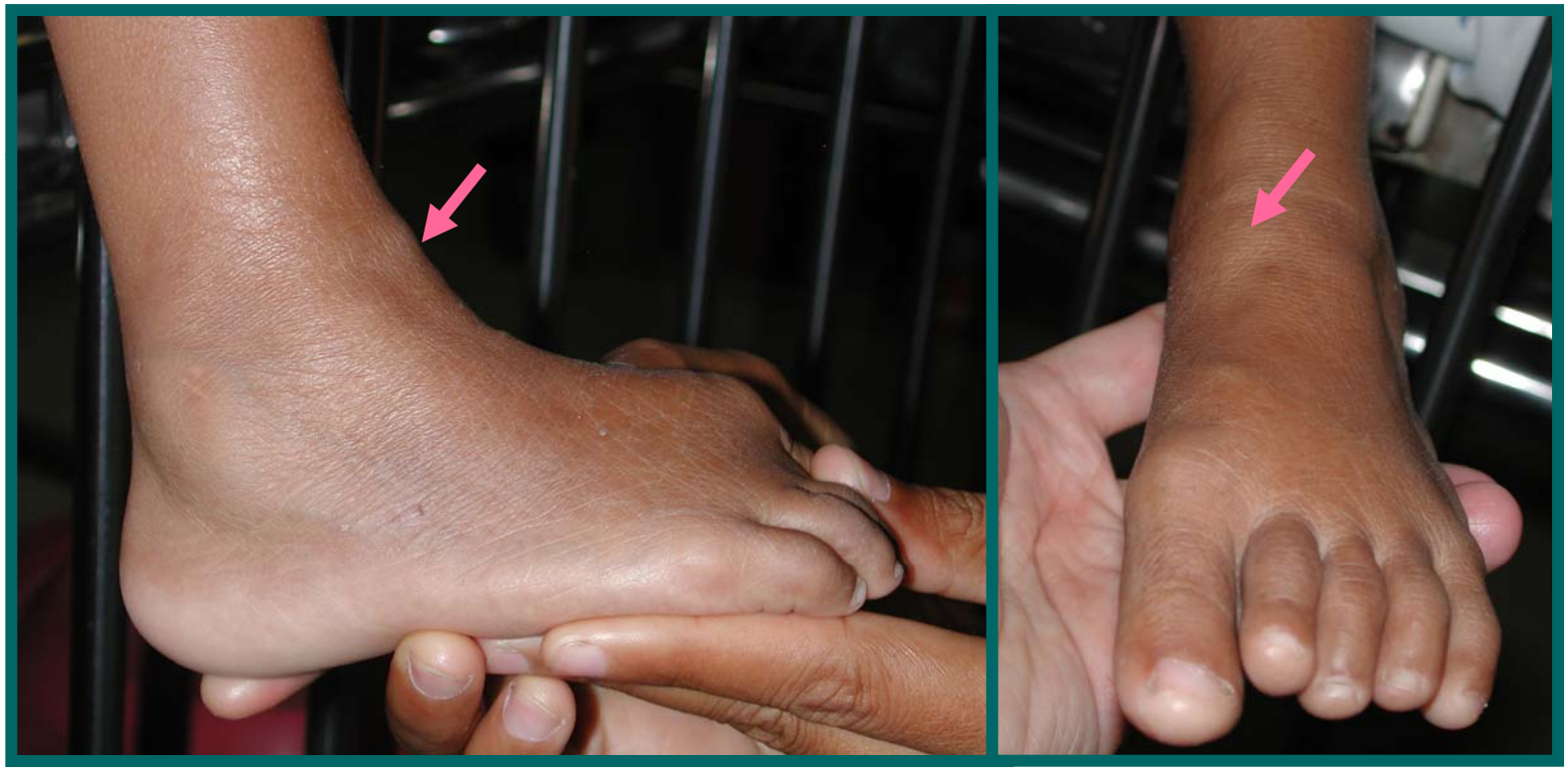


Knees

Joint Swelling

Knees

Joint Swelling



Ankles

Joint Swelling

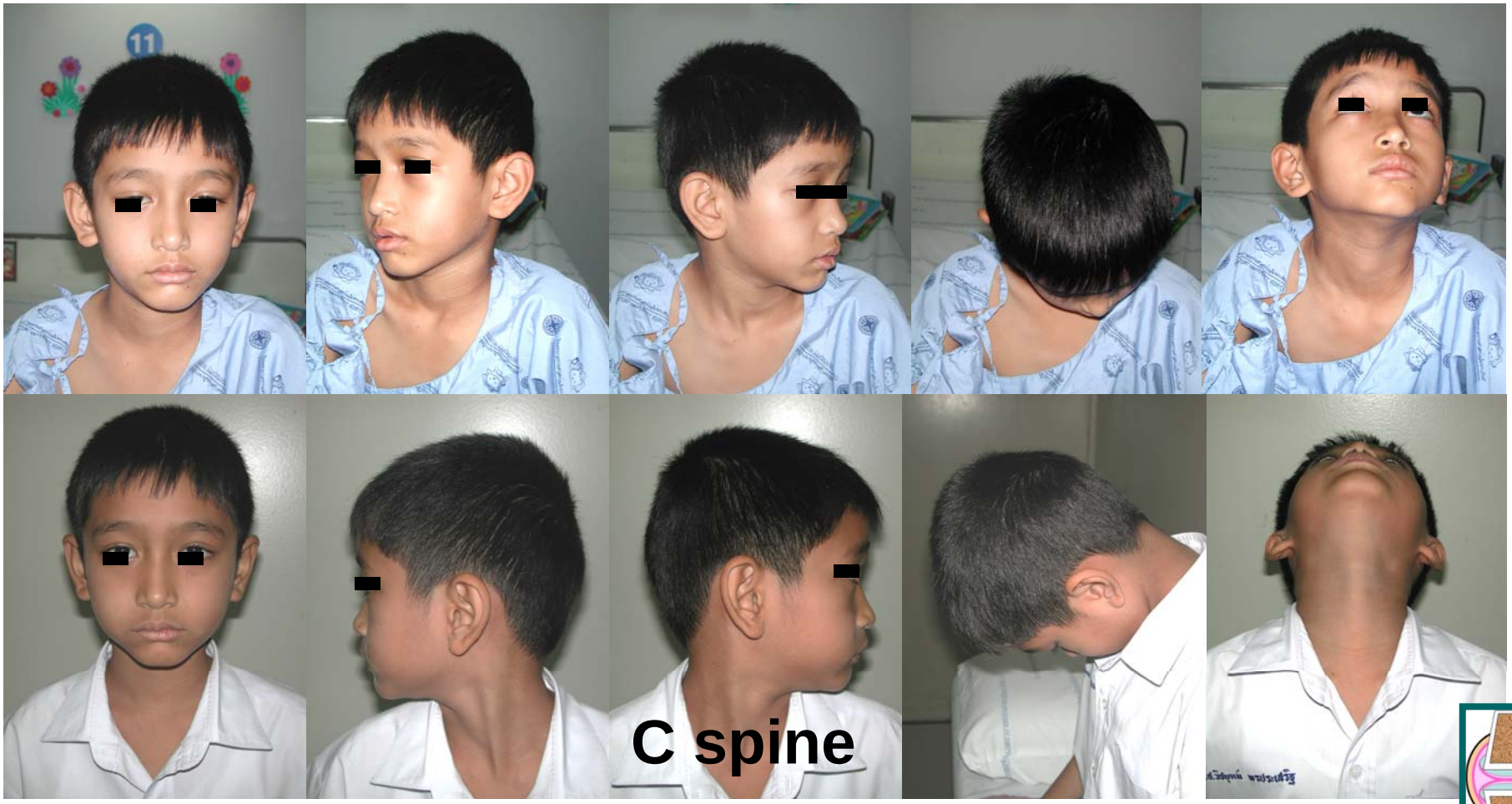
MCPs

Limited Range of Motion

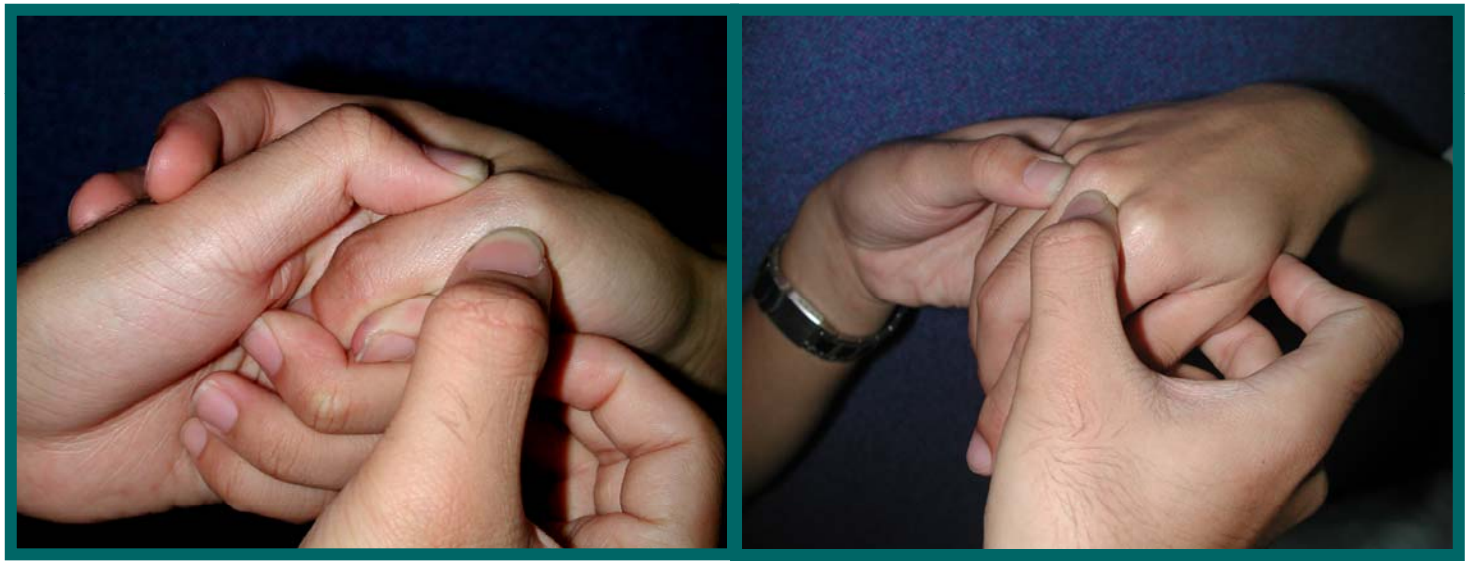
Limited Range of Motion

Shoulders

Limited Range of Motion

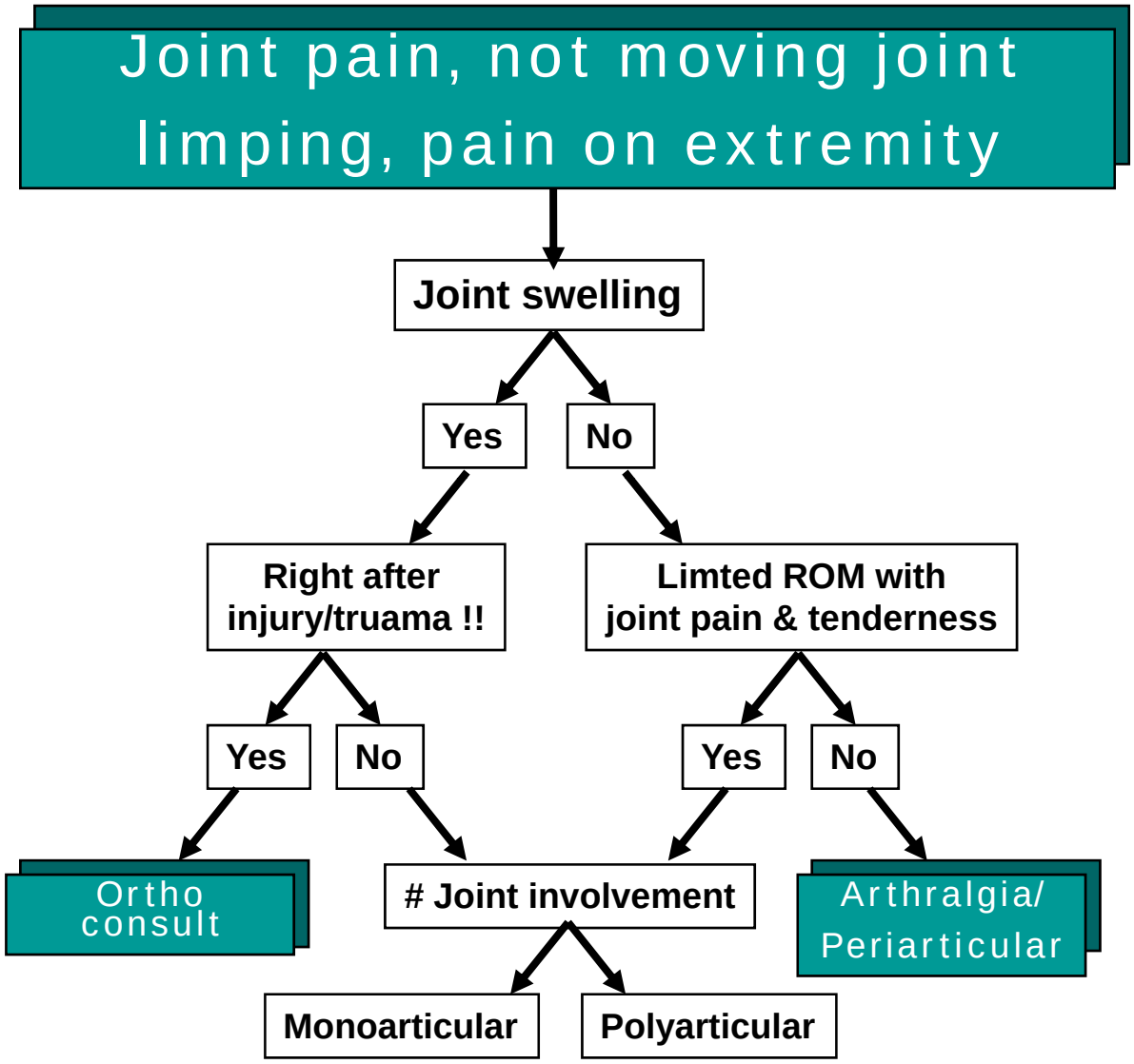


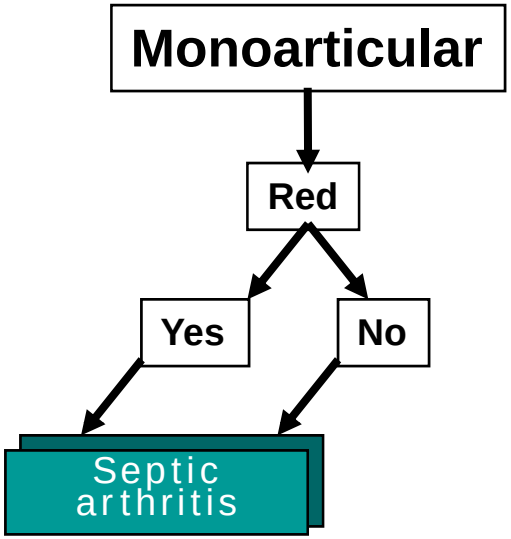
Joint Tenderness



MCP

Joint Effusion

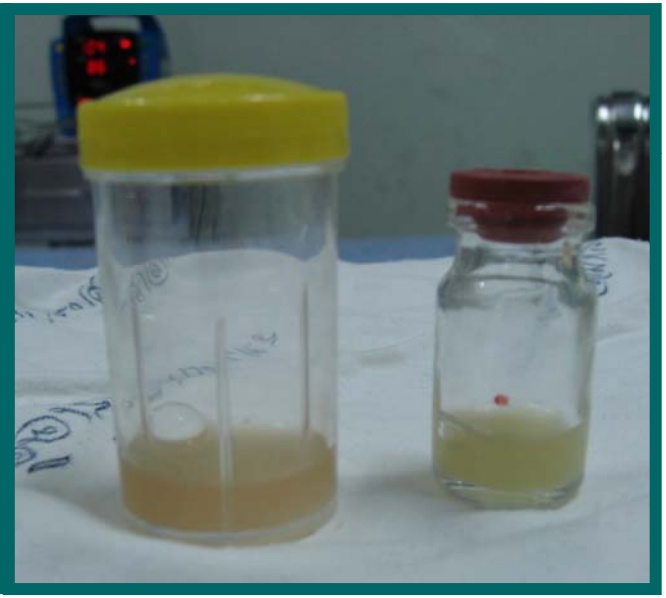

Joint pain, not moving joint
limping, pain on extremity
Joint swelling
Yes
No
Right after injury/truama !!
Limted ROM with joint pain & tenderness
Yes
No
Yes
No
Ortho consult
Joint involvement
Arthralgia/ Periarticular
Monoarticular
Polyarticular


Monoarticular
Red
Yes
No
Septic arthritis

Acute Thigh Pain with Limping

An 8yo boy with fever for 5 days, anterior right thigh pain with limping for 3 days.

Acute Thigh Pain with Limping



Dx: Septic hip

Synovial Fluid Analysis

Most helpful:

- Differential count, leukocyte count,
- Culture, Crystal search (no need in kids)

Less helpful:

- Gram stain
- Glucose determination with simultaneous serum glucose
- Inclusion cells
- Mucin test
- Protein determination
- Lactic acid level

Specific but rare findings:

- LE cells
- Acid-fast organisms
- Giant cells

Synovial Fluid Analysis

Total WBC Count/mm3	%PMN	Apperance	Fluid Type
0-200	<10%	Clear, viscous, pale, yellow	Normal
200-2000	<20%	Clear to slightly turbid	Non-inflammatory
2000-50,000	20-70%	Slightly turbid	Inflammatory
100,000 or more	>70%	Turbid to very turbid	Septic arthritis

Acute Thigh Pain with Limping

A 13 YO boy with Rt thigh pain for 2 wks.

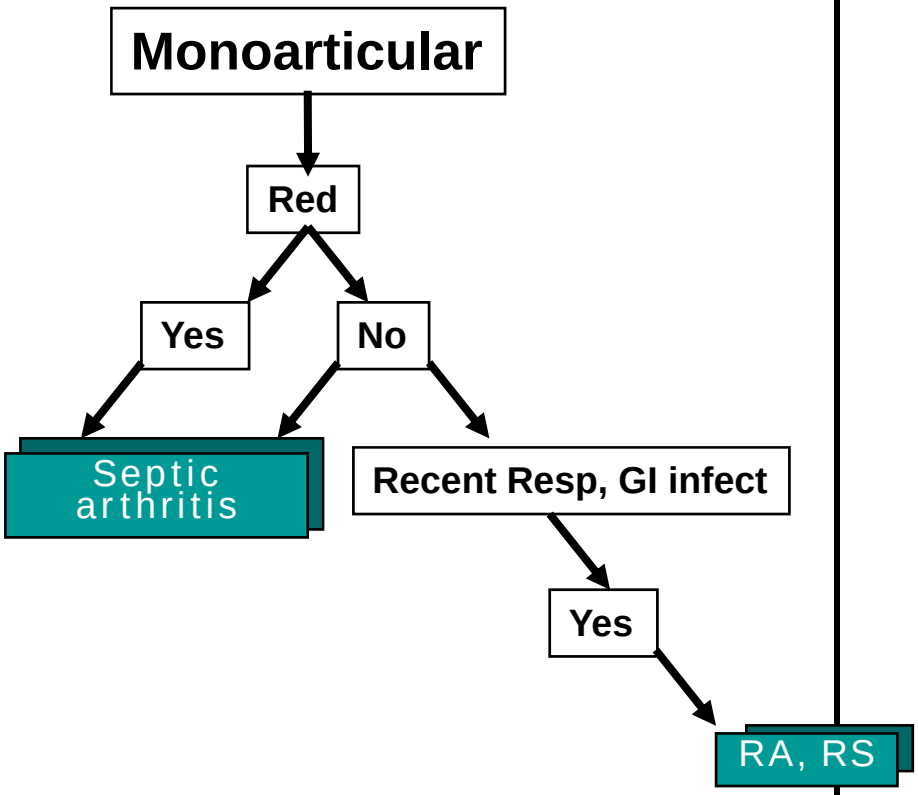
The pain relieved by pills taken for 5 days.

Limping was noted for 2 days.

Acute Thigh Pain with Limping

- **US revealed no significant fluid in both hips with normal CBC, ESR. Naproxen was prescribed. A week after _ _ _ _ _**

Dx: Transient Toxic synovitis



RA = Reactive arthritis, RS = Reiter syndrome, SS =Serum sickness, DILE = Drug induced lupuse

Acute Right Knee Swelling

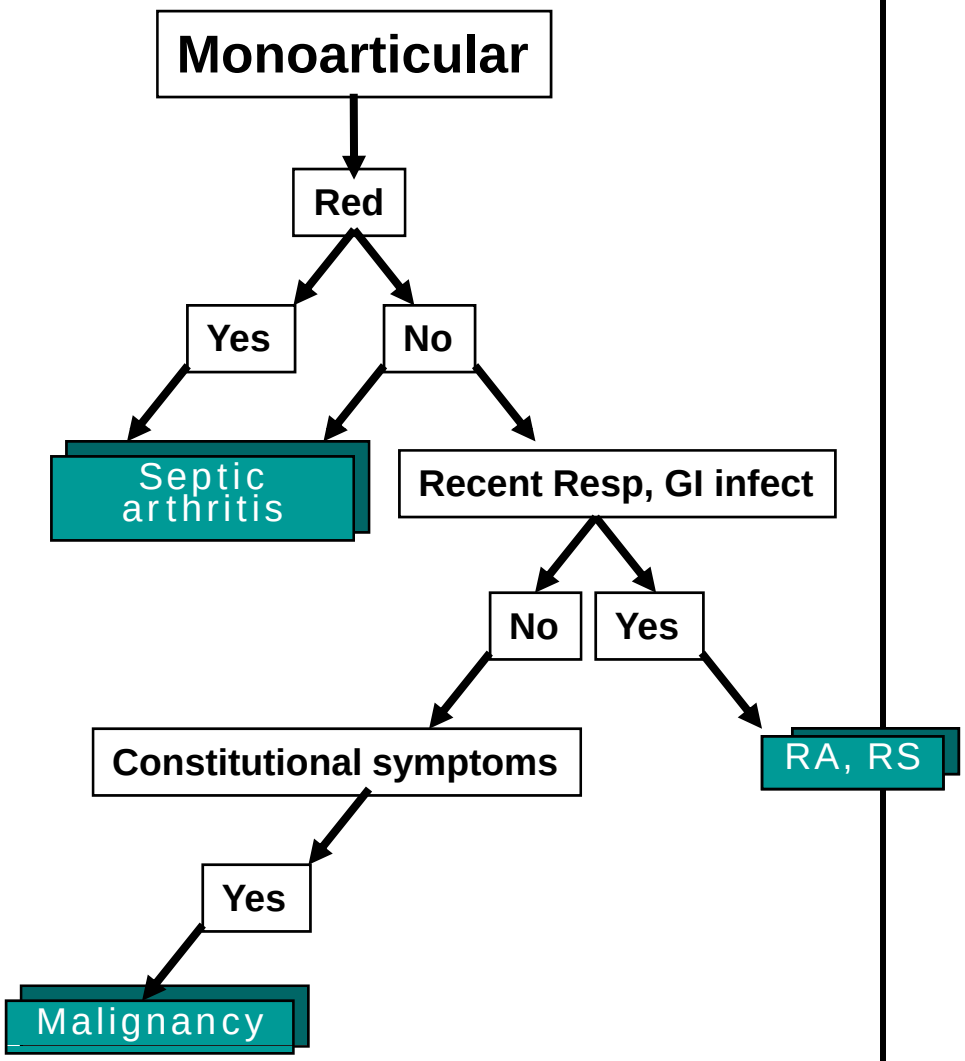
A 13 yo girl with swelling left knee and limping for 2 days. A history of sorethroat 4 weeks ago and diarrhea 1 week ago was noted.

PE: Marked swelling left knee with warmth, painful limitation of movement.

Acute Right Knee Swelling

- **Labs:**
  - **CBC: Hb 12, Hct 36% WBC 12,000, N65%, L35%, Eo2%, Mo8%**
  - **UA: normal**
  - **ESR 40**
  - **Synovial fluid analysis: WBC 85,000**
    PMN 80%, Mo20%
  - **Synovial culture: Neg**

Dx: Reactive arthritis



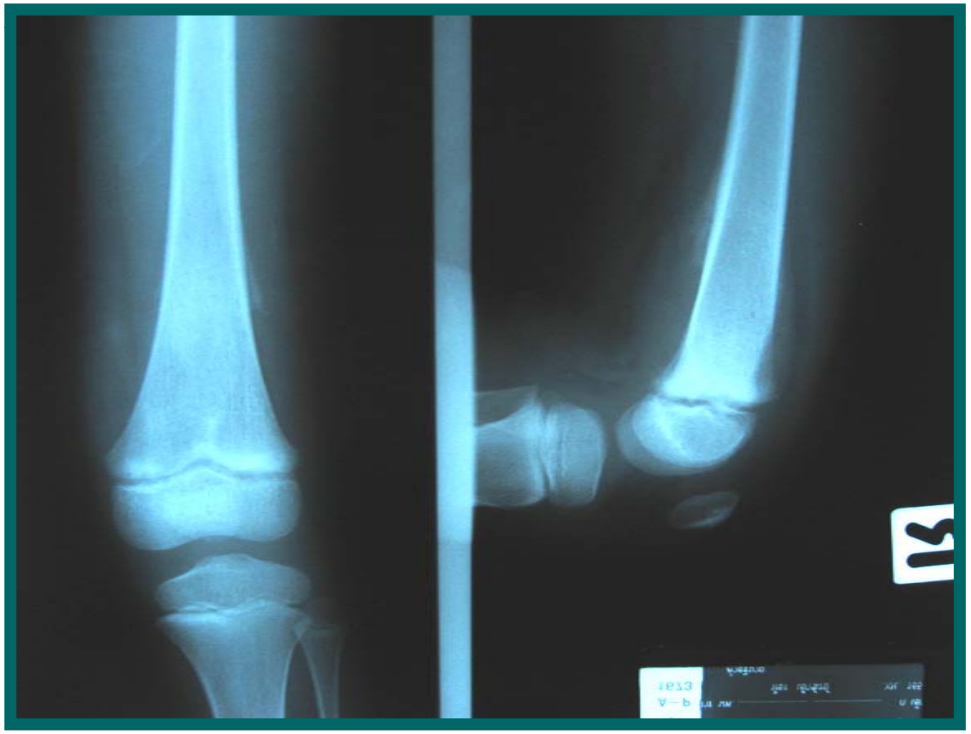
RA = Reactive arthritis, RS = Reiter syndrome, SS =Serum sickness, DILE = Drug induced lupuse

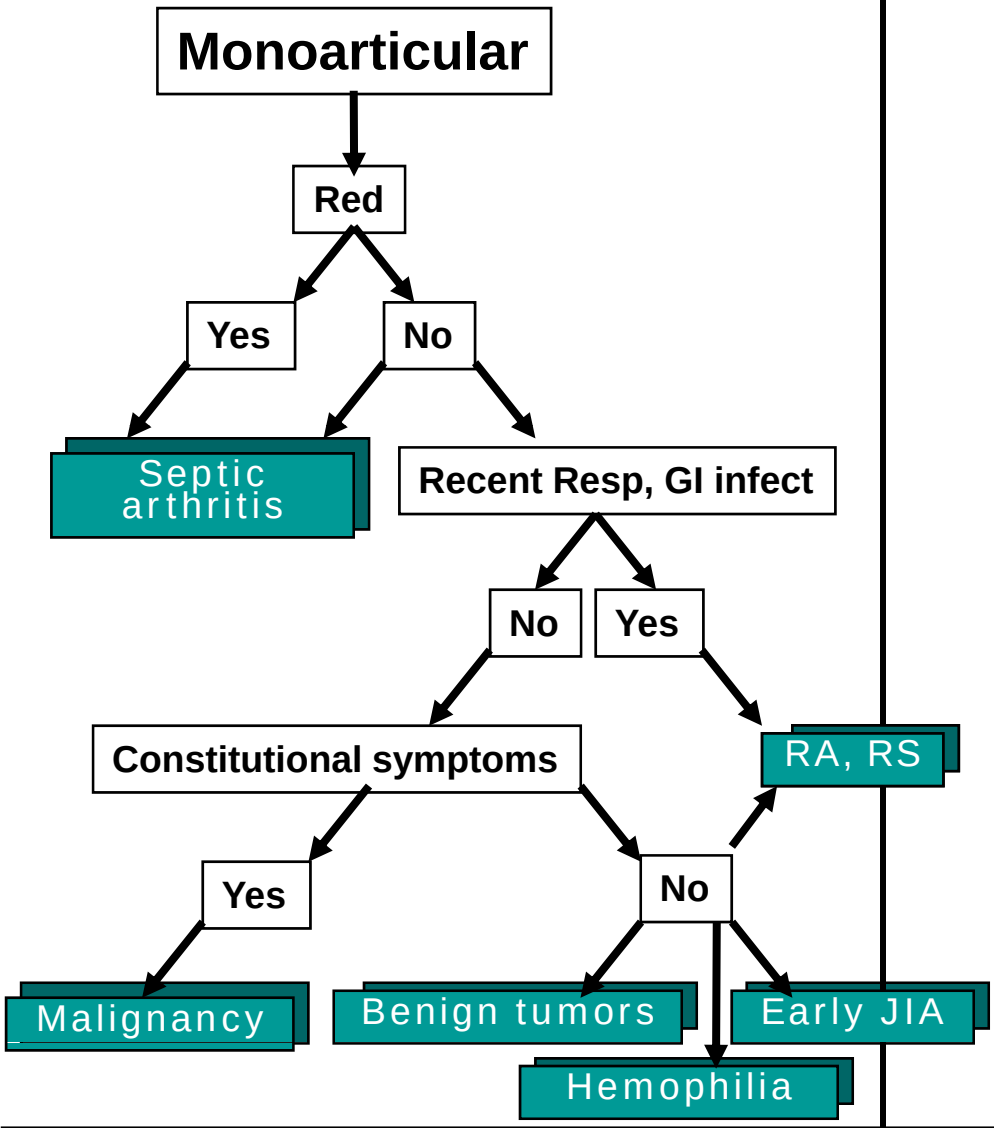
Acute Right Knee Swelling and Weight Loss

A 5 YO girl with right knee pain at night for 1wk with weight loss 1 kg.

Acute Right Knee Swelling and Weight Loss

A 5 YO girl with right knee pain at night for 1wk with weight loss 1 kg.





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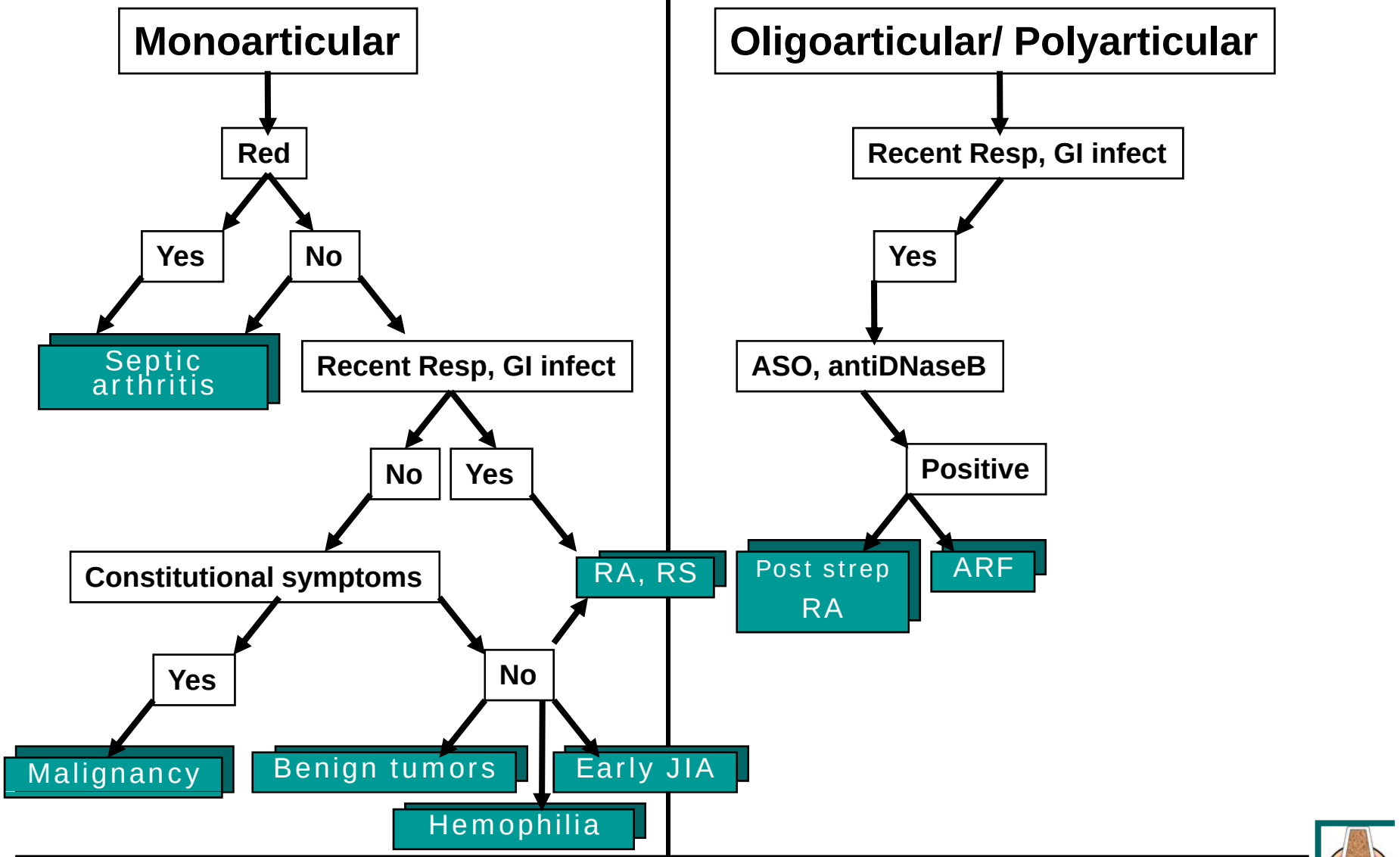
Right Knee Swelling with Limping

Dx: Monoarticular JRA

6 weeks after injection



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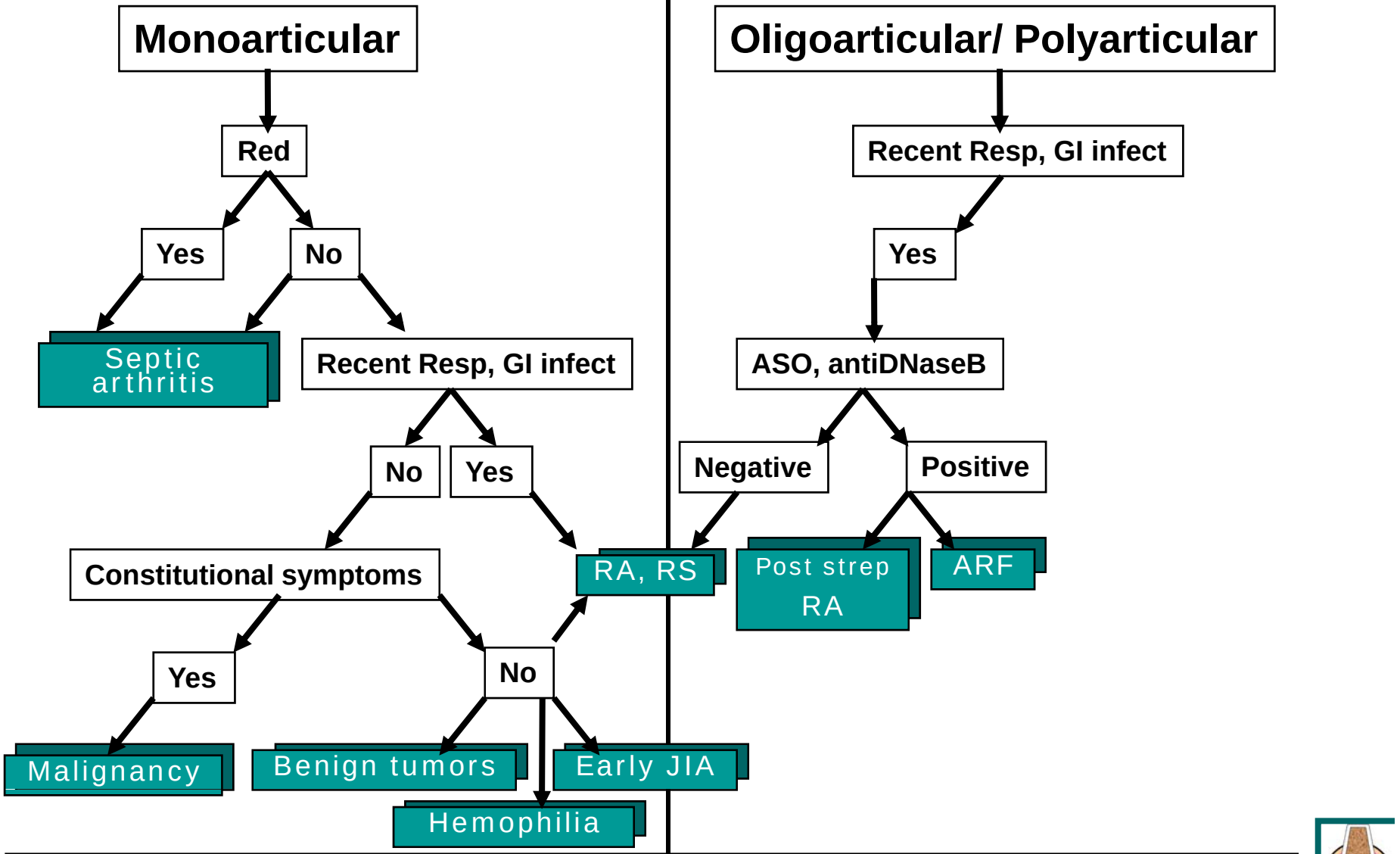
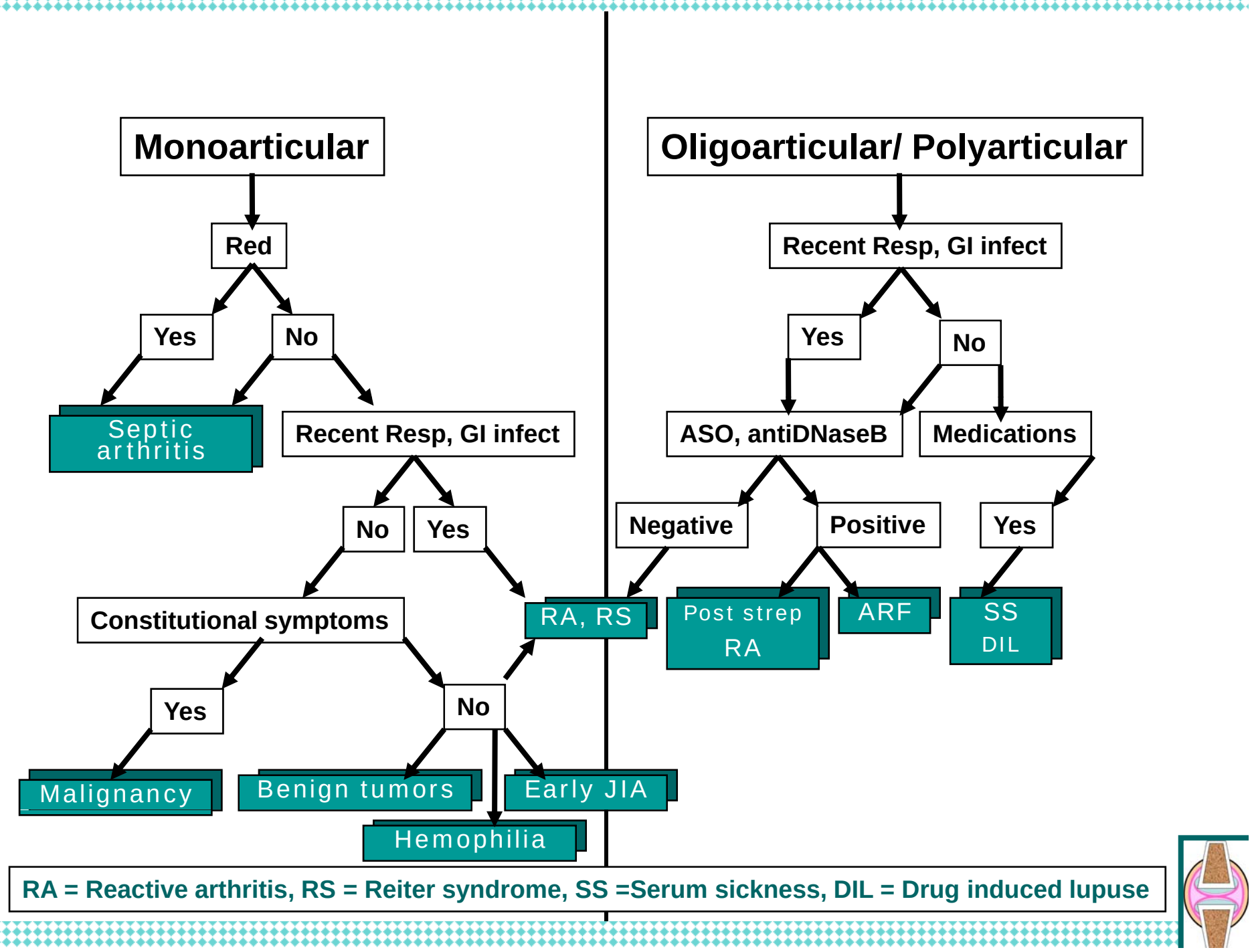

Monoarticular
Red
Yes
No
Septic arthritis
Recent Resp, GI infect
No
Yes
Constitutional symptoms
Yes
No
Malignancy
Benign tumors
Early JIA
Hemophilia
RA, RS
Oligoarticular/ Polyarticular
Recent Resp, GI infect
Yes
ASO, antiDNaseB
Negative
Positive
Post strep RA
ARF
RA = Reactive arthritis, RS = Reiter syndrome, SS =Serum sickness, DIL = Drug induced lupus

Acute Polyarthritis

A 7 YO girl presented with mulitiple joint pain & urticarial rash for 3 days and a history of diarrhea for 1 wk.

Acute Polyarthritis

1 day after naproxen started


Monoarticular
Red
Yes
No
Septic arthritis
Recent Resp, GI infect
No
Yes
Constitutional symptoms
Yes
No
Malignancy
Benign tumors
Early JIA
Hemophilia
RA, RS
Oligoarticular/ Polyarticular
Recent Resp, GI infect
Yes
No
ASO, antiDNaseB
Medications
Negative
Positive
Yes
Post strep RA
ARF
SS DIL
RA = Reactive arthritis, RS = Reiter syndrome, SS =Serum sickness, DIL = Drug induced lupuse

Drug-Induced Lupus (DIL)

Clinical features	SLE	DIL
Constitutional	40-85	40-50
Arthralgias/arthritis	75-95	80-95
Myalgias	40-80	35-57
Rash	50-70	0-30
Lymphadenopathy	23-67	<15
Pleurisy	42-60	0-52
Pleural effusion	16-20	0-33
Pulmonary infiltrates	0-10	5-40
Pericarditis	20-30	0-18
Hepatomegaly	10-31	0-25
Splenomegaly	9-46	0-20
Renal involvement	50	0-13
Neurologic involvement	25-70	0-2

Lahita RG, *SLE* 3ed

Drug-Induced Lupus (DIL)

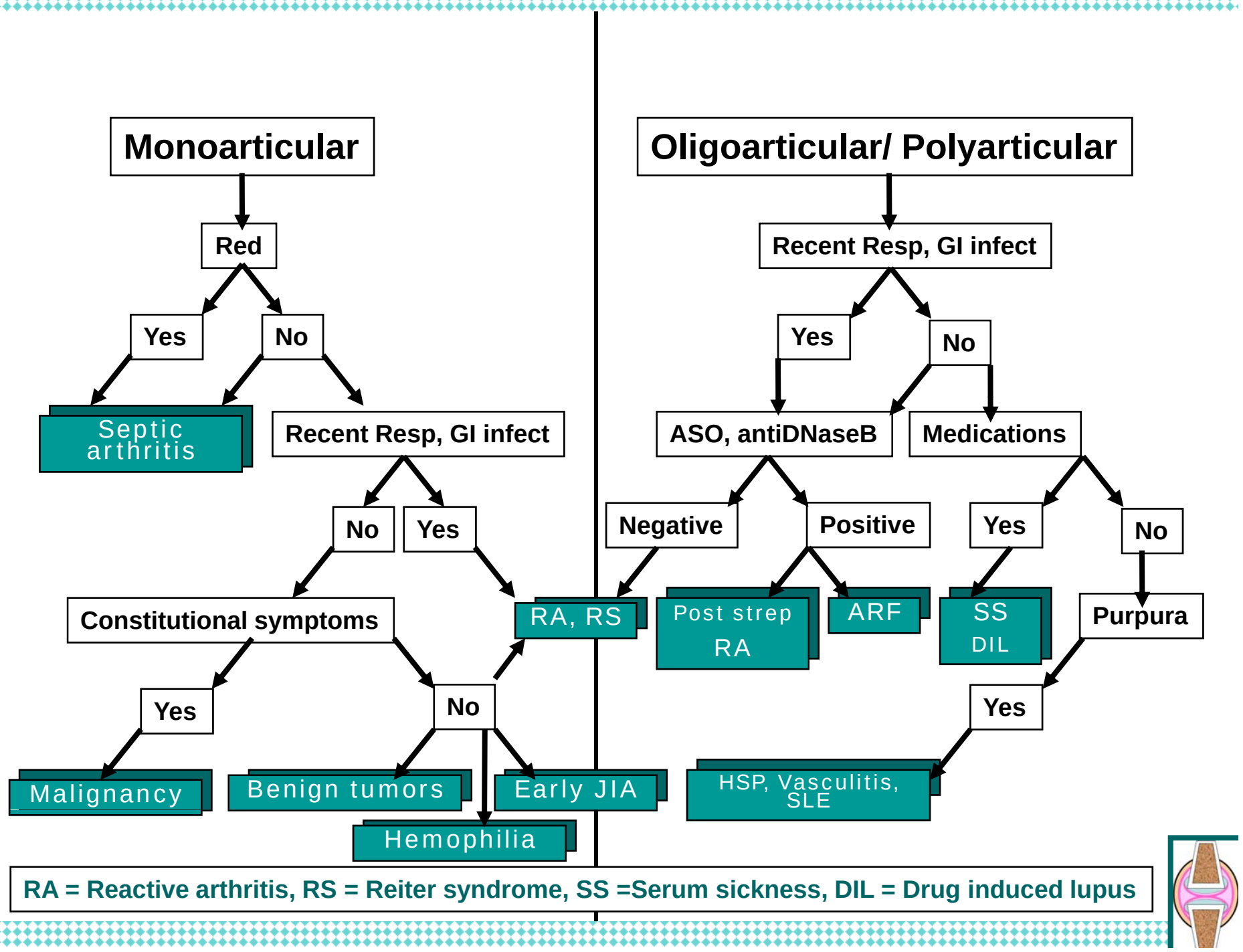
Lab features	SLE	DIL
Anemia	30-90	0-53
Leukopenia	35-66	0-33
Thrombocytopenia	20-50	0-10
+ Coomb's test	18-30	0-23
Elevated ESR	50-70	60-93
ANA	>95	100
Anti-histone	50-70	>95
Anti-dsDNA	50	<5
Anti-Sm	25	<5
Hypocomplementemia	40-65	0-25
RF	25	20-40

Lahita RG, *SLE* 3ed

Drug-Induced Lupus (DIL)

Drug definitively associated with drugs-related lupus:	Drug associated with drugs-related lupus:
Minocycline Procainamide Hydrylazine Methydopa Chlorpromazine Quinidine	Anti-TNF: Etanercept, infliximab Antiepileptic drugs: Valproate, carbamazepine, phenytoin, phenobarbital, ethosuximide Antibiotics: Penicilline, tetracyclines, streptomycin nitrofurantoinNalidixic acid, Griseofulvin NSAID: Ibuprofen, diclofenac, phenylbutazone, sulindac B-blocker: Propranolol, atenolol Clonidine, cimetidine, enalapril, estrogen, PTU, spironolactone sulfasalazine

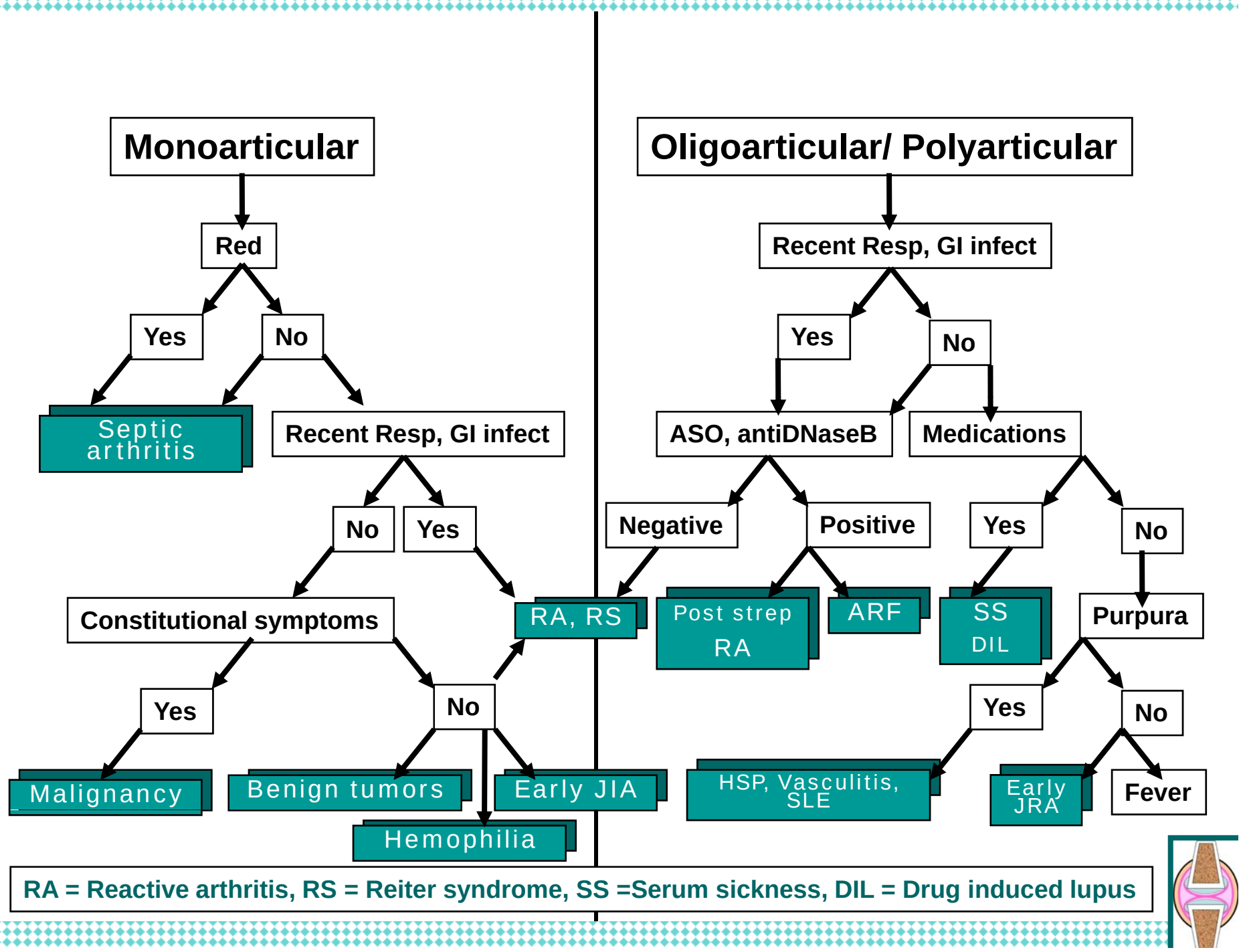
Lahita RG, *SLE* 3ed


Monoarticular
Red
Yes
No
Septic arthritis
Recent Resp, GI infect
No
Yes
Constitutional symptoms
Yes
No
Malignancy
Benign tumors
Early JIA
Hemophilia
RA, RS
Oligoarticular/ Polyarticular
Recent Resp, GI infect
Yes
No
ASO, antiDNaseB
Medications
Negative
Positive
Post strep RA
ARF
Yes
No
SS DIL
Purpura
Yes
HSP, Vasculitis, SLE
RA = Reactive arthritis, RS = Reiter syndrome, SS =Serum sickness, DIL = Drug induced lupus

Acute Left Ankle Swelling and Purpura

HSP

Clinical manifestations	Organ involvement (%)	N
Skin involvement	47	100
Palpable purpura	47	100
Edema	6	12.8
GI involvement	35	74.5
Abdominal pain	30	63.8
Nausea/ vomiting	20	42.6
Hematochezia	11	23.4
Renal involvement	22	46.8
Isolated hematuria	13	27.7
Hematuria with proteinuria	5	10.6
Nephrotic syndrome	4	8.5
Arthralgia or arthritis	20	42.6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Constitutional symptoms
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Malignancy
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RA, RS
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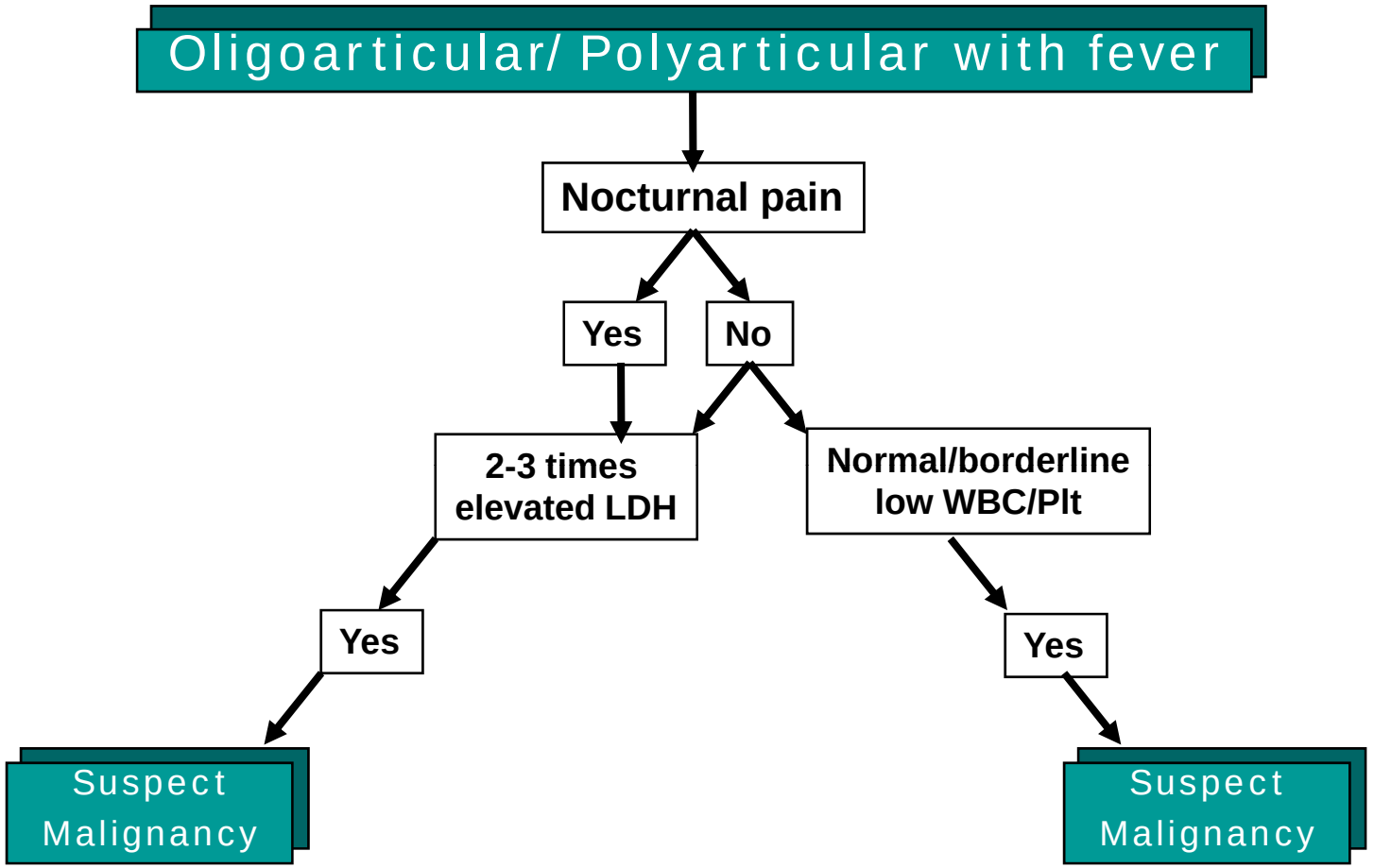
Oligoarticular/ Polyarticular
Recent Resp, GI infect
Yes
No
ASO, antiDNaseB
Medications
Negative
Positive
Post strep RA
ARF
Yes
No
SS DIL
Purpura
Yes
No
HSP, Vasculitis, SLE
Early JRA
Fever
RA = Reactive arthritis, RS = Reiter syndrome, SS =Serum sickness, DIL = Drug induced lupus


Oligoarticular/ Polyarticular with fever
Nocturnal pain
Yes
No
2-3 times elevated LDH
Normal/borderline low WBC/Plt
Yes
Yes
Suspect Malignancy
Suspect Malignancy

When to Suspect Malignancy

- **Child appears miserable**
- **Pain and loss of function out of proportion to physical findings**
- **Night pain & Nocturnal awakening**
- **Periarticular bony tenderness rather than synovial tenderness**
- **Pain in both bones and joints**
- **Presence of petechiae/ecchymosis**
- **Hematologic abnormalities**
- **Elevated LDH, elevated Uric acid**

Occult malignancy must be excluded.!!!!

Malignancy with Musculoskeletal pain

- **Leukemia**
- **Lymphoma**
- **Neuroblastoma**
- **Histiocytosis**
- **Osteogenic sarcoma**
- **Ewing’s sarcoma**
- **Metastatic tumor (very rare)**

When to suspect malignancy

The 3 most important factors predicting ALL

1. **Low WBC (4,000)**
2. **Low-normal platelet count 150,000-250,000**
3. **Nighttime pain**

All 3 factors: 100% sensitivity, 85% of specificity

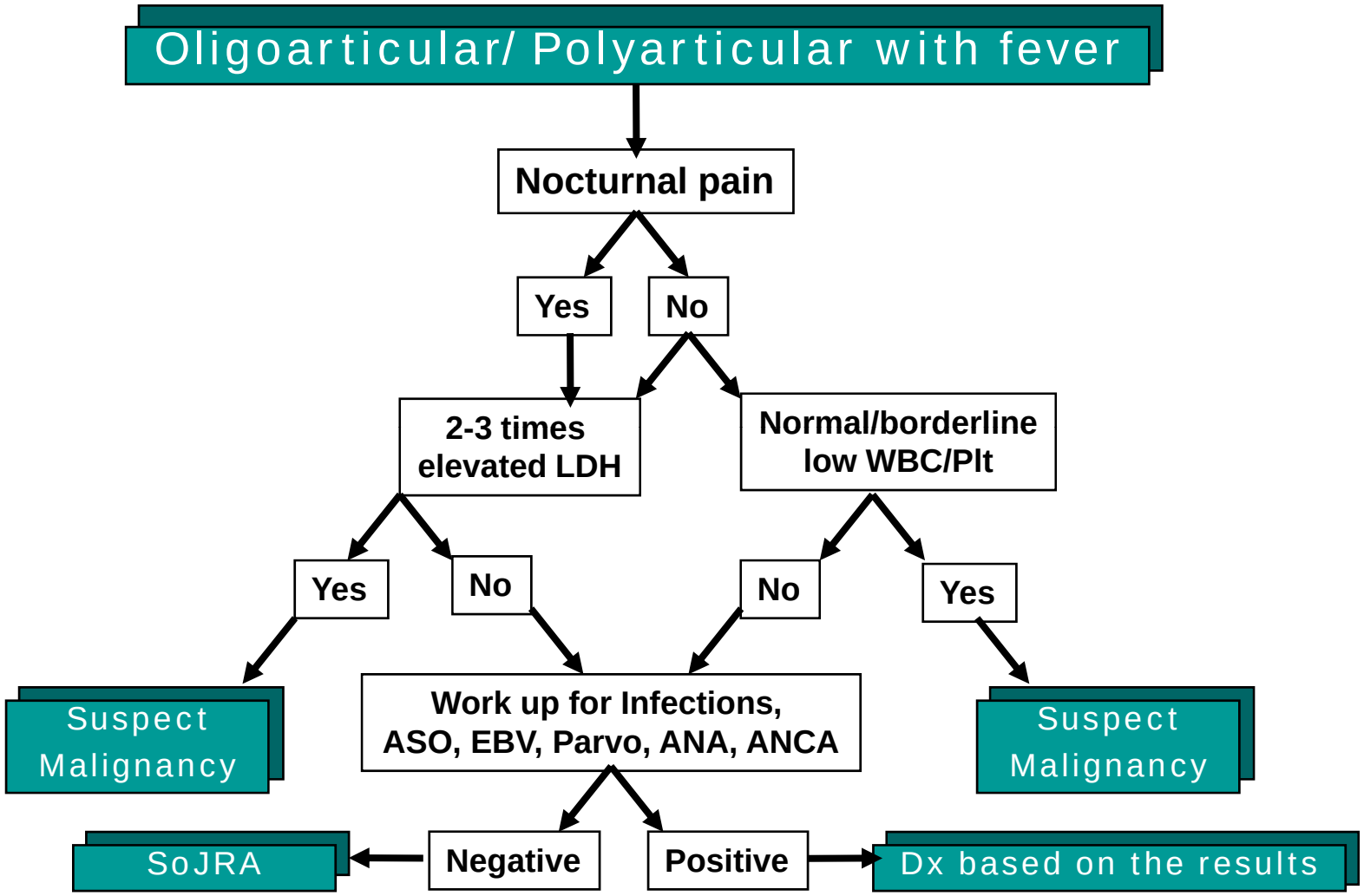
TABLE 2 Predictive Value of Complete Blood Count Changes and Nighttime Pain for ALL

Diagnostic Marker[a]	Blast-Negative ALL, *n/N* (%)	JRA, *n/N* (%)	*P*[b]	Sensitivity (95% CI)	Specificity (95% CI)
1 CBC parameter	41/52 (79)	71/205 (34)	<.001	37 (31–43)	92 (89–93)
2 CBC parameter	24/52 (46)	1/205 (.4)	<.001	96 (94–98)	88 (84–92)
1 CBC parameter and nighttime pain	23/52 (44)	18/205 (9)	<.001	56 (50–62)	87 (83–91)
2 CBC parameters and nighttime pain	15/53 (29)	0/205 (0)	<.001	100	85 (81–29)

A Multicenter Case-Control Study on Predictive Factors Distinguishing Childhood Leukemia From Juvenile Rheumatoid Arthritis

PEDIATRICS
OFFICIAL JOURNAL OF THE AMERICAN ACADEMY OF PEDIATRICS

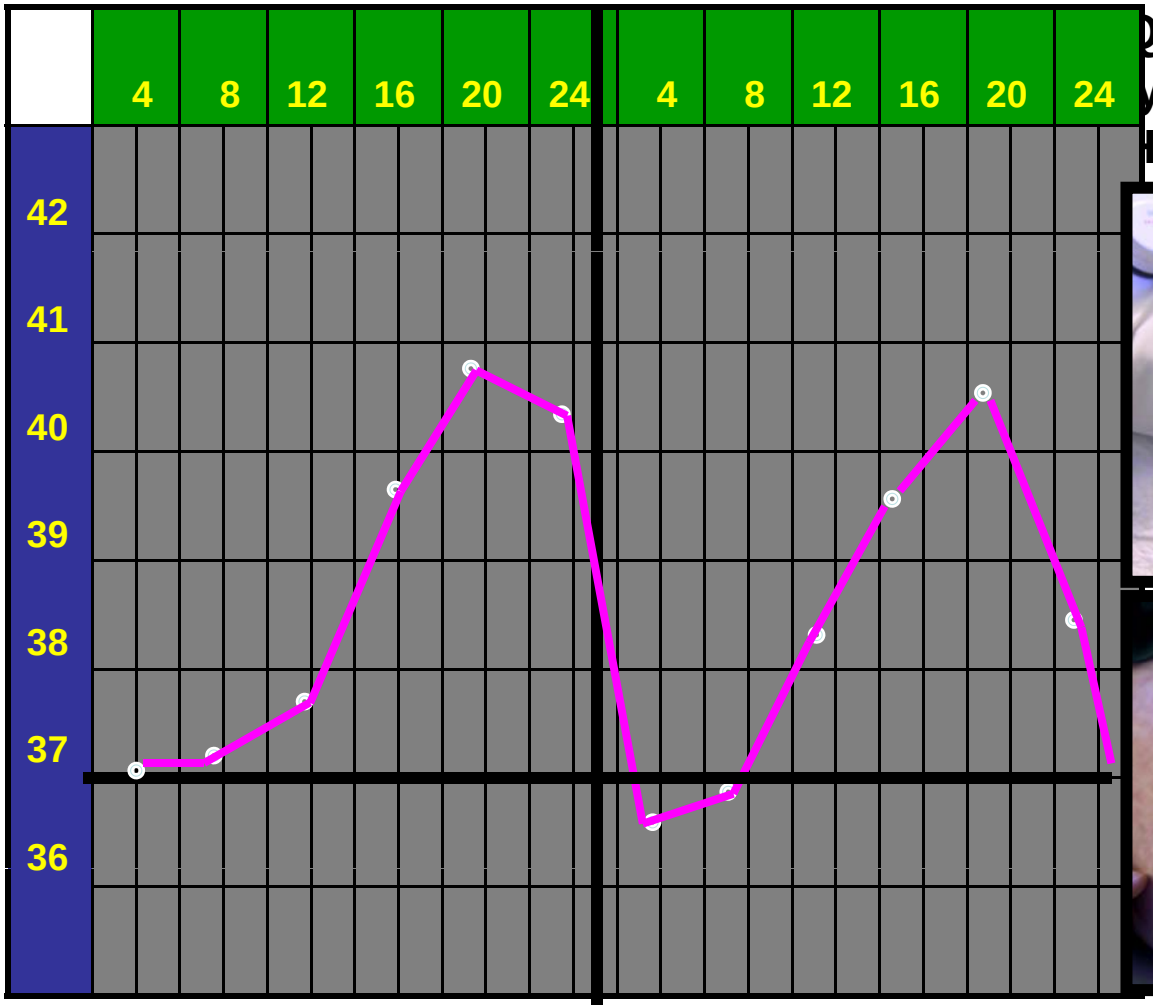
May 2006


Oligoarticular/ Polyarticular with fever
Nocturnal pain
Yes
No
2-3 times elevated LDH
Normal/borderline low WBC/Plt
Yes
No
No
Yes
Suspect Malignancy
Work up for Infections, ASO, EBV, Parvo, ANA, ANCA
Suspect Malignancy
SoJRA
Negative
Positive
Dx based on the results

Systemic Onset JIA

- **Arthritis in 1 or more joints with or preceded by fever of at least 2 weeks' duration ("quotidian" for at least 3 days) and 1 or more of the following:**
  - **Evanescent (nonfixed) erythematous rash**
  - **Generalized lymph node enlargement**
  - **Hepatomegaly and/or splenomegaly**
  - **Serositis**

Systemic Onset JIA

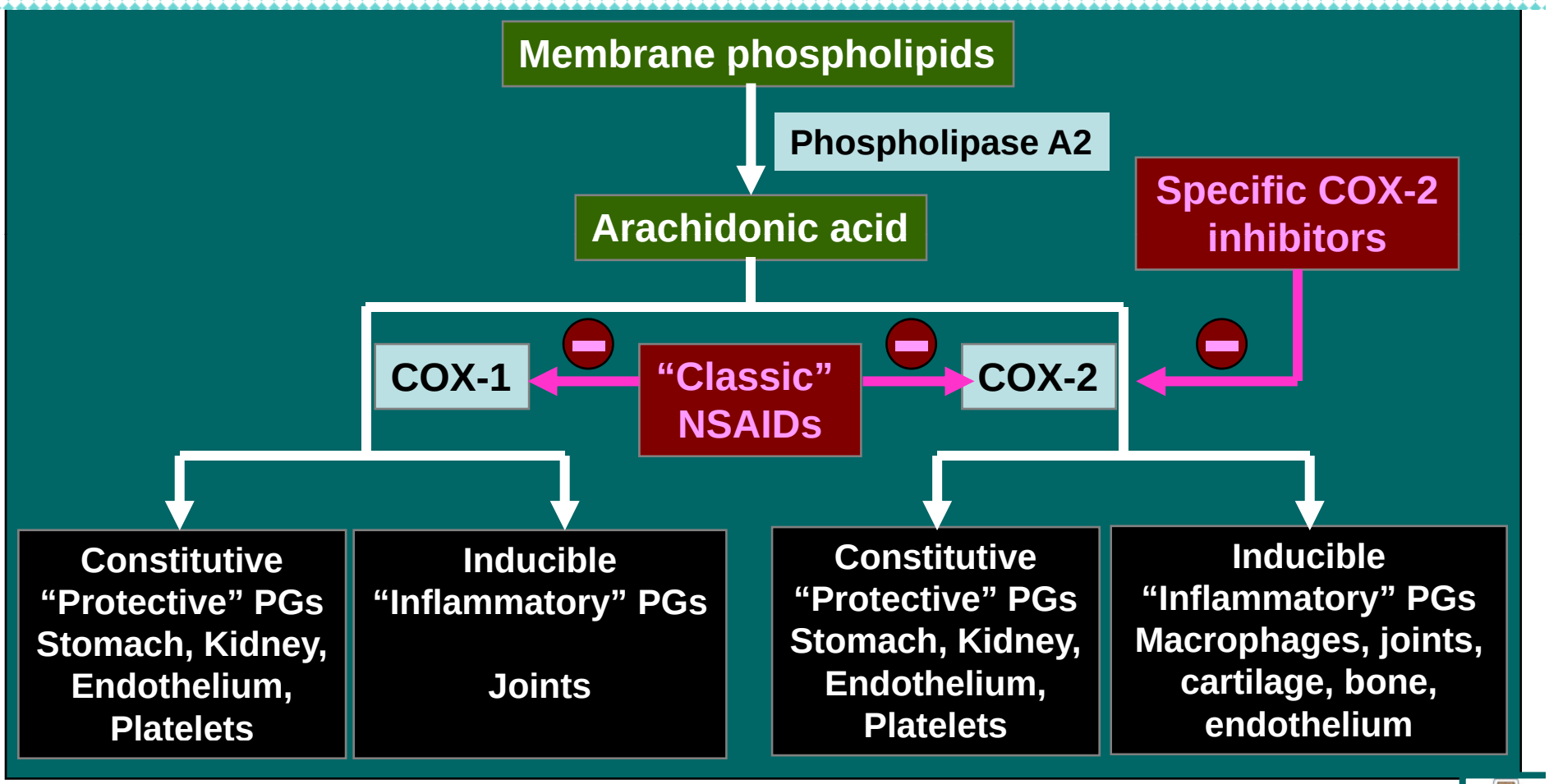


Quotidian fever, rash
ymphadenopathy
HSM, serositis, arthritis

Medical Treatment

- **NSAIDs**
- **Corticosteroid considered only for SoJRA**
- **Specific treatments**
  - **Penicillin and penicillin prophylaxis for ARF, PSRA**
  - **Cloxacillin or others for septic arthrtis**
  - **HCQ, methotrexate for SLE**
  - **Chemotherapy/ cancer therapy**

NSAID



Paediatr Drug 2001: 3(11)

NSAID

NSAIDs	JRA Trials	Doses (per day)	Dosage (mg/kg/day)	Max Dose (mg/day)
Aspirin (81, 325mg)	Y	3-4	80-100	4900
Ibuprofen (200mg)	Y	3-4	30-50	2400
Diclofenac (25mg)	Y	3	2-3	150
Indomethacin (25mg)	??	3	1.5-3.0	200
Naproxen (250mg)	Y	2	10-20	1000
Meloxicam (7.5mg)	Y	1	0.25	15
Piroxicam	Y	1	5mg OD(15-30kg) 10mg OD(31-45kg) 15mg OD(46-55kg)	N/A
Celecoxib	Y	2	50mg BID (10-25kg) 100 mg BID (>25kg)	N/A

NSAID

Toxicity	ASA	Ibuprofen	Naproxen	Indomethacin	Sulindac
GI irritation	+++	+	++	++++	++
Peptic ulcer	++	+	++	+++	+
CNS	+	+/-	+	++++	+
Tinnitus	+++	+	+	+	+
Hepatitis	++	+	+	+	+
Asthma	++	+	+	+	+
Renal function	+	+	+	++	+/-
Bone marrow	-	+	+	+	+

Question 7

7. A 6 year-old girl presents with left knee/ankle swelling and limping, no fever for 2 days. Yesterday, her mother noticed bruises on both legs. The patient had URI 2 weeks before limping. ROS is negative.

   Which one is the most likely diagnosis?

   A. Reactive arthritis

   B. Septic arthritis

   C. HSP

   D. Leukemia

   E. Hemophilia