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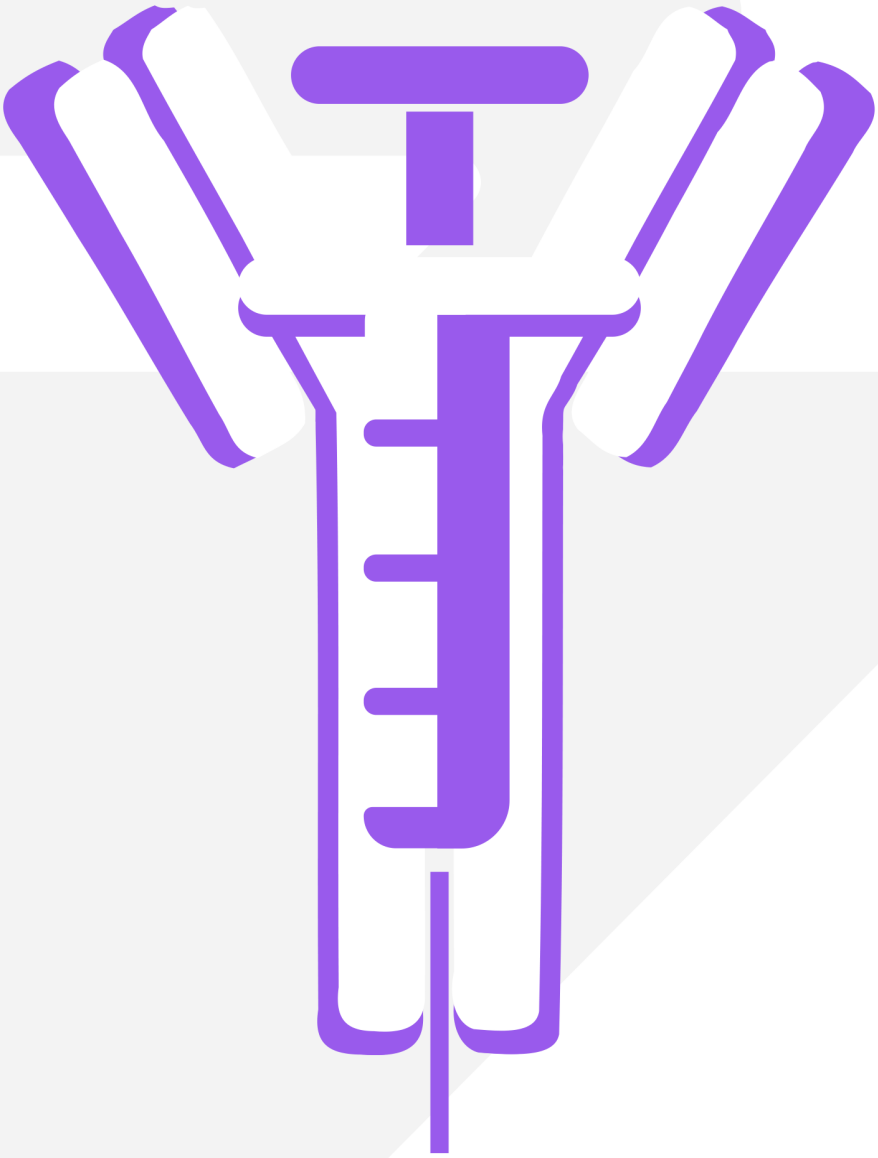
Pediatrics

IMMUNOLOGY



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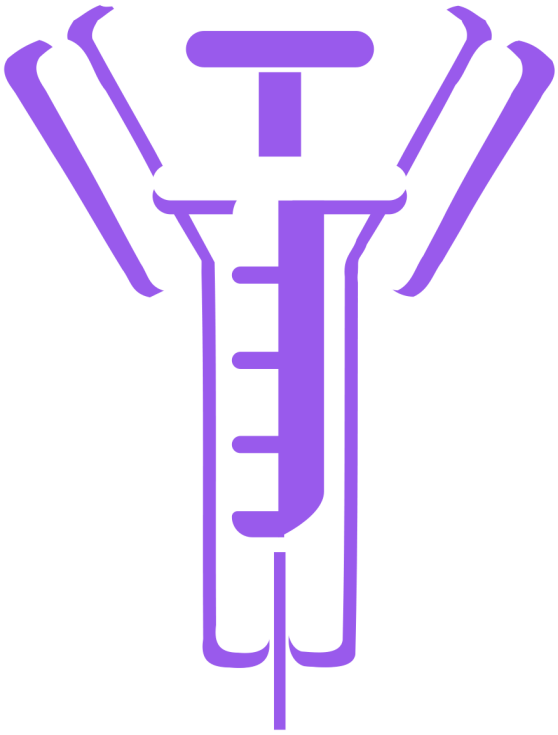

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TABLE OF CONTENTS

"The pursuit of knowledge is without end, for knowledge is never a thing complete."

Will you take on the endeavor?

PEDIATRIC ALLERGIC DISORDERS

Introduction

Definitions and Pathogenesis

Allergy: Abnormal response leading to **allergic symptoms and signs.**

Atopy

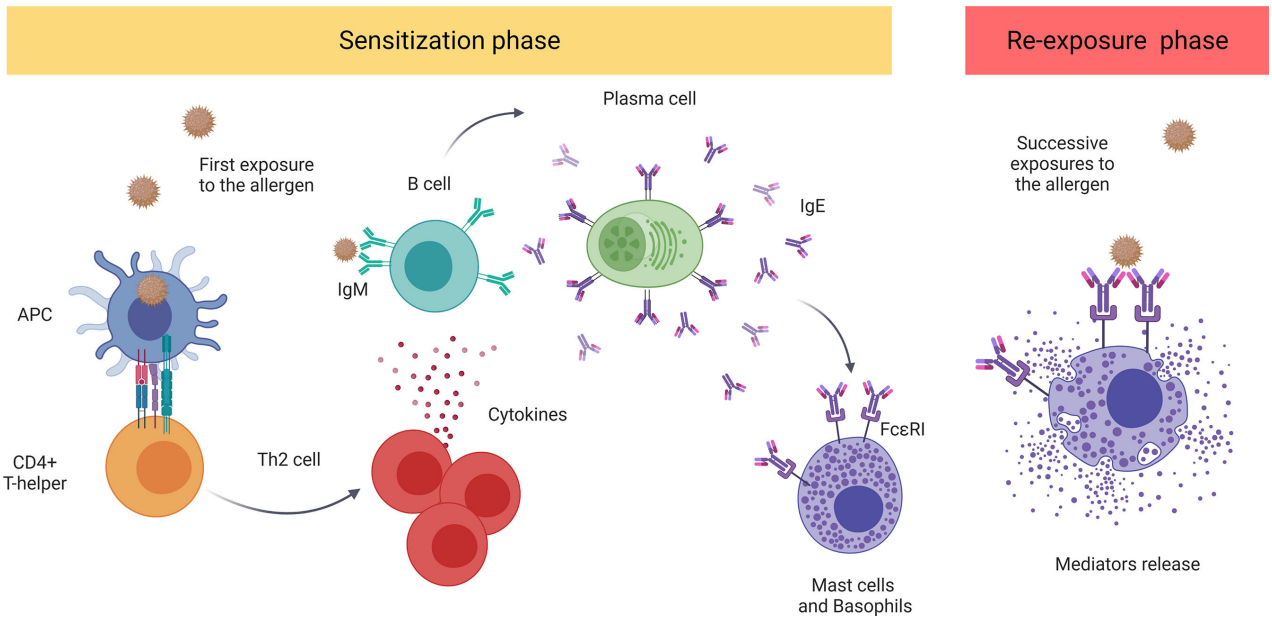
- **Hereditary** susceptibility to allergy.
- An atopic person develops specific IgE against environmental allergens.

Sensitization

- **First exposure** to an allergen (even in tiny amount) leads to formation of **specific IgE** in atopic individuals. IgE binds to mast cells and basophils.

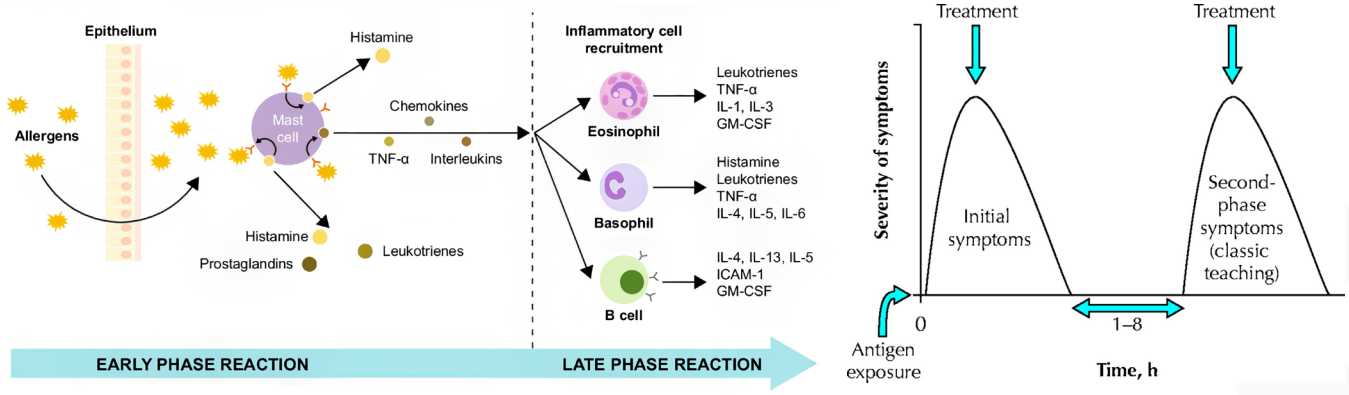
Allergic Reaction

- Upon **re-exposure** to the same allergen, it binds to its specific IgE on the mast cell and/or basophil surface causing **disruption of mast cells and release of mediators** e.g. histamine.
- Symptoms differ according to the reaction site.



Phases of allergic reactions:

- **Early phase reaction:** immediately after allergen exposure, mast cell and basophil disruption causes allergic symptoms.
- **Late phase reaction:** after some hours (usually 6 - 8 hours), manifestations recur without further allergen exposure due to release of mediators from more immune cells.



The spectrum of allergens includes any and everything under the sun, including the very sun itself.

Principles of diagnosis of allergic reactions

Clinical evaluation: most important

In vitro tests: Eosinophil count, and specific IgE assay

In vivo tests: Skin prick test (SPT), provocation (challenge) testing

Clinical evaluation

History of exposure to a certain food, drug, indoor allergen or irritant (e.g. tobacco).

Timing of symptoms e.g. seasonal symptoms as pollen allergy or spring catarrh.

- An increase of symptoms **by night** may suggest **bedroom allergens.**
- **Weekend** remissions suggest **school place allergens.**

Family history of allergy even in other anatomic sites.

Precipitating factors e.g. exercise-induced asthma or aspirin-induced allergy.

Site of affection e.g. bronchial asthma, allergic rhinitis, ocular allergies, skin allergy or combined lesions which are common.

Complications such as barrel shaped chest in **asthma,** mouth breathing and dark discoloration of lower eyelids in **allergic rhinitis** and roughness of skin in **atopic dermatitis.**

A history of **improvement on or adverse effects** of **previous treatment** may be beneficial in the management.

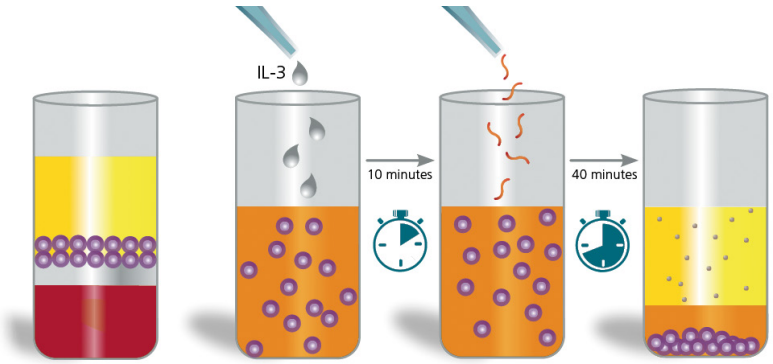
In vitro tests

Eosinophilia: Total eosinophils **> 700/mm³ in blood** or **> 5-10% eosinophils in cells** of nasal secretions is highly suggestive of allergy.

Total and specific serum IgE:

- Concentrations vary with age.
- Total IgE is **usually elevated** in atopic persons.
- However, a **very low level is more useful in excluding** atopy than **elevated levels in confirming** the diagnosis because it may be elevated in other conditions e.g. parasitosis, Hodgkin disease and hyper IgE syndrome.

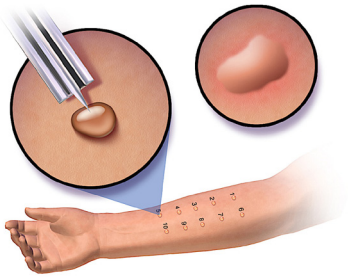
Leukocyte histamine release test: It measures the amount of histamine release-ability from basophils in response to challenge with a specific antigen.



In vivo tests

Skin prick testing:

- A small quantity of an allergenic extract is introduced into the skin by puncture
- This indicates that specific IgE antibody is present on the mast cells of the patient but it does not indicate that the patient will necessarily have clinical symptoms on exposure to the allergen.
- One must be guided by the history in order to avoid over-interpretation of skin test results.
- Not all allergens are available as commercial extracts



Wheal and flare of SPT:

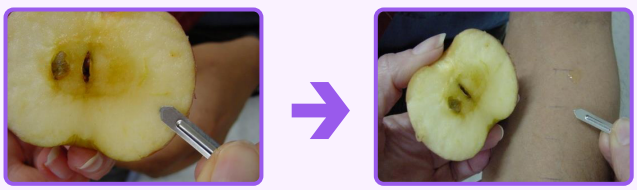
- **Wheal diameter < 3 mm** = **negative**
- **Wheal diameter > 8 mm** = **confirmed** allergy
- **Wheal diameter 3 - 8 mm** = **needs confirmation** by challenge test

Note

Wheal is the swelling

Flare is the surrounding redness.

Prick Prick Test (PPT)



Provocation (challenge) testing:

- Direct exposure of the mucous membrane of the affected organ to the suspected antigen can cause the symptoms.
- More accurate than skin testing but is sometimes risky and should be carried out in a hospital e.g. bronchial challenge and oral food challenge tests.
- **Open challenge** is usually performed in children
- **Blinded testing** is meant to avoid psychic false reaction. It is used in adults but sometimes needed in adolescents especially females

> **Note**
>
> Challenge testing could be **oral** (in food allergy) or **bronchial** (by inhalation in respiratory allergy). The latter is **not used in young children.**

Food Challenge Testing

- The **most confirmatory** method
- Feeding with gradually increasing amounts of the suspected food
- Should be performed **in hospital under close observation**
- Measures of treatment of anaphylaxis should be ready in hand (Challenge testing can be dangerous and may lead to anaphylaxis)

Principles of treatment of allergic reactions

Successful management of allergic disorders is based upon 4 principles:

1. Avoidance of allergens or irritants
2. Pharmacologic therapy
3. Immunotherapy
4. Prevention

I. Avoidance

- This is the ***corner stone of the management.***
- A **careful history** can aid in identification of allergens to be avoided.
- **Serum specific IgE** or **skin prick testing** might help.
- **Food allergy in particular** is to be considered as well as pets and insects.
- **Avoidance of irritants** is also very important e.g. tobacco smoke.

II. Pharmacologic therapy

- This varies according to the **allergic disorder** (e.g inhalation therapy in bronchial asthma), **site of affection** and **individual response**.
- It generally includes **antihistamines, adrenergics** (short or long acting), **corticosteroids** (whether inhaled, topical or systemic), **theophylline, anticholinergics**, and **leukotrienes receptor antagonists..**

III. Specific immunotherapy

- **Subcutaneous injection or sublingual administration** of **aqueous extracts of allergens** under careful medical supervision.
- It is resorted to in cases with **allergy to unavoidable antigens** such as pollens, house dust mite and venom allergy. Efficacy in some other allergens is not guaranteed.

Precautions

- It carries the **risk of anaphylaxis** sometimes especially in the **subcutaneous type.**
- Subcutaneous immunotherapy (SCIT) is **not generally approved before 5 years** of age (so precautions are necessary) and is **not used in food allergy** at any age.
- Sublingual immunotherapy (SLIT) is now available now but **not for food allergy** as well.

IV. Prevention

Primary (Debatable)	**Secondary** (Mainstay)	**Tertiary** (Important)
Breast feeding - Delayed weaning - Indoor allergen avoidance	**Identification and Elimination of triggers**	**Proper management to avoid complications**

- It is appropriate to recommend breast feeding for infants born to families with strong histories of atopy and to delay for 6 months the introduction of solid foods into the diet.
- **Environmental exposure to inhalant allergens** such as dog, cat and bird allergens should be avoided as well as exposure to tobacco smoke since intrauterine life and afterwards.
- **Day care nurseries** carry the **risk of repeated viral chest infections** which may aid in **early sensitization.**

Allergic rhinitis

Prevalence: 20 - 30%

Etiology and triggers:

- **Outdoor allergens** e.g., pollens, and molds
- **Indoor allergens** e.g., house dust mites, animal dander, molds, and insects (e.g., cockroach allergen)
- **Potentiating factors:** tobacco smoke, nonsteroidal anti inflammatory drugs (NSAIDs), and air pollution.

Two clinical forms have been described:

Intermittent (seasonal allergic rhinitis - hay fever)

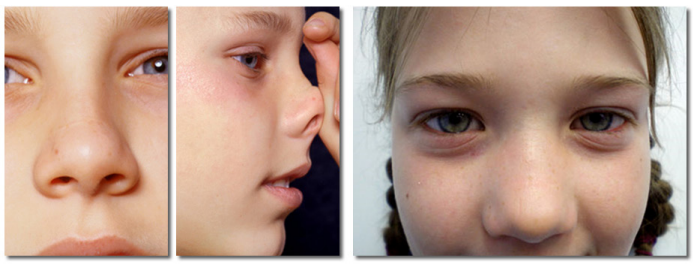
- A symptom complex seen in children who have become sensitized to wind-borne pollens of trees, grasses and weeds.
- It is **rare before 4-5 years of age.**

Persistent (perennial allergic rhinitis)

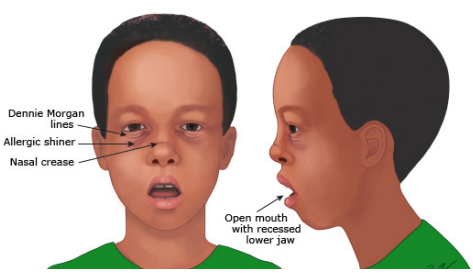
- In which the patient has symptoms year-round.
- The child may be sensitive to house dust, feathers, pet allergens and sometimes food.
- **It may occur at any age.**

Clinical picture

- Symptoms include paroxysmal sneezing, rhinorrhea, nasal obstruction and itching of the nose, palate, pharynx and ears.
- The child commonly **wrinkles the nose (rabbit nose)** or **rubs it (allergic salute).**
- **Mouth breathing** is common and **dark circles under the eyes** have been attributed to venous stasis due to blood flow interference caused by edematous nasal mucosa.



Nasal crease | Allergic salute | Dark circles



Features of chronic nasal obstruction

Comorbidities

- **Allergic Conjunctivitis**
- **Sinusitis**
- **Asthma / COPD**
- Otitis Media With Effusion
- Nasal Polyps
- Upper Respiratory Infection
- Obstructive Sleep Disorders

Prognosis

- Most patients develop asthma or wheezing later, so **avoidance of causative allergens** should be attempted promptly.

Treatment

It follows the general principles of treatment of allergic disorders.

- Oral antihistamines
- Steroid nasal sprays
- Cromolyn nasal solutions
- Saline nasal wash
- Specific immunotherapy: especially pollen and mite allergy
- **Treatment of comorbidities** e.g., asthma, sinusitis, allergic conjunctivitis

Atopic dermatitis (atopic eczema)

A chronic inflammatory skin disorder characterized by erythema, edema, intense pruritis, exudation, crusting and scaling.

Scratching → induction of **eczematous skin lesions**

Timing: 80% of cases develop illness before 5 years, so it is typically a pediatric disease.

Clinical picture

- The disease most often begins in infancy usually during the first 2-3 months of life.
- The earliest lesions are erythematous patches on the cheeks with subsequent extension to the remainder of the face, neck, wrists, hands, trunk, and extensor aspects of the extremities.
- Involvement of flexural areas appears later in the form of popliteal and antecubital dermatitis.

Diagnosis is based on three major features:

- Pruritus
- Typical eczematous dermatitis
- Chronic or relapsing course

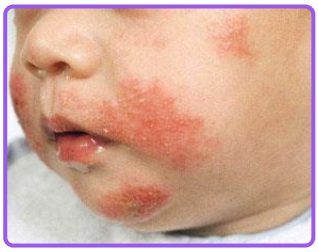
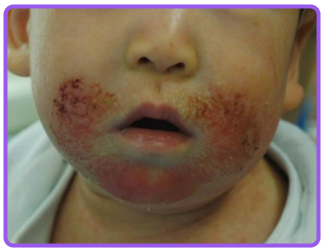
- ***Pruritis:*** is marked and a light mechanical stroke of the skin may cause a white line with surrounding blanched area (phenomenon of white dermatographism).
- ***Dermatitis:*** The onset of dermatitis frequently coincides with the introduction of certain foods into the infant's diet especially cow's milk (most frequent cause), eggs, wheat, soy, fish, peanuts, tree nuts or some fruits.
- ***Course:*** The disease shows a tendency to remission at 3-5 years of age. During childhood, antecubital and popliteal involvement becomes common.

> **Note**
>
> - The face takes a whitish hue as increased capillary permeability results in edema and blanching of surrounding tissues. This is sometimes called **"the mask of atopic dermatitis".**
> - Hyperpigmentation, scaling and lichenification of the skin may become prominent.

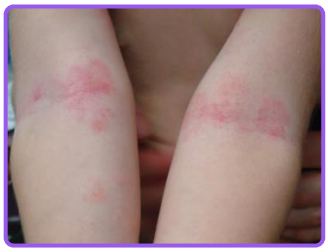
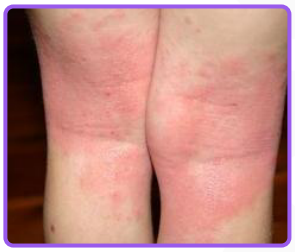
In infancy

- AD is more **acute**
- Involves the face, scalp, and extensor surfaces of the extremities
- The **nose and diaper area are usually spared**

Older children Usually have rash in the **flexural folds** of the extremities

In infants (note sparing of the nose)

In older children

Other features of atopic dermatitis:

- Dry skin (Xerosis)
- Ear and retroauricular eczema
- Dennie Morgan lines
- Perioral dermatitis due to licking of lips
- Eczema due to hand sucking

Examples of an itch that rashes

Complications

Secondary infections: bacterial, viral (herpes simplex and warts), and fungal.

Disfigurement: due to lichenification and hyperpigmentation

Lack of sleep: due to pruritis

Psychological disturbances: due to lack of sleep and/or disfigurement

Prognosis

- **Spontaneous resolution** in 40 - 60% after five years of age
- Patient may experience a **relapse** in adulthood
- Progress through the **allergic march** (About 30% of children with eczema develop asthma)

Infants with atopic dermatitis tend subsequently to experience several allergic disorders such as allergic rhinitis and/or asthma along the years starting from infancy and going through the pediatric age group. This is called the *allergic march.*

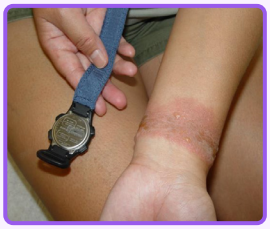
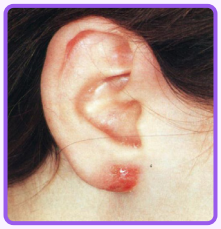
Treatment

It follows the general principles of prevention and treatment of allergic disorders.

- **Emollients and topical corticosteroids** are the **main lines of treatment.**
- **Antihistamines** with sedative action
- Other **immunosuppressive topical agents** are also used.
- **Cotton clothes** are preferred
- **Avoidance** of **perfumed soaps and lotions and irritants** is important.
- **Avoidance** of an **offending food,** in case of food allergy, helps a lot.

Allergic Contact Dermatitis

- Is another cause of eczema


Urticaria & Angioedema

Urticaria (hives): is a common skin disorder characterized by usually well circumscribed but sometimes coalescent raised skin lesions **(wheals)** of various sizes which are intensely pruritic.

Angioedema (angioneurotic edema):

- The **deeper layers** of skin and SC tissues are involved.
- There is acute onset of edema that involves the **eyelids, lips, genitalia and extremities.**
- The URT and GIT are common target organs.

> **Note**
>
> A dangerous site for edema is **the pharynx.**

Etiology

Urticaria and angioedema may be caused by:

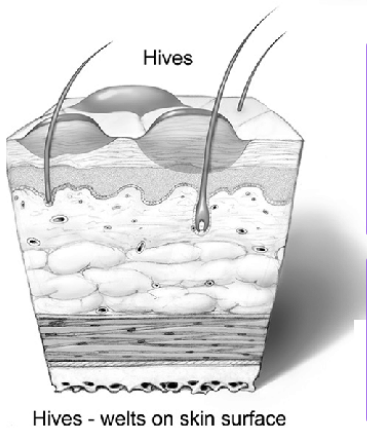
- **Ingestants:** food and food additives
- **Contactants:** e.g. animal saliva, topical drugs and latex
- **Injectants:** e.g. drugs like penicillin, blood transfusion, SCIT (immunotherapy), and insect bites.
- **Inhalants:** e.g. pollens and animal dander
- **Infectious agents:** e.g. parasites and bacteria like streptococcus
- **Physical factors:** e.g. cold, pressure, and aquagenic (post-shower) urticaria

Treatment

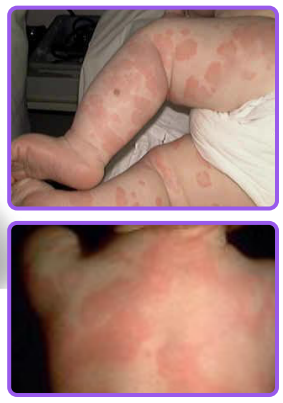
Mainstay: Antihistamines, as in most instances, urticaria is a self-limited illness requiring little treatment other than rapidly acting antihistamines.

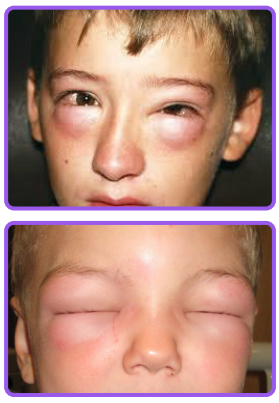
In severe cases: IM Epinephrine 0.01 mg/kg body weight (maximum 0.3 mg) usually offers rapid relief of acute severe urticaria.

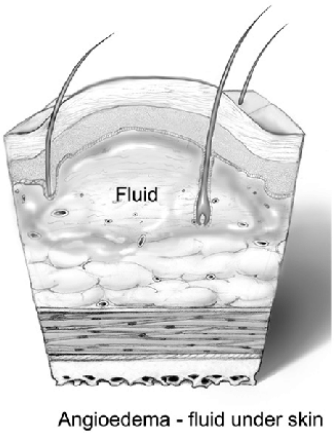
Rarely, in cases with prolonged symptoms: Systemic corticosteroids are needed.



Hives - welts on skin surface

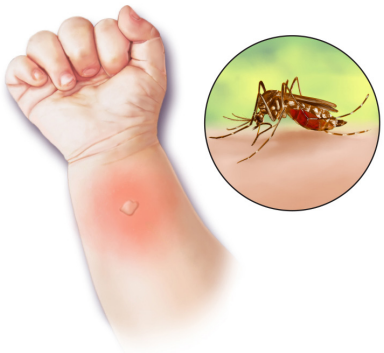






Angioedema - fluid under skin

Insect Allergy



Globally common especially in hot and humid regions

Forms of Insect Allergy

Local Reactions:

- Large local reactions may be caused by hypersensitivity reactions to **insect's saliva (papular urticaria)**
- The most common insects are mosquitoes, fleas, and ants.

Papular urticaria Vs. Chickenpox

Papular urticaria		Chickenpox
Papules, vesicles & crusts	**Rash**	Papules, vesicles & crusts
Very itchy	**Pruritus**	Very itchy
Contact with insects	**History**	Contact with a case of chicken pox
Mainly on the **limbs**	**Distribution** (most important)	Starts on the **trunk**
Not present	**Fever**	Present

Systemic reactions:

- May occur from **venom producing insects** (e.g. bees, wasps, and fire ants)
- May lead to **anaphylaxis** that can be fatal.

Inhalant allergy:

- Example: **Cockroach allergy**
- Allergens derived from cockroach saliva, secretions, fecal material, or debris from dead cockroaches may cause respiratory allergy e.g. asthma

Treatment of insect allergy

Systemic reactions:

- Treatment of anaphylactic attacks
- Specific immunotherapy (effective in > 90%)

Respiratory allergy:

- Treatment of asthma and/or allergic rhinitis
- Indoor measures (insect control)

Local reactions:

- Soothing creams and lotions
- Antihistamines in severe itching
- Avoidance of insects

Food allergy

Adverse Reactions to Food

Non-toxic

Immune-mediated (Allergy)

Non IgE mediated

IgE mediated

Non immune-mediated (Intolerance)

Enzymatic

Pharmacologic

Undefined

Toxic

Prevalence of food allergy

Adults: 1.4 - 2.4%

Children < 3 years: 6%

- 2.5% Cow s milk allergy
- 1.5% Egg allergy
- 0.6% Peanut allergy

Food allergy is the most common cause of anaphylaxis in children

Most infants outgrow cow's milk allergy: 50% by 2 3 years, 85% by 10 years

80% of children with peanut or sea food allergy retain it for life

Types of food allergens

Class I food allergens: milk, egg, seafood, peanut, tree nuts, wheat, and soy.

Class II food allergens:

- **Fruits and vegetables** (food pollen syndrome which means that a person who is allergic to a certain pollen will get symptoms when exposed to a fruit or vegetable that cross reacts with that pollen)

Class I food allergens are more common and cause more serious reactions than class II allergens

Food Pollen Syndrome (Oral Allergy Syndrome)

Cross reactive allergens between certain foods & airborne pollens

- **Grass pollen:** Melons - Tomatoes - Oranges.
- **Ragweed pollen:** Banana - Cantaloupe - Cucumber - Watermelon - Zucchini.

Hidden allergens in food: Poor labeling of market foods; a marketed food that you buy might contain an allergen that is not written in its ingredients.

Reactions to food additives:

- Symptoms to multiple unrelated foods
- Allergy to a food when commercially prepared but not when home made

Treatment

- Avoidance is the mainstay of treatment
- **Correct diagnosis (essential):** challenge test
- Dietician's role is crucial

Note

Very restrictive diets can lead to malnutrition

Anaphylaxis

Definition

Anaphylaxis represents the most severe type of allergic reaction and is considered a medical emergency.

- Anaphylaxis is an acute potentially life threatening hypersensitivity reaction; most cases are mild but any anaphylaxis has the potential to become life threatening.
- It occurs within minutes up to a few hours, after exposure to a provoking agent (trigger)
- Caused by rapid and massive release of mediators from mast cells and basophils that follows the interaction of allergens with specific cell-bound IgE.

Etiology of anaphylaxis in children

The causative agents are the same like those of urticaria and angioedema but sometimes may be idiopathic:

- Food allergy is the most common cause in pediatrics especially peanut, tree nuts, sea food, eggs, and milk.
- Other important causes are insect bites (e.g. bees & wasps), latex (e.g. gloves and toys), drugs (e.g. antibiotics), contrast media, and intravenous immunoglobulin (IVIG) therapy.
- Anaphylaxis can even be idiopathic

Etiology according to the venue:

Inside the hospital	Outside the hospital
• Latex • Antibiotics (especially intravenous) • Intravenous immunoglobulin • Radiocontrast dye	• Food • Insect sting • Oral medications • Exercise • Idiopathic

Co-factor induced anaphylaxis

- **Co-factors** are sometimes required for an allergen to provoke an anaphylactic reaction.
- This is called **"summation anaphylaxis"** and it may explain intermittent anaphylaxis despite previous safe allergen exposure.
- **Common co-factors are:**
  - Concurrent infection
  - Medications: B-adrenergic blockers, ACE inhibitors, and NSAIDs.
  - Alcohol or spicy food
  - Exercise

Clinical manifestations

Earliest Symptoms and Signs:

- Often the first symptom is a **tingling sensation around the mouth or in the face** followed by a feeling of warmth, difficulty in swallowing and tightness in the throat and/or chest.

Within seconds:

- The patient becomes **flushed**, usually has urticaria/angioedema, and may develop stridor, and may develop inspiratory stridor, dysphagia, nasal congestion, wheezing and **abdominal cramps.**
- The child may then become **hypotensive**, lose consciousness, become hypotensive and develop bradycardia or arrhythmias.
- Cardiorespiratory arrest and death may ensue.

Usually there is generalized giant urticaria and angioedema, however, not all symptoms will be present during an attack and not all patients will have rash.

Late Phase Reaction:

- Biphasic course is reported in **20%**
- Second phase usually occurs after **8 - 10 hours**, but could be as late as 38 hours.
- Biphasic anaphylaxis may be related to delayed treatment

Diagnosis

Is mainly based on clinical data:

- Particularly the **timing of reaction** in relation to the suspected trigger
- If the trigger is not clear, a detailed review of all exposures over the preceding 24 hr is required

Serum tryptase (mast cell enzyme):

- If elevated, it indicates **mast cell activation and degranulation.**
- It is **not always helpful**

Other investigations to detect the causative allergen are later on indicated.

Treatment

Emergency Treatment

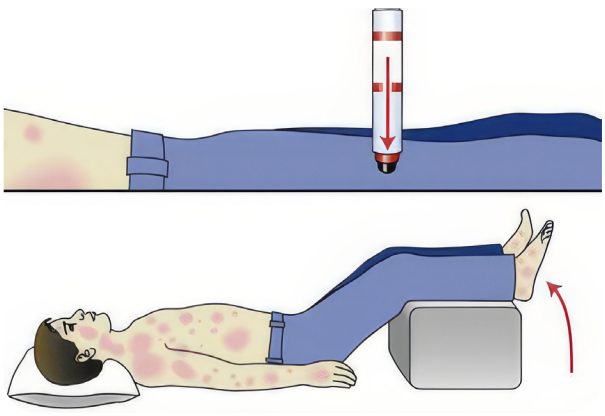
IM Epinephrine:

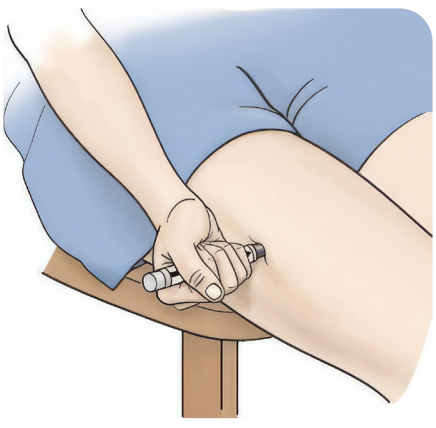
- **Dose: 0.01 mg/kg** (**maximum of 0.3 mg** of a concentration of 1:1000 (1 mg/ml)
- Injected into the **upper lateral aspect of the thigh** (vastus lateralis muscle)
- Can be repeated at **5 - 15 minute intervals**

> **Why Intramuscular?**
>
> - Absorption is rapid reaching the central circulation immediately.
> - Rapid absorption is critical as the median time to respiratory or cardiac arrest is 15 min in venoms and 30 min in food.

Positioning:

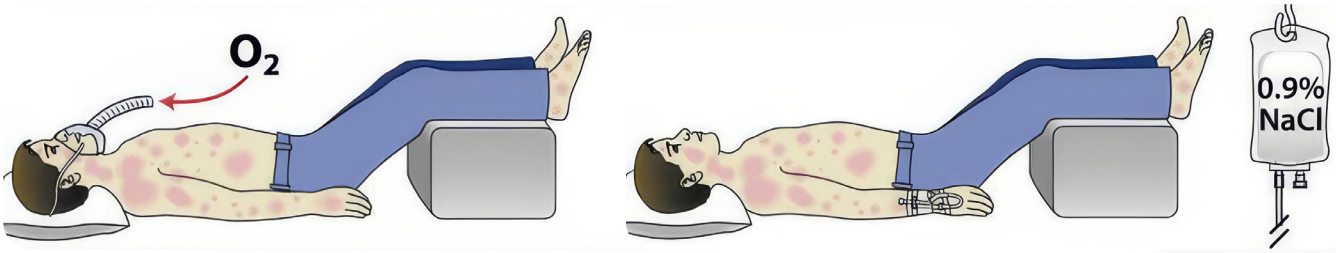
- Patients with anaphylaxis should be placed **supine** (on their back) with **lower extremities elevated**
- **If short of breath and/or is vomiting,** should be placed **on side or semi upright** in a position of comfort with the **lower extremities elevated**





ABC:

- **A (Airway):** Oxygen therapy, oropharyngeal airway, sometimes endotracheal intubation.
- **B (Blood Pressure):** Rapid infusion of **normal saline** (0.9%) for **hypotension** (20 ml/kg, repeated up to a total of 50 ml/kg over one hr)
- **C (Cardiac monitoring).**



Other (non life-saving):

- **H1-Antihistamines IV** for **relief of itching** but it is not life saving.
- **Nebulized beta 2 stimulant** to **improve the bronchospasm** but it is not life saving.
- **Corticosteroids (systemic)** may **prevent the late phase reaction** but it is not life saving.

Hospitalization for 24hrs is usually necessary to guard against the late phase reaction.

In refractory cases

- **IV epinephrine:** central line, 1:10,000 concentration, given by infusion pump.
- **Vasopressors:** dopamine, vasopressin.
- **Glucagon:** in patients receiving beta-blockers.
- **Atropine:** in persistent bradycardia.
- **Cricothyrotomy:** trained personnel.

Long Term Management

Patients who experienced anaphylaxis even once:

- Must carry an ***epinephrine self injector (Epipen)*** or an epinephrine ampoule and syringe **all the time** to guard against further attacks
- Should be **evaluated by an allergist** for the trigger (allergen)
- **Training of contacts** to administer epinephrine
- Patients should **not be given beta blockers for any reason** (interferes with the action of epinephrine)
- **Medical Alert bracelet** or equivalent

2 PEDIATRIC RHEUMATIC DISEASES

Rheumatic diseases are defined by the constellation of results of the physical examination, autoimmune markers, tissue pathology, and imaging

Defined diagnostic criteria exist for most rheumatic diseases Recognition of clinical patterns is essential for diagnosis because there is no single diagnostic test, and results may be positive in the absence of disease

Further complicating the diagnosis, children sometimes present with partial criteria that evolve over time or with features of more than one rheumatic disease

Juvenile idiopathic arthritis (JIA)

Arthritis **is defined as swelling or effusion, or the presence of 2 of the following signs: limitation of range of motion, tenderness or pain on motion, increased heat) in 1 joint**

Juvenile idiopathic arthritis (JIA) **is defined by the International League of Associations for Rheumatology (as arthritis of unknown etiology that begins before the sixteenth birthday and persists for at least 6 weeks with other known conditions excluded**

Prevalence: It is a common rheumatic disease of children (around 113/100,000 children) and a major cause of chronic disability.

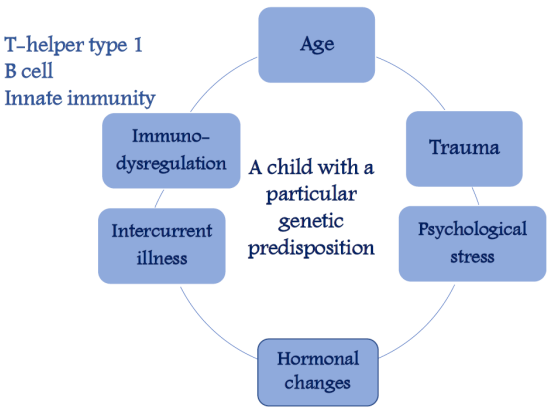
Etiology

The etiology is unknown.

It is multifactorial; at least two necessary events are postulated:

- Immunogenetic susceptibility, and
- An external, presumably environmental, trigger.

Specific HLA subtypes confer varying degrees of susceptibility.



Classification

According to the International League of Associations for Rheumatology (ILAR), JIA is not regarded as a single disease but as a category of diseases.

Categories

Systemic JIA: Arthritis in **≥ 1** joint with, or preceded by, fever of at least 2 wk in duration that is documented to be daily (quotidian) for at least 3 days and accompanied by **≥ 1 of the following:**

1. Evanescent (nonfixed) erythematous rash
2. Generalized lymph node enlargement
3. Hepatomegaly or splenomegaly or both
4. Serositis

Exclusions:

a. Psoriasis or a history of psoriasis in patient or first-degree relative
b. Arthritis in an HLA-B27—positive boy beginning after 6th birthday
c. Ankylosing spondylitis, enthesitis-related arthritis, sacroiliitis with IBD, Reiter syndrome, or acute anterior uveitis, or history of 1 of these disorders in first-degre relative
d. Presence of IgM RF on at least 2 occasions at least 3 mo apart

Oligoarthritis: Arthritis affecting **1 - 4 joints** during 1st 6m of disease; **2 subcategories** exist:

1. **Persistent oligoarthritis** affecting **≤ 4 joints** throughout the disease course
2. **Extended oligoarthritis** affecting **> 4 joints** after 1st 6m of disease

Exclusions: a, b, c, d + e: Presence of systemic JIA in the patient

Polyarthritis (RF negative):

1. Arthritis affecting **≥ 5** joints during 1st 6m of disease
2. A test for RF is negative

Exclusions: a, b, c, d, e

Polyarthritis (RF postitive):

1. Arthritis affecting **≥ 5** joints during 1st 6m of disease
2. **≥ 2 tests** for RF at least 3m apart during 1st 6m of disease are positive

Exclusions: a, b, c, e

Psoriatic arthritis: Arthritis and psoriasis, or arthritis and at least 2 of the following:

1. Dactylitis
2. Nail pitting & onycholysis
3. First-degree relative psoriasis

Exclusions: b, c, d, e

Enthesitis-related arthritis: Arthritis and enthesitis, or arthritis and at least 2 of the following:

1. Sacroiliac tenderness or inflammatory lumbosacral pain, or both
2. Presence of HLA-B27 antigen
3. Onset of arthritis in a male > 6 yr old
4. Acute (symptomatic) anterior uveitis
5. History of ankylosing spondylitis, enthesitis-related arthritis, sacroiliitis with IBD, Reiter syndrome, or acute anterior uveitis in first-degree relative

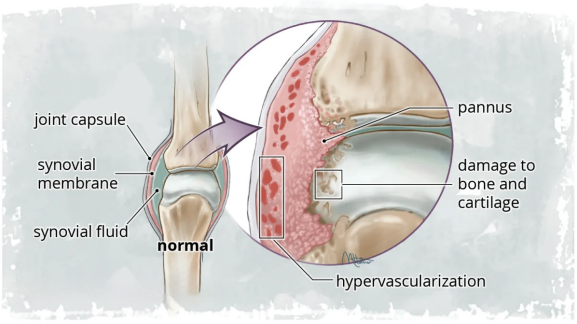
Exclusions: a, d, e

Undifferentiated Arthritis: Arthritis that fulfills criteria in 0 or in ≥ 2 of the above cate ories.

Pathology

The synovitis of JIA is characterized pathologically by **villous hypertrophy and hyperplasia** with **hyperemia and edema** of the sub-synovial tissues and vascular endothelial hyperplasia.

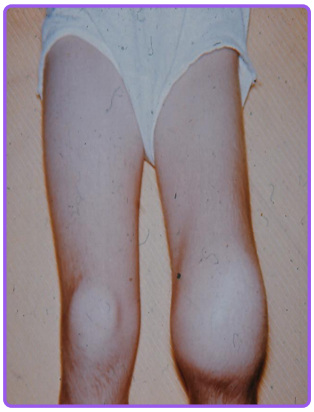
Pannus formation, which is an inflammatory exudate over the synovial lining, occurs in advanced uncontrolled disease and results in progressive erosion of articular cartilage and contiguous bone.



Common clinical features

I- Musculoskeletal manifestations

Joint pain:



- The child may not complain of pain at rest
- **Active or passive motion** of a joint elicits pain in the inflamed joint, particularly at the extremes of the range of motion
- Pain is usually described as **aching or stretching** and is of **mild to moderate** severity

Joint stiffness:

- May occur, commonly described as **slowness or awkwardness of the gait**
- **Most marked** in the **morning or prolonged sitting**
- **Improves** with **activity or the application of heat** to the affected area

Joint inflammation:

- An actively inflamed joint exhibits the cardinal signs of inflammation swelling, pain, heat, loss of function, but **almost never erythematous.**

Muscle atrophy:

- Atrophy and weakness of muscles around inflamed joints occur frequently
- Atrophy of the **vastus medialis** muscle is characteristic of arthritis in the **knee**

Osteopenia

Tenosynovitis

II- Extraarticular Manifestations:

Generalized and /or localized abnormalities of **Growth.**

Ocular Disease:

- Uveitis is characteristically chronic and asymptomatic, except in enthesitis related arthritis, where it is usually characterized by acute onset of painful pink eye.
- **Positive antinuclear antibody (ANA) titer** increases risk for chronic uveitis particularly in young girls with oligoarticular and RF seronegative polyarticular JIA.

Hepatosplenomegaly and lymphadenopathy

Cardiac/pulmonary disease

Characteristic clinical features of JIA categories

Systemic JIA

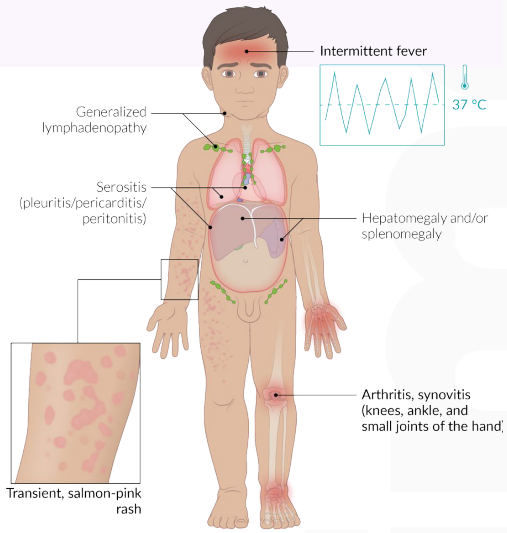
Peak age at onset: 1 - 5 years

Sex: no sex predilection.

I- Extraarticular manifestations

Fever and constitutional symptoms:

- Children with systemic-onset JIA may have significant malaise, anorexia and decreased activity.
- The temperature rises to 39°C or higher on a daily or twice daily basis, with a rapid return to baseline or below the baseline.
- The fever may occur at any time of the day but is characteristically present in the late afternoon to evening in conjunction with the rash



Skin rash:

- The rash of systemic JIA is faint erythematous salmon colored macular rash It is typically evanescent and occurs at times of high fever
- The rash is often distributed in groups with a linear distribution most commonly over the trunk and proximal extremities, non pruritic
- Individual lesions may be elicited by rubbing or scratching the skin ***(the Koebner phenomenon)*** or by a hot bath or psychological stress

Cardiac disease:

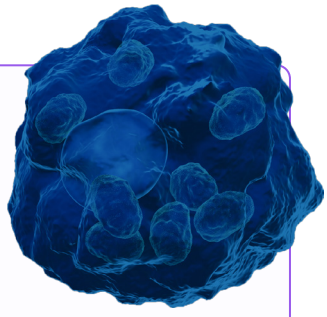
- Pericarditis and pericardial effusion can occur
- Myocarditis is much less common than pericarditis
- Coronary artery abnormalities have been reported in children with SJIA who are febrile

Heaptosplenomegaly and lymphoadenopathy

II- Musculoskeletal disease

Arthritis:

- The arthritis is commonly polyarticular in nature the knees, wrists, and ankles are most commonly involved
- Joint disease usually increases in extent and severity over weeks or months
- Sometimes, the arthritis of JIA follows the systemic inflammation by 6 weeks to 6 months



MACROPHAGE ACTIVATION SYNDROME (MAS)

MAS, the most devastating complication of SJIA most often occurs during periods of active disease, especially early on in the disease course, with approximately 20% of MAS episodes occurring at the time of initial diagnosis.

- **MAS is characterized clinically by the rapid development of:**
  1. Unremitting fever
  2. Hepatosplenomegaly and lymphadenopathy
  3. Hepatic dysfunction (and even liver failure)
  4. Encephalopathy
  5. Purpura, bruising, and mucosal bleeding.
  6. Severe cases rapidly progress to multiorgan involvement , hypotension and shock.
- **Laboratory studies:**
  1. **Blood picture:**
     - Cytopenia, especially thrombocytopenia.
     - Normal or even elevated neutrophil counts may be seen in the early stages of MAS
  2. **ESR:** drop sharply in association with hypofibrinogenemia,
  3. **CRP:** is typically elevated
  4. Elevated **liver enzymes**, with low **serum albumin**
  5. **Coagulation profile:** Prolonged PT and PTT with marked elevation of D dimers
  6. **Elevated lactate dehydrogenase, triglycerides, and ferritin** levels, sometimes with extreme hyperferritinemia above 10 000 µ g /L
  7. **Prominent hemophagocytosis** may be present in the bone marrow or other tissues such as lymph nodes, liver, or spleen

Oligoarticular JIA

Peak age at onset: 2 - 4 years

Sex: Female predominance.

Arthritis:

- The arthritis is found in medium sized to large joints the knee is the most common joint involved, followed by the ankle and the wrist
- It is unusual for small joints to be involved Also, neck and hip involvement is very uncommon at presentation

Chronic uveitis is common in ANA positive girls

Children with oligoarticular JIA may be otherwise well without any clinical or laboratory evidence of systemic inflammation

Polyarticular JIA

Peak age at onset:

- **Rh-negative:** 2 - 4 and 10 - 14 years
- **Rh-positive:** 9 - 12 years

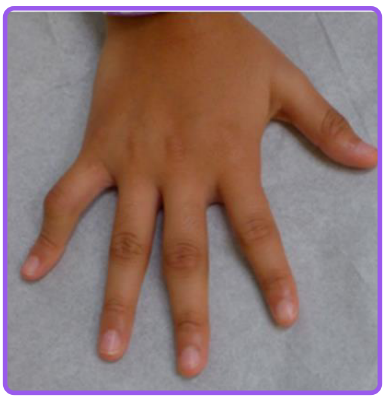
Sex: Female predominance

Arthritis:

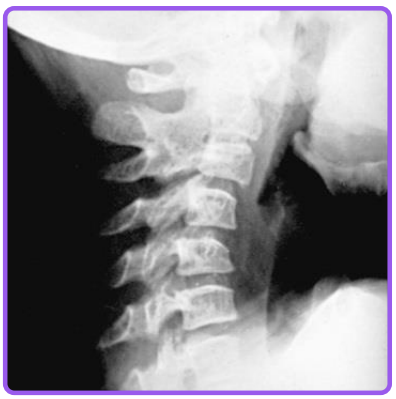
- Children with polyarticular JIA tend to have **symmetric** arthritis, which can affect any joint but typically involves the small joints of the hands, feet, ankles, wrists, and knees
- The **cervical spine** can be involved, leading to fusion of the spine over time.
- Involvement of the **tempromandibular joint** can be complicated by decreased mouth opening, impaired chewing and speaking, malocclusion or micrognathia.

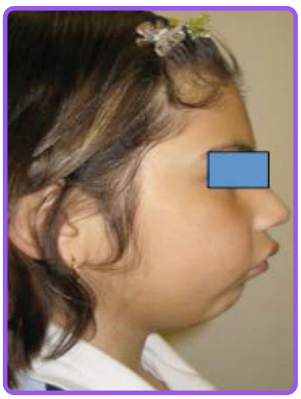
Systemic: Patients can present with evidence of systemic inflammation, including malaise, low-grade fever, growth retardation.

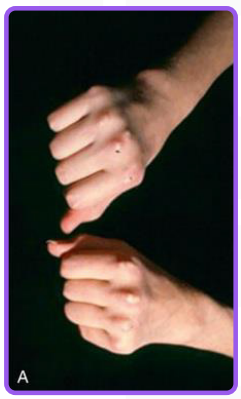
Rheumatoid nodules on the extensor surfaces of the finger joints, elbows and over the Achilles tendons, are features of **Rh-positive polyarthritis** and are associated with a **more severe course.**



Proximal interphalangeal joint arthritis together with joint contracture in the little finger







Micrognathia complicating TMJ arthritis

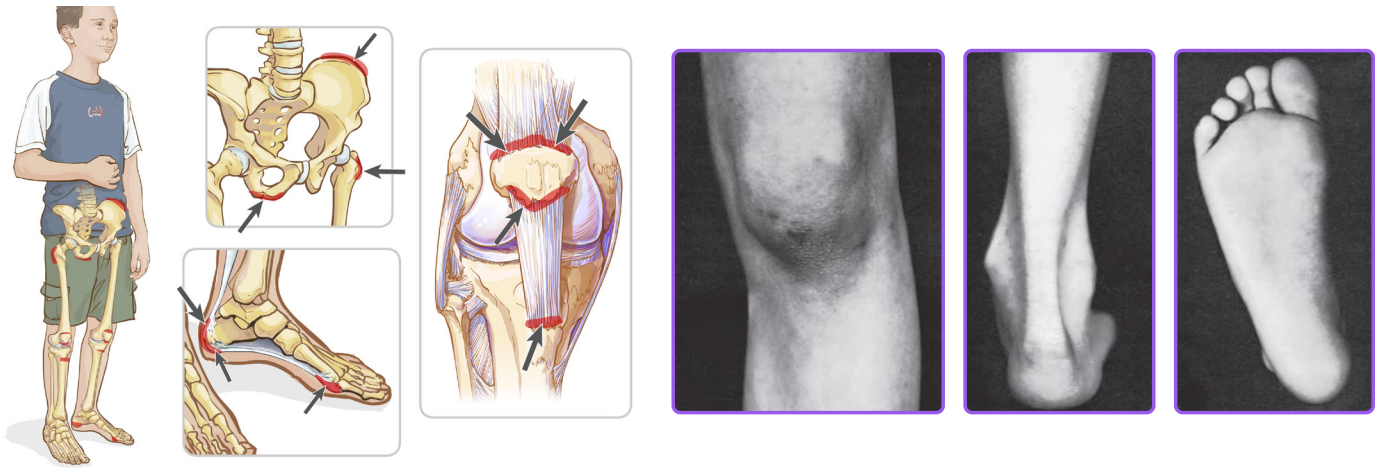
Enthesitis-related arthritis (ERA)

Peak age at onset: 9 - 12 years

Sex: Male predominance

- The peripheral arthritis in ERA is often oligoarticular, asymmetrical and mainly involves the lower extremities.
- Hip involvement at disease onset and during the disease course is common.

Entheses—the sites of attachment of ligament, tendon, fascia, or capsule to bone—are characteristic sites of inflammation, especially in the lower limbs.



Psoriatic JIA

Peak age at onset: 2 - 4 and 9 - 11 years

Sex: Female predominance

Psoriatic arthritis tends to be somewhat asymmetrical and involves both large and small joints, sometimes including the distal interphalangeal joints

Investigations

Laboratory work up

I- Routine lab.:

CBC:

- Leucocytosis, thrombocytosis and anemia (normocytic or microcytic) are typical in systemic JIA and to a lesser extent in polyarticular JIA.
- Normal CBC is a common finding in oligoarticular JIA and can be seen in ERA and PA.

ESR and CRP

- Particularly **elevated** in systemic JIA and polyarticular JIA
- **Normal** results may be seen in other subtypes of JIA

Liver function and kidney function tests

II- Immunological lab Investigations

- **Antinuclear antibody titer (high in at least 40–85%):** Commonly present in oligoarticular and Rh negative polyarthritis, less commonly in systemic JIA
- **Rheumatoid-factor (present in 8%):** It is an antibody against the Fc portion of IgG, predominantly of IgM isotype
- **Anti-cyclic citrullinated peptide antibody:** commonly present in RF positive polyarthritisand to lesser extent in RF negative polyarthritis

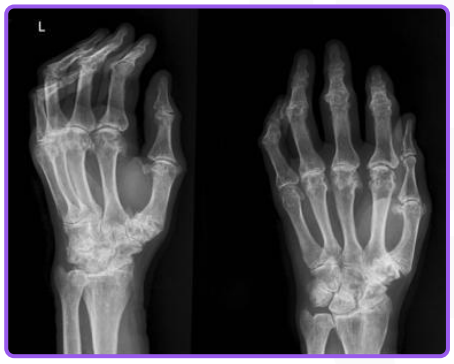
Both RF and anti-CCP indicate more aggressive disease.

Radiological studies

Changes:

- **Early:** soft tissue swelling, regional osteoporosis, and periosteal new-bone apposition about affected joints.
- **Late:** subchondral erosions and narrowing of cartilage space, bony destruction and, potentially, fusion.

Modalities:



Utrasound of the joint

- Will indicate effusion & synovial thickening.
- Also, can **detect enthesitis.**

MRI of the joint

- In case of **marked damage** for further assessment.
- More sensitive in detecting early, minimal changes.

Plain X ray of the joint:

- It is normal early in the course of the disease
- Over time, **periarticular osteopenia, is most commonly found**
- Bone erosion is a late finding

Treatment

Goals of treatment:

- To achieve disease remission
- Prevent or halt joint damage and risk of adverse effects
- Foster normal growth and development, enabling the child to lead as normal a life as possible.

Periodic slit lamp ophthalmologic examinations to monitor for asymptomatic uveitis

1- Diet: ensure appropriate calcium, vitamin D, protein, and caloric intake.

2- Physical therapy

3- A social worker can be an invaluable resource for families.

4- Medications:

For oligoarthritis: Nonsteroidal anti-inflammatory drugs (NSAIDs)

For polyarticular or systemic-onset disease: Use combination therapy beginning with NSAIDs, proceeding through one or more of the DMARDs such as methotrexate and possibly TNF-α inhibitors.

***First line drugs*: NSAIDs**, e.g. ibuprofen, naproxen, tolmetin, diclofenac, and indomethacin.

- They inhibit prostaglandin synthesis.
- **Adverse effects:** Gastritis, bone marrow suppression, hepatitis, interstitial nephritis.
- **Used in:** Oligoarthritis, Polyarthritis, and Probable systemic JIA

> **Note**
>
> Aspirin is no longer the drug of choice.

***Second line drugs*: Disease modifying anti-rheumatic drugs (DMARDs):**

- These are agents that retard radiologic progression of disease.
- **Non-biological:**
  - **Low dose methotrexate (+ folic acid):**
    - Considered the safest, most efficacious, and least toxic for initial adjunctive therapy with an NSAID.
    - It is given once weekly either orally or subcutaneously.
  - **Sulfasalazine**
  - **Leflunomide.**

- **Biological:**
  - **TNF-α inhibitors:** (Etanercept, Infliximab, Adalimumab)
  - **IL-1 receptor antagonist:** (Anakinra, canakinumab)
  - **IL-6 inhibitor:** Tocilizumab
  - **Co-stimulation inhibitor:** Abatacept (CTLA-4Ig).
  - **Anti-CD20:** Rituximab

Other DMARDs include hydroxy-chloroquine, gold salts and d-penicillamine.

Glucocorticoids:

- **Intra-articular (Triamcinolone hexacetonide):** in **persistent limited joint disease.**
- **Systemic Steroids (Oral Prednisone or IV Methylprednisolone):**
  1. **Systemic JIA**
  2. **Overwhelming disease**
  3. **Bridge therapy** in polyarthritis for a child who has not yet responded to conventional therapy
  4. **Ocular control of uveitis**

Steroids are effective but they impose the risk of severe toxicities, including Cushing syndrome, growth retardation, and osteopenia.

Autologous stem cell transplantation.

ⓘ Differential diagnosis of Arthritis (Self learning)

Hematologic/Oncologic disorders

- Leukemia
- Lymphoma
- Sickle cell disease
- Hemophilia
- Malignant and benign tumors of bone, cartilage, or synovium
- Metastatic bone disease

Reactive arthritis

- Poststreptococcal arthritis.
- Rheumatic arthritis
- Toxic synovitis
- Reactive arthritis following genitourinary or gastrointestinal infections

Infectious arthritis

- Bacterial arthritis (mycobacterium tuberculosis, staphylococcus aureus, salmonella)
- Viral arthritis (HBV, HCV, HIV, Mumps, Rubella, EBV, CMV)
- Fungal arthritis (Aspergillus)
- Lyme disease (Borrelia burgdorferi)

Collagen vascular diseases

- SLE
- Juvenile dermatomyositis
- Systemic vasculitis
- Scleroderma
- Sarcoidosis
- Juvenile idiopathic arthritis

Causes of arthritis

1- Rheumatic diseases

- Mainly rheumatic fever arthritis
- Juvenile idiopathic arthritis, SLE and other rheumatic diseases

2- Infection

A- Septic arthritis: Acute medical emergency caused by microbial invasion of joint space:

Etiology:

- Mostly Staph. aureus, less commonly group A streptococci and pneumococci
- In neonates: group B streptococci and gram –ve enteric bacilli
- In sickle cell anemia: salmonella.

Clinical picture:

- It is more common in males with a peak age < 3 years.
- The onset is acute with limping, erythema, warmth, pain and swelling with limitation of movement of the affected joint which is usually the hip.
- It is monoarticular in over 90% of cases

Laboratory investigations:

- PMN leucocytosis.
- Raised ESR
- Positive blood culture
- Joint fluid aspiration and culture.
- U/S and MRI (detection of effusion)
- Scintigraphy (associated osteomyelitis).

Treatment:

- Parenteral antibiotics for a minimum of 3-4 weeks
- Repeated aspiration of joint effusion
- Surgical drainage for large effusions of the hip.

B- Mycobacterial arthritis:

- It is a slowly progressive monoarthritis mostly affecting the knee or hip joints.
- Pain is felt long before signs of inflammation.
- **Diagnosis and treatment:** (revise tuberculosis in respiratory chapter)

C-Fungal arthritis: occurs in immunocompromised patients and is diagnosed by synovial fluid culture.

D-Viral arthritis: caused by rubella, mumps, varicella, HIV etc..

- May be due to direct viral invasion or through an immune-complex mechanism.
- There is arthralgia rather than arthritis.
- It is migratory.

3-Post-infectious & reactive arthritis: Sterile inflammatory arthritis following recent infection.

A- Post-infectious arthritis: It is transient sterile inflammatory arthritis following upper respiratory tract infection.

- **Clinical picture:** Most common cause of hip pain and limp in 3-10 years old children. The limb takes a flexed abducted position.
- **Laboratory:** WBC count and ESR are usually normal or mildly elevated but do not escalate on serial measurements.
- **Treatment:** NSAIDs ± skin traction with the hip in 45o flexion.

B- Reactive arthritis: It is sterile inflammatory arthritis in association distant infection;

- **Enteric** (Salmonella, Shigella, Yersinia, Campylobacter, Giardia intestinalis)
- **Urogenital** (Chlamydia trachomatis).
- **Clinical picture:** Large joint arthritis in the presence of diarrhea or genitourinary infection. It may remit or progress to chronic spondyloarthritis.
- **Treatment:** NSAIDs together with treatment of the infection.

4-Joint pain and swelling: may occur due to trauma, leukemia, hemophilia (hemarthrosis).

Other rheumatic diseases

- Rheumatic diseases are a group of diseases characterized by inflammatory changes in various connective tissues throughout the body.
- The pathogenesis of these illnesses involves immunodysregulation with failure of the immune system to maintain unresponsiveness to self-antigens.

Systemic lupus erythematosus (SLE)

SLE is a multisystem disorder characterized by a production of large amounts of circulating autoantibodies. These antibodies form immune complexes that become trapped in the microvasculature, leading to wide spread inflammation of the affected organs that may be multiple organs.

Etiology

Its cause is unknown.

Its etiopathogeneis is complex involves the interaction between individual genetic susceptibility with hormonal and environmental factors:

- There is **persistent polyclonal B-cell activation** that results in widespread tissue deposition of immune complexes.
- Such immune complexes fix complement and initiate an **inflammatory reaction** causing tissue damage.
- **Disease exacerbations** appear related to intercurrent infections and perhaps to sunlight exposure.

Lupus-like syndrome

Lupus-like syndrome occurs after exposure to a number of drugs: Hydralazine, sulfonamides, procainamide and anticonvulsants.

Epidemiology

The disease is **not rare**

It is highest in **eastern asians.**

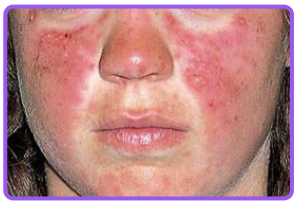
Age:

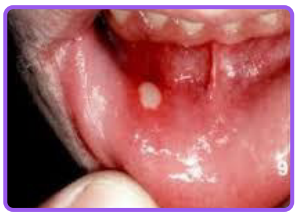
- It usually affects **children over 8 years**
- Disease onset before 8 years of age is unusual, although lupus has been diagnosed even in the 1 st yr of life.

Sex: **Female predominance,** varying from 4 : 1 before puberty to 8 : 1 afterward

Clinical manifestations

According to the revised criteria of the American Rheumatism Association (ACR)





- **1- Malar rash:** erythematous flat or raised over malar eminences
- **2- Discoid rash:** erythematous scaly raised patches
- **3- Photosensitivity**
- **4- Oral or nasopharyngeal ulcers:** painless
- **5- Arthritis:** non-erosive, involving 2 or more joints
- **6- Serositis:** pleuritis or pericarditis
- **7- Nephritis:** persistent proteinuria or cellular casts
- **8- Neurological disorder:** seizures or psychosis
- **9- Hematologic disorder:** hemolytic anemia or lymphopenia or thrombocytopenia
- **10- Immunologic disorder:** positive anti-phospholipid antibodies or anti-ds DNA or anti-Sm antibodies.
- **11- Positive anti-nuclear antibody test**

A person is said to have SLE if any 4 or more of the 11 criteria are present, serially or simultaneously, during any period of observation.

TARGET ORGAN	POTENTIAL CLINICAL MANIFESTATIONS
Constitutional	Fatigue, anorexia, weight loss, fever, lymphadenopathy
Musculoskeletal	Arthritis, myositis, tendonitis, arthralgias, myalgias, avascular necrosis, osteoporosis
Skin	Malar rash, discoid (annular) rash, photosensitive rash, cutaneous vasculitis (petechiae, palpable purpura, digit ulcers, gangrene, urticaria), livedo reticularis, periungual capillary abnormalities, Raynaud phenomenon, alopecia, oral and nasal ulcers, panniculitis, chilblains, alopecia
Renal	Hypertension, proteinuria, hematuria, edema, nephrotic syndrome, renal failure
Cardiovascular	Pericarditis, myocarditis, conduction system abnormalities, Libman-Sacks endocarditis
Neuropsychiatric	Seizures, psychosis, cerebritis, stroke, transverse myelitis, depression, cognitive impairment, headaches, migraines, pseudotumor, peripheral neuropathy (mononeuritis multiplex), polyneuropathy, myasthenia gravis, chorea, optic neuritis, cranial nerve palsies, plexopathy, acute confusional states, dural sinus thrombosis, aseptic meningitis, depression, psychosis, anxiety disorder
Pulmonary	Pleuritis, interstitial lung disease, pulmonary hemorrhage, pulmonary hypertension, pulmonary embolism
Hematologic	Immune-mediated cytopenias (hemolytic anemia, thrombocytopenia or leukopenia), anemia of chronic inflammation, hypercoagulability, thrombocytopenic thrombotic microangiopathy
Gastroenterology	Hepatosplenomegaly, pancreatitis, vasculitis affecting bowel, protein-losing enteropathy, peritonitis
Ocular	Retinal vasculitis, scleritis, episcleritis, papilledema, dry eyes, optic neuritis
Other	Macrophage activation syndrome

According to the Systemic Lupus International Collaborating Clinics (SLICC) criteria

Clinical Criteria

Acute cutaneous lupus: malar rash, bullous lupus, toxic epidermal necrolysis variant of SLE, maculopapular lupus rash, photosensitive lupus rash, or subacute cutaneous lupus.

Chronic cutaneous lupus: Classic discoid rash, lupus panniculitis, mucosal lupus, lupus erythematous tumidus, chilblains lupus, discoid lupus/ lichen planus overlap.

Oral or nasal ulcers

Nonscarring alopecia

Synovitis (≥ 2 joints)

Serositis: Pleurisy or pericardial pain ≥ 1 day, pleural effusion or rub, pericardial effusion or rub, ECG evidence of pericarditis.

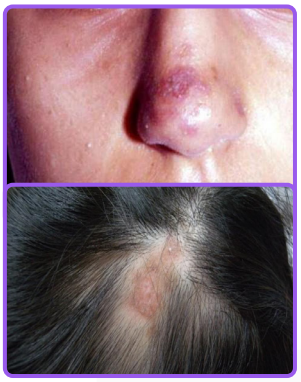
Renal: Presence of red blood cell casts or urine protein/creatinine ratio representing > 500 mg protein/24 hr

Neurologic: Seizures, psychosis, mononeuritis multiplex, myelitis, peripheral or cranial neuropathy, or acute confusional state.

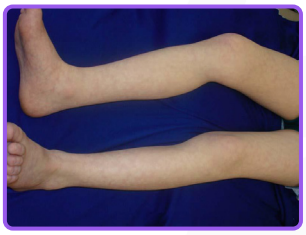
Hemolytic anemia

Leukopenia (< 4,000/mm^3) or **lymphopenia** (< 1,000/mm^3)

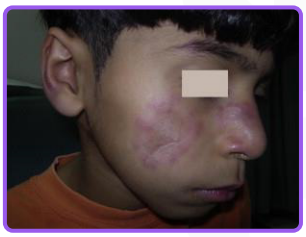
Thrombocytopenia (< 100,000/mm^3)



Discoid lupus



Livedo reticularis



Facial lupus panniculitis

Immunologic Criteria

Positive antinuclear antibody

Positive double-stranded DNA antibody

Positive anti-smith antibody

Antiphospholipid antibody positivity:

- Positive lupus anticoagulant
- False-positive test for rapid plasrma regain
- Mediunl-to-high titer anticardiolipin antibody level (IgA, IgG, IgM)
- Positive anti-$ß_2$-glycoprotein-1 antibody (IgA, IgG, IgM)

Low complement: Low C3, C4, or CH_{50} level.

Positive direct coombs test

The presence of 4 criteria (including at least 1 clinical and 1 immunologic criterion) establishes the diagnosis of SLE.

Biopsy-proven lupus nephritis with positive ANA or anti double-stranded DNA also satisfies the diagnosis of SLE.

Drug-induced lupus

- A lupus like disease that is precipitated by **exposure to certain drugs**, notably many **anticonvulsants, sulfonamides** and **antiarrhythmic** agents.
- Patients may have 1+ criteria of SLE but almost always no major organ involvement.
- It is commonly resolved after several weeks or months of stopping the drug.

Investigations

Routine work up:

- CBC with differential leucocytic count
- ESR
- CRP
- Liver and kidney function tests
- Urine analysis
- 24 hours urinary proteins.
- Creatinine clearance
- Serum lipids

Pulmonary function test by spirometery

Immunological work up:

- Antinuclear antibody (ANA) titer.
- Anti double stranded deoxy ribonuclease (anti-dsDNA) titer
- Anti-smith (anti-sm) antibody titer
- Serum level of C3, and C4
- Anti-Ro (SSA) and anti-La antibodies (SSB)
- **Antiphospholipid antibodies:** Lupus anticoagulant, anticardiolipin antibodies IgM and IgG.
- Coombs test

Renal biopsy

- Is done in case of **clinical or laboratory evidence of renal involvement** to determine the **histopathological class** of lupus nephritis and to **treat accordingly.**

Imaging studies:

- **Dual energy X ray absorptiometry (DEXA) scan:** measure bone mineral density
- **Abdominal ultrasound**

Whenever indicated:

- **High-resolution computer tomography (CT)** scanning to diagnose for Interstitial lung disease in case of restrictive pulmonary function tests.
- **Magnetic resonance imaging (MRI)** of the brain
- **Brain MRAngiography** to diagnose cerebral vasculitis, or arterial/venous thrombosis.

Treatment

Avoidance of sun exposure even during winter.

Vitamin D and calcium supplementations.

Corticosteroids: Most patients require systemic steroids.

- **Oral prednisone** in divided daily doses (1-2 mg/Kg/24 hr).
- **High lupus activity** may require **high dose pulsed IV methylprednisolone.**

Hydroxychloroquine is indicated in **all SLE patients**, it helps to:

- Reduce the risk of thromboembolic disease (decrease platelet aggregation)
- Lower lipid levels.

Cytotoxic therapy: patients with severe renal or CNS disease usually require **pulse intravenous cyclophosphamide.**

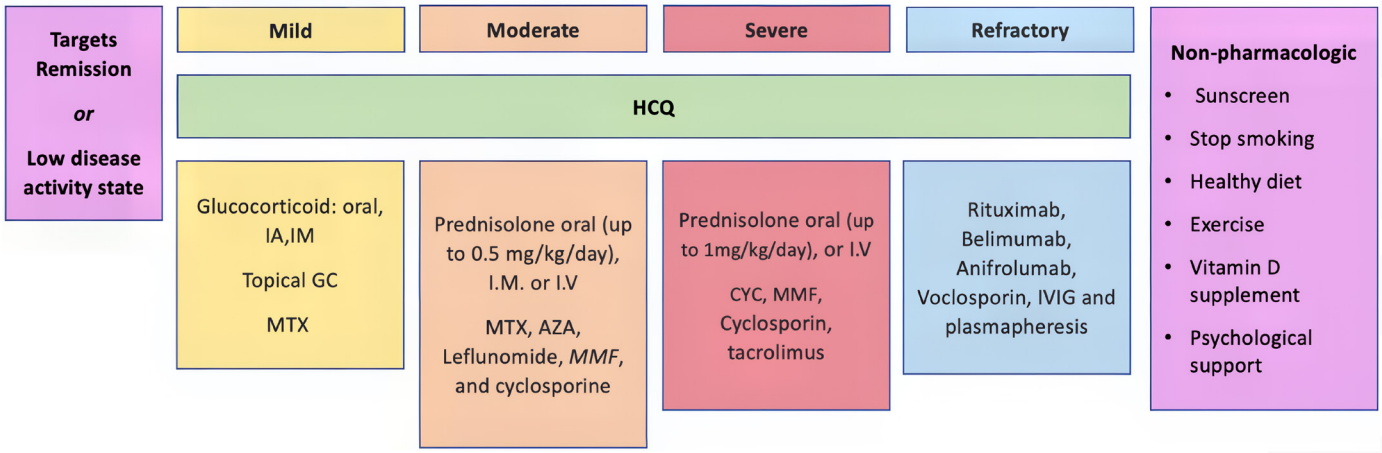
Maintenance steroid-sparing drugs include: azathioprine, cyclosporine, & mycophenolate mofetil.

Biological therapies: Targeting B cells (e.g. Rituximab) are now being used in **severe resistant cases.**

Plasmapheresis

IV immunoglobulins

In mild disease without nephritis, NSAIDs, topical steroids and hydroxy chloroquine provide relief for the joint and skin manifestations respectively.



Prognosis

- The disease is **potentially life long.**
- **Fatalities result from:** Nephritis, CNS lupus, infections, pulmonary lupus and myocardial infarction

Neonatal lupus erythematosus

Neonatal lupus erythematosus (NLE) is not an autoimmune disease of the fetus but instead results from passively acquired autoimmunity, when maternal autoantibodies cross the placenta and enter the fetal circulation.

The vast majority of NLE cases are associated with maternal anti Ro (also known as anti-SSA), anti-La antibodies (also known as anti-SSB), or anti-RNP (antiribonucleoprotein) autoantibodies.

Clinical manifestations include:

- A characteristic **annular or macular rash** typically affecting the face (especially the periorbital area), trunk, and scalp. The rash can be present at birth but more often appears within the first 6 - 8 weeks of life, after exposure to UV light, and typically lasts 3 - 4 months.
- Third-degree congenital heart block is permanent.
- Cytopenias and hepatitis.

Juvenile dermatomyositis

Juvenile dermatomyositis (JDM) is the most common inflammatory myositis in children, distinguished by proximal muscle weakness and a characteristic rash.

Peak age at onset: 4 - 10 years

Sex: Female predominance

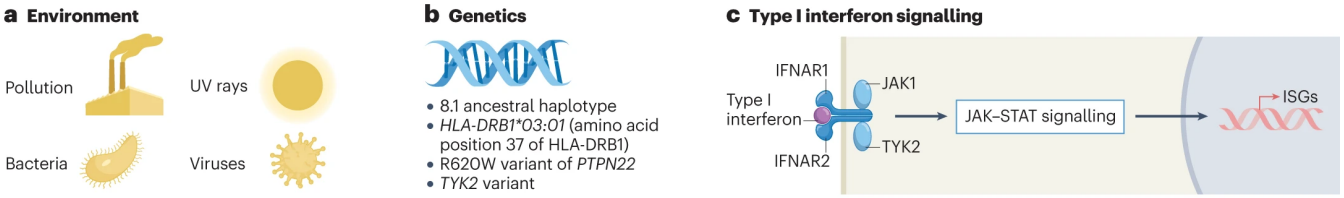
Etiology

The etiology of JDM is multifactorial, based on:

- Genetic predisposition
- And an unknown environmental trigger

Resulting in:

- Immune mediated vascular and muscle inflammation
- With predominance of type 1 interferon response



Clinical picture

I- Cutaneous features

Photosensitive erythematous skin rash in sun exposed area (upper chest & neck): **(Shawl sign)**

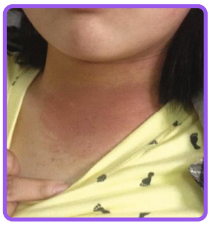
Characteristic **heliotrope rash** is a **blue violet discoloration of the eyelids** that may be associated with periorbital edema.

Facial erythema crossing the nasolabial folds is also common.

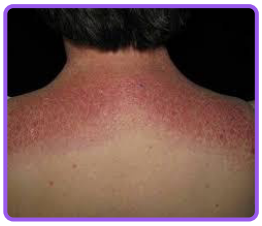
Classic **Gottron papules** are **bright-pink or pale, shiny, thickened or atrophic plaques** over the proximal interphalangeal joints and distal interphalangeal joints (knuckles) and occasionally on the knees and elbows.

Calcinosis is associated with long-standing poorly controlled or undertreated disease: Dystrophic deposition of calcium hydroxyapatite crystals occurs in subcutaneous plaques or nodules, resulting in painful ulceration of the skin with extrusion of crystals or calcific liquid.

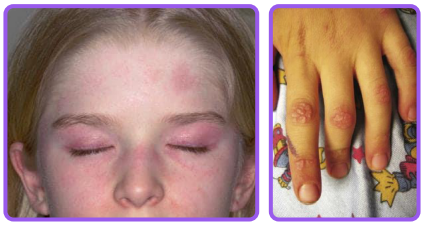
- This is preceded by non-pitting edema and thickening (tightness) of the skin.



Shawl sign



Heliotrope rash



Gottron papules

Calcinosis

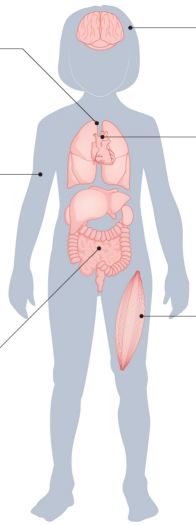
II- Myositis

- Weakness associated with JDM is often insidious affecting **proximal muscles** such as the neck flexors, shoulder girdle, and hip flexors (with elevated CPK and AST)
- Parents may report **difficulty climbing stairs, combing hair, and getting out of bed.**
- Examination reveals **positive Gower sign** (use of hands on thighs to stand from a sitting position).
- Approximately half of children exhibit muscle tenderness.
- **Pharyngeal, esophageal and respiratory muscles** are also affected, resulting in nasal tone of speech, nasal regurgitation, difficulty in swallowing, aspiration, dysphonia and respiratory failure respectively. Dysphagia, abdominal pain and intestinal perforation are causes of death.

Pulmonary involvement or ILD
- Risk increased with anti-MDA5, anti-ARS or anti-Ro52 antibodies
- Increased risk in myositis overlap syndromes

Severe skin disease
- Skin ulceration
- Widespread oedema or anasarca
- Worse skin disease with anti-TIF1 or anti-MDA5 antibodies
- Risk of calcinosis increased with anti-NXP2 and anti-PM/Scl antibodies

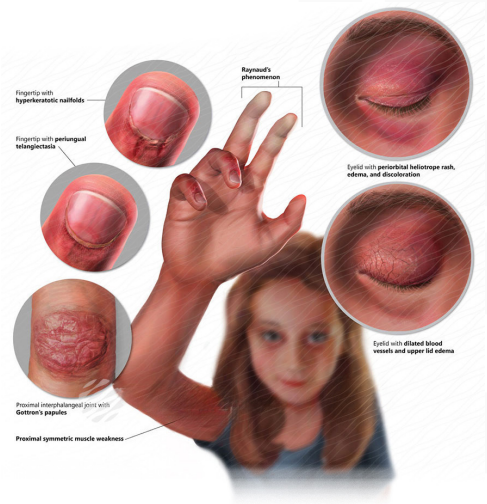
Bulbar weakness or gastrointestinal vasculopathy
- Gastrointestinal vasculitis or perforation
- Dysphagia (aspiration risk)
- Increased risk of dysphagia with anti-NXP2, anti-SRP, anti-HMGCR or anti-SAE antibodies
- Patients positive for anti-SRP or anti-SAE antibodies might also be at an increased risk of dysphagia



CNS involvement
- CNS vasculitis (seizures and hallucinations)
- Retinal vasculopathy

Cardiac involvement
- Increased risk of cardiopulmonary involvement in myositis overlap syndromes
- Patients positive for anti-SRP antibodies possibly have an increased risk of cardiac disease

Muscle involvement
- Severe weakness: CMAS <15 or MMT-8 <30
- Muscle cell necrosis or severe inflammation on muscle biopsy
- IMNM phenotype (positivity for anti-SRP or anti-HMGCR antibodies or MSA negative)



Diagnosis

Diagnostic Criteria for Juvenile Dermatomyositis	
Classic rash	• Heliotrope rash of the eyelids • Gottron papules
Plus 3 of the following:	
Weakness	• Symmetric • Proximal
Muscle Enzyme Elevation (≥ 1)	• Creatine kinase • Aspartate transaminase • Lactate dehydrogenase • Aldolase
Electromyographic Changes	• Short, small polyphasic motor unit potentials • Fibrillations • Positive sharp waves • Insertional irritability • Bizarre, high-frequency repetitive discharges
Muscle Biopsy	• Necrosis • Inflammation

Treatment

- **Avoidance of sun exposure** even during winter.
- **Vitamin D and calcium** supplementations.
- **Physical and occupational therapy (treatment of calcinosis)**
- **Corticosteroids:**
  - **Oral prednisone** in divided daily doses (1-2 mg/Kg/24 hr).
  - **IV high dose pulsed methylprednisolone** in severe cases.
- **Hydroxychloroquine** in **skin disease**
- **SC Methotrexate**
- **In severe unresponsive cases:**
  - IV cyclophosphamide
  - IV immunoglobulins
  - Mycophenolate mofetil

Note

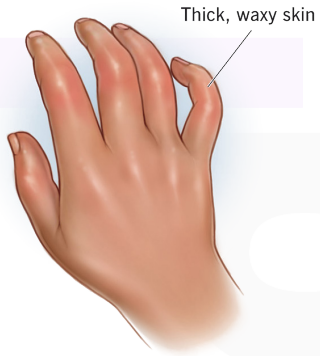
Dexamethasone and triamcinolone should be **avoided** (cause steroid myopathy)

Scleroderma

"Hard Skin"

It is a chronic fibrotic disturbance of connective tissue involving the skin but may also affect the GIT, heart, lung, kidney and synovium (systemic sclerosis).

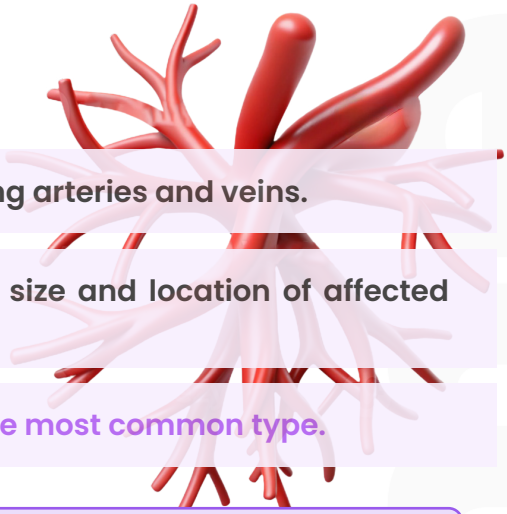
The skin is waxy with extensive fibrosis resulting in crippling contractures.



Treatment

- **For cutaneous lesions:** topical steroids
- **For systemic disease:** steroids, penicillamine or cytotoxic drugs
- **Vigorous physical therapy** to minimize contractures

Childhood Vasculitis



Vasculitis is an inflammatory process affecting arteries and veins.

The various patterns of this condition depend on the size and location of affected vessels.

In childhood, Henoch-Schönlein vasculitis is the most common type.

Predominantly large vessel vasculitis

Takayasu arteritis

Predominantly medium vessel vasculitis

- Childhood polyarteritis nodosa
- Cutaneous polyarteritis nodosa
- Kawasaki disease

Predominantly small vessel vasculitis

Granulomatous:

- Granulomatosis with polyangiitis (Wegener's)
- Eosinophilic granulomatosis with polyangiitis (Churg-Strauss syndrome)

Nongranulomatous:

- Microscopic polyangiitis
- Henoch-Schönlein purpura (IgA vasculitis)
- Isolated cutaneous leukocytoclastic vasculitis
- Hypocomplementemic urticarial vasculitis

Other vasculitides

- Behçet disease
- Vasculitis secondary to infection (including hepatitis B–associated polyarteritis nodosa), malignancies, and drugs (including hypersensitivity vasculitis)
- Vasculitis associated with connective tissue disease
- Isolated vasculitis of central nervous system
- Cogans syndrome
- Unclassified

Henoch-Schönlein Purpura (HSP)

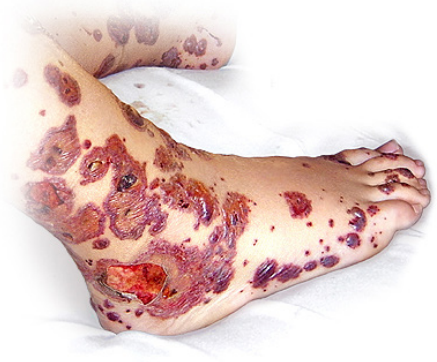
Henoch Schönlein purpura (HSP) is the most common vasculitis of childhood and is characterized by immunoglobulin A deposition in the small vessels in the skin, joints, gastrointestinal tract, and kidney.

Cause: Unknown - Follows **upper respiratory tract infection** and Group A ß hemolytic y streptococci.

Clinically

Skin rash: The hallmark of HSP.

- Starts as urticarial then becomes **palpable purpura** that is usually symmetric and occur in gravity-dependent areas **(lower extremities),** extensor aspect of the upper extremities or on pressure points **(buttocks)**
- The skin lesions typically last **3 - 10 days,** and **may recur up to 4 months after** initial presentation.
- **Subcutaneous edema** localized to the dorsa of hands and feet, periorbital area is common.



Musculoskeletal involvement:

- **Arthritis and arthralgias** are common. Arthritis occurs in **2/3 of cases.**
- The arthritis tends to be **self limited and oligoarticular**, with a predilection for **large joints** such as the knees and ankles.

GIT manifestations:

- Common and include abdominal pain, vomiting, diarrhea, paralytic ileus, and melena.
- Intussusception and mesenteric ischemia, are **rare but serious complications.**

Renal involvement: Occurs in 25-50%

- Less common and manifests as **microscopic hematuria and proteinuria.**
- **Rarely** as hypertension, frank nephritis, nephrotic syndrome, and acute/chronic failure.

Hepatosplenomegaly, lymphadenopathy and CNS manifestations.

Investigations

No laboratory finding is diagnostic of HSP.

- Common but nonspecific findings include mild leukocytosis, thrombocytosis, and anemia, as well as mild elevations of ESR and CRP.
- IgA may be increased.
- Urine analysis shows the presence of RBCs, leukocytes, casts and albuminuria.

ⓘ Assessment of renal involvement with BP, urinalysis, and serum creatinine is necessary

Treatment

Treatment for mild and self limited HSP is supportive, with an emphasis on ensuring adequate hydration, nutrition, and analgesia.

- **Supportive:** Acetaminophen, hydration, rest and scrotal elevation
- **Corticosteroids** for severe cases with renal, intestinal or CNS manifestations.
- **Thrombotic tendency:** baby aspirin.

Prognosis

Excellent;

- <1% persistent renal disease
- 5-10% relapse

Death rarely from severe disease

Kawasaki Disease (KD)

Kawasaki disease (KD) is a systemic inflammatory disorder manifesting as a vasculitis with a predilection for the coronary arteries.

In **developed countries**, Kawasaki disease has replaced acute rheumatic fever as the **most common cause of acquired heart disease in children.**

The cause is unknown; probably an infectious origin together with a genetic role in the pathogenesis of the disease.

Clinical picture

KD can be divided into 3 clinical phases:

The acute febrile phase: is characterized by **fever and the other acute signs** of illness and usually lasts **1 - 2 weeks** but may be as short as 5 days or may persist for 3 - 4 weeks.

The subacute phase: is associated with **desquamation, thrombocytosis, development of CAA**, and the **highest risk of sudden death** in patients who develop aneurysms it generally lasts **3 weeks.**

The convalescent phase: begins when all clinical signs of illness have disappeared and continues until the erythrocyte sedimentation rate (ESR) returns to normal, typically **6 - 8 weeks** after the onset of illness.

Diagnosis

The diagnosis of KD should be considered for any infant with prolonged, unexplained fever.

Diagnostic guidelines for classic Kawasaki disease:

1ST **Exclusion of other similar illnesses**

Fever lasting more than 5 days
High spiking (38.3°C) unremitting, and unresponsive to antipyretics.

+

1 Polymorphous rash

2 **Bilateral conjunctival injection**
(with limbal sparing)

3 **Mucous membrane changes:**
Diffuse injection of oral and pharyngeal mucosa
OR
Erythema or fissuring of the lips
OR
Strawberry tongue

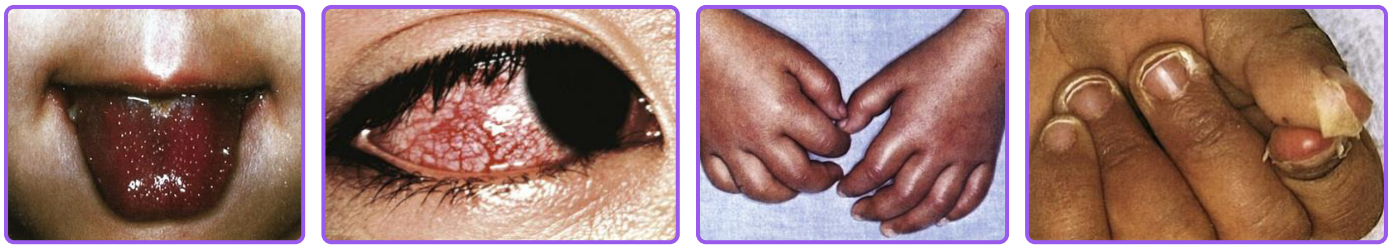
4 **Acute, nonpurulent cervical lymphadenopathy**
(one lymph node must be >1.5 cm)

5 **Extremity changes:**
Erythema of palms and/or soles
OR
Indurative edema of hands and/or feet
OR
Membranous desquamation of the fingertips

4 of the previous 5 criteria

The diagnostic criteria of classic KD require the presence of fever for at least 4 days and at least 4 of 5 of the other principal characteristics of the illness. The diagnosis of KD should be made within 10 days, and ideally within 7 days, of fever onset to improve coronary artery outcomes.

In atypical or incomplete KD patients (most frequently infants) have persistent fever but < 4 of the 5 characteristic clinical signs In these patients, laboratory and echocardiographic data can assist in the diagnosis.



Note

- **Perineal desquamation** is common in the **acute phase.**
- **Periungual desquamation** of the fingers and toes begins **2 - 3 weeks after the onset** of illness and may progress to involve the entire hand and foot.

Investigations

- **The leukocyte count** is often **elevated**, with **neutrophils & immature form** predominance.
- **Normocytic, normochromic anemia** is common.
- **The platelet count** is generally **normal in the 1st week** of illness and **rapidly increases by the 2nd to 3rd week** of illness, sometimes exceeding 1 million/ul.
- **An elevated ESR or CRP** value is **universally present** in the acute phase of illness.

Complications

Coronary artery aneurysms:

- The **most significant and characteristic** complication of KD
- Occurs in **up to 25%** of untreated patients.

Differential diagnosis

- Includes **poststreptococcal scarlet fever**, and **viral illnesses** such as measles.

Treatment

High dose IVIG: Patients with acute KD should be treated with 2 g/kg of IVIG as a single infusion, usually administered over 10 - 12 hr within 10 days of disease onset, and ideally as soon as possible after diagnosis.

Aspirin:

- **Antiinflammatory dose** (80-100 mg/kg/day): In the **acute febrile stage, until the patient has been afebrile for 48 hr.**
- **Antithrombotic dose** (3-5 mg/kg/day): in the **convalescent stage, continued for its until 6 - 8 weeks after onset and discontinued if normal echocardiography findings.**

Patients should be followed for early detection of coronary involvement.

Autoinflammatory diseases

Autoinflammatory diseases (AIDs) include all diseases that present with seemingly unprovoked episodes of inflammation, without the high titer autoantibodies or antigen specific T cells typically seen in autoimmune diseases.

AIDs exhibit **episodic or persistent inflammation** characterized by an **acute phase response with elevation of the ESR, CRP, and serum amyloid A (AA).**

In some patients, untreated AIDs over time will lead to **AA amyloidosis**.

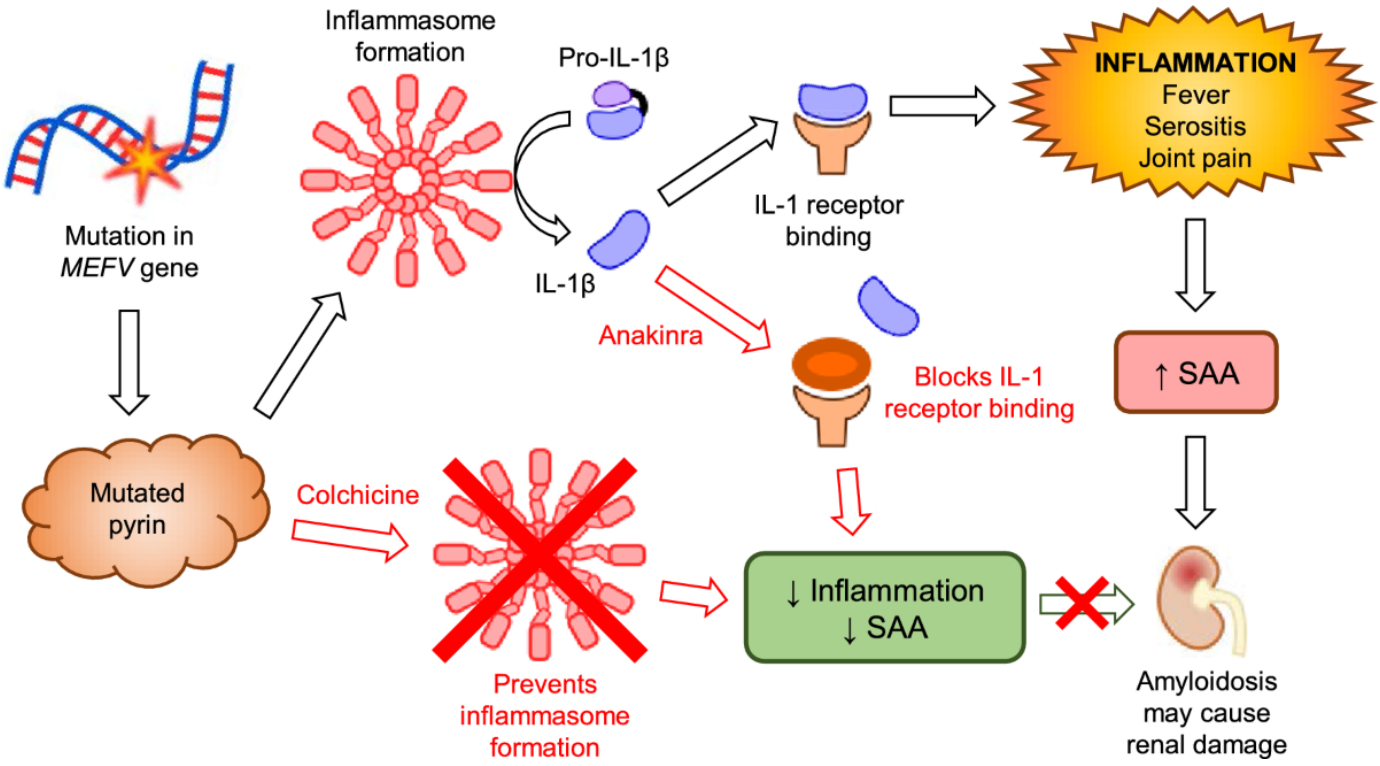
Familial mediterranian fever (FMF)

FMF is an autosomal recessive disorder characterized by brief, acute, self-limited episodes of fever and polyserositis that recur at irregular intervals.

Etiology:

- FMF is commonly caused by **autosomal recessive mutations** in MEFV gene
- **Homozygosity** for the M694V mutation may be associated with an earlier age of onset, arthritis, and an increased risk of amyloidosis.

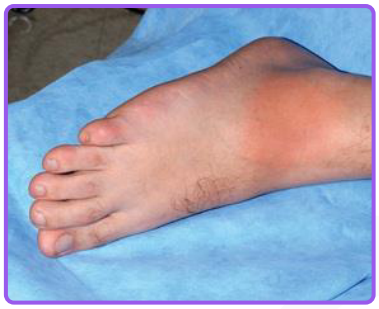
Epidemiology: FMF occurs primarily among ethnic groups of **Mediterranean ancestry**, most frequently Jews, Turks, Armenians, Arabs, and Italians.



Clinical features

The typical acute episode lasts 1-4 days.

- **Fever**
- **Serositis** presenting as pleuritic chest pain (usually unilateral) or severe abdominal pain (generalized or localized), arthritis, and rash.
- **FMF-associated arthritis** occurs primarily in the **large joints**, and is usually nonerosive and nondestructive.
- **Rash:** The hallmark cutaneous finding is an **erysipeloid erythematous rash** that overlies the ankle/dorsum of the foot.



Criterion	Description
Fever	Axillary temperature > 38°C, lasting 6 – 72 hours, with ≥ 3 attacks
Abdominal pain	6 – 72 hours of duration, with ≥ 3 attacks
Chest pain	6 – 72 hours of duration, with ≥ 3 attacks
Arthritis	6 – 72 hours of duration, with ≥ 3 attacks; oligoarthritis
Family history of FMF	
Diagnosis is by the presence of at least two out of five criteria, with 86.5% sensitivity and 93.6% specificity	

Turkish Pediatric Criteria for the diagnosis of familial Mediterranean fever in childhood

Treatment

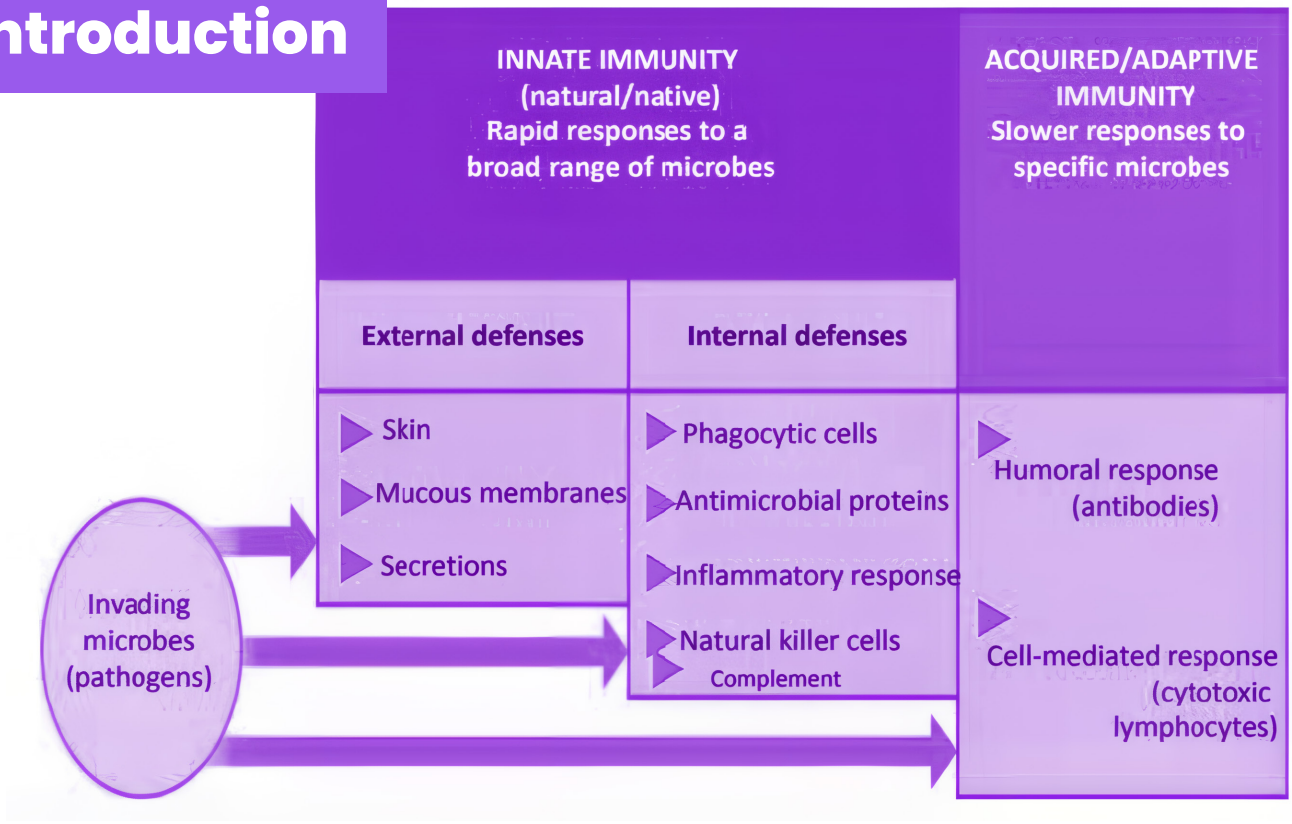
Colchicine:

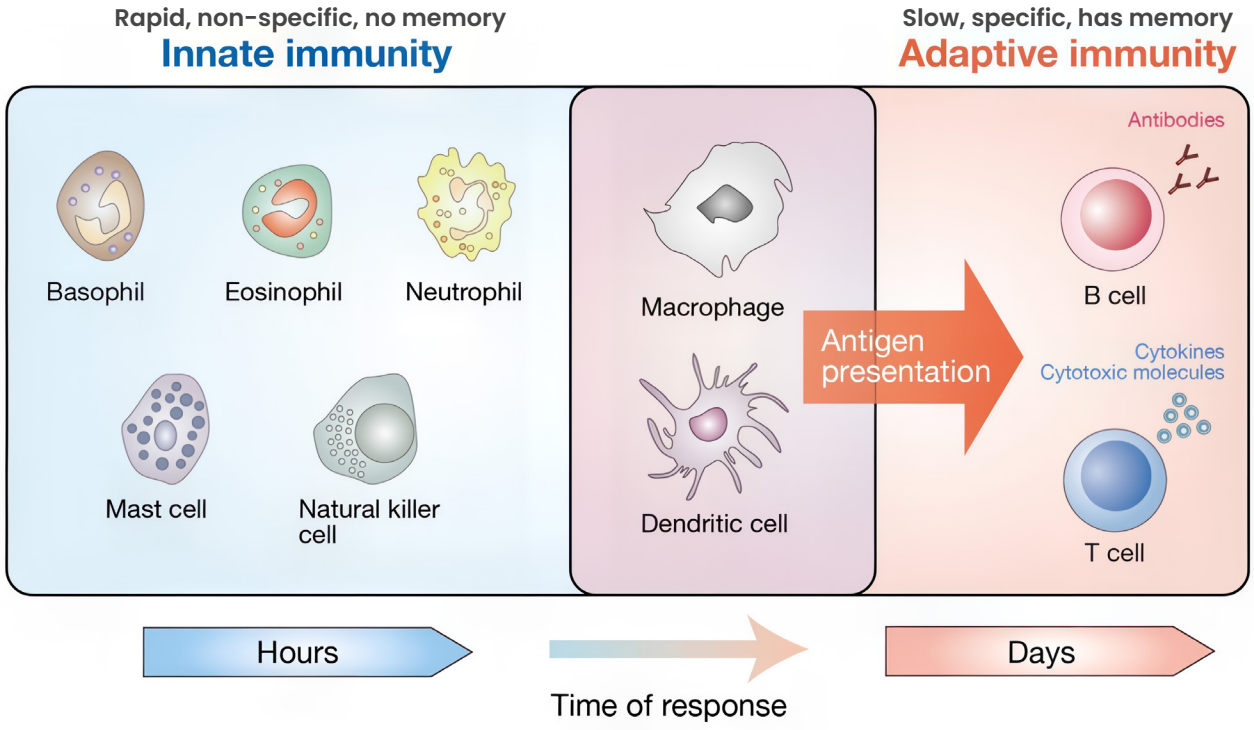
- Attacks of FMF can be prevented by **prophylactic colchicine** (0.02-0.03 mg/kg/day; maximum 2 mg/day) in 1 to 2 divided doses.
- Daily oral colchicine decreases the frequency, duration, and intensity of FMF flares aiming to prevent the development of systemic AA amyloidosis

IL 1 inhibitors: In patients unresponsive to or intolerant of therapeutic doses of colchicine.

IMMUNODEFICIENCY DISORDERS

Introduction





Cont. Introduction

Infection in childhood is **extremely common and often self-limiting.**

Children and young people are expected to have a **higher frequency of infection** than adults.

It is important to identify those with recurrent infections and merit further investigation from those who have a normal frequency of childhood infection.

What is normal?

Expert opinion suggests that **6 – 10 self-limiting viral infections per year** are within the normal range.

More frequent infections can be expected in the winter, and an infection may last for 1 – 2 weeks. Therefore, it may seem like a normal child is unwell for most of the winter period.

Young children with siblings, children attending day care and those exposed to smoking or living in deprived areas are known to have increased infection rates compared with those who do not have these risk factors. Most of them will not have an inborn error of immunity.

When to suspect immunodeficiency? When the infections are:

- Unusually **recurrent**
- Unusually **severe**
- **Unusual organism**

Definitions

Inborn errors of immunity (IEI) / Primary immunodeficiency (PID) diseases

- Are a **heterogenous group of genetic disorders** of the immune system, that manifest with various clinical phenotypes
- This may include infection, allergy, autoimmunity, autoinflammation, and malignancy.

Secondary immunodeficiency

- **More common**
- The individual is born with normal immunity, but a **secondary factor** (acquired) affects the **number and/or the function** of the immune cells.

Inborn Errors Of Immunity (IEI) Diseases (Primary Immunodeficiency Disorders)

Incidence: 1 : 300 – 1 : 20,000 live births.

- The reported overall prevalence of IEI varies significantly depending on the context and definition used.

Age at onset of symptoms:

- **Severe forms** start during the **first year of life.**
- **Mild forms** may show up later

Inheritance: AR, AD or X-linked

Sex: Male to female ratio is 5 : 1

IEI diagnosis can be easily missed if not suspected:

- Primary immunodeficiency (PID) diseases are **more common than generally acknowledged**
- Recurrent infection may be **accepted as variations of normality** rather than investigated
- There are **no specific features** that distinguish IEI from other more familial conditions
- **No screening test** for IEI during the perinatal period or early childhood
- **Extensive use of antibiotics** **masks the classic presentation** of many IEI diseases

The Ten Warning Signs of inborn errors of immunity

1. ≥ 4 new ear infections within 1 year
2. ≥ 2 serious sinus infections within 1 year
3. ≥ 2 months on antibiotics with little effect
4. ≥ 2 episodes of pneumonia within 1 year
5. Failure to thrive in an infant
6. Recurrent deep skin, or internal organ abscesses
7. Persistent oral candidiasis or fungal skin infections
8. Need for intravenous antibiotics to clear infections
9. ≥ 2 deep seated infections, including septicemia
10. A family history of IEI

Immunodysregulatory phenomena are common features of IEI:

- ***Allergies*** may be presenting features of some IEI syndromes, usually severe/refractory to conventional treatments.
- ***Lymphoproliferation*** can be a presenting feature
- ***Autoimmunity*** is a common feature of IEI e.g. autoimmune cytopenia, inflammatory bowel disease, and arthritis.

Some immunodeficiencies are recognized in the context of syndromes e.g. facial dysmorphic features and congenital cardiac abnormalities

Clinical features of IEI

PIDs often present with very common symptoms and signs

Major groups of inborn errors of immunity:

- Immunodeficiency affecting cellular and humoral immunity (T cell, B cell, NK cell)
- Predominantly antibody deficiency (B cell)
- Defects in phagocytes number or function (neutrophils, macrophages)
- Complement defects
- Autoinflammatory disorders (e.g. FMF)
- Diseases with immune dysregulation (prominent autoimmune/allergic features
- Bone marrow failure
- Others

Age of presentation, presenting symptom, site of infection and the pathogen identified helps to guide further work up.

Symptoms and signs that raise suspicion of PID:

The key to detect PID is to "Keep a high index of suspicion".

Medical History	Physical Examination
• Infections caused by an unexpected or opportunistic pathogen • Generalized long-lasting warts or mollusca contagiosa • Delayed (>4 weeks) separation of the umbilical stump • Unexplained bronchiectasis • Atypical autoimmune disease and/or lymphoproliferation • Family history of unexplained infant deaths, or consanguinity of the parents	• Dysmorphic features • Partial albinism, severe eczema, telangiectasia, or oral ulcers • Abnormal wound healing • Absence tonsils or lymphadenopathy • Lymphadenopathy and organomegaly • Ataxia,encephalitis/meningitis • Vasculitis
Imaging (Xray)	• Absent or small thymus (DiGeorge or SCID) • **Lungs:** pneumonia, bronchiectasis, granuloma, abscess, or pneumatoceles

	Combined T-cell and B-cell	Predominantly Antibody deficiency	Phagocyte and complement	PID syndromes
Onset age	0-6 months	6 months - 2nd decade	Any age	Any age
Isolated pathogens	**Intracellular & opportunistic organisms:** • Pneumocystis jirovecii • CMV • Candida.	**Extracellular organisms:** • Pneumococcus, • Haemophilus, • Giardia.	Staphylococcus, atypical Mycobacteria, Aspergillus Encapsulated bacteria (for complements)	Intra- and extracellular organisms
Clinical manifestations	• Interstitial pneumonitis (CMV, P. jirovecii) • Chronic diarrhea • Growth retardation • Malnutrition • Persistent oral thrush.	• Recurrent pneumonia • Otitis media • GE/Diarrhea • Skin infection • Bronchiectasis	• Liver • Skin or lung abcesses • Oral ulcers & Periodontitis • Delayed separation of umbilical stump • Poor wound healing	• Ataxia + Telangiectasia + Eczema + Purpura + Tetany + Cardiac anomaly + Facial dysmorphism.
Laboratory findings	• Lymphopenia • Abnormal lymphocyte subsets • Low IgG, IgA, IgM levels.	• Protein electrophoresis • Low IgA, IgG and/or IgM levels • B cell number	• Neutropenia/neutrophilia • NBT • DHR • CH50	• a-foetoprotein • Thrombocytopenia • Hypocalcemia • High IgE
Treatment	• HSCT • IV or SC immunoglobulin • Cotrimoxazole	• IV or SC immunoglobulin • Antibiotics	• Itraconazole • Cotrimoxazole, • G-CSF	• HSCT • Cotrimoxazole
Examples	**Severe combined immunodeficiency (1)**	• **X-linked agammaglobulinemia (2)** • CVID • Selective IgA deficiency	• Severe or cyclic neutropenia • **CGD (3)** • **LAD (4)** • Complement deficiencies	• **AT (5)** • **WAS (6)** • **DiGeorge syndrome (7)** • **Hyper IgE syndrome (8)**

G-CSF: Granulocyte-Colony stimulating factor, HSCT: Hematopoietic stem cell transplantation, NBT: Nitroblue tetrazolium test, DHR: Dihydrorhodamine, CH50: Complement hemolytic 50, IV: intravenous, SC: Subcutaneous, CVID: common variable immunodeficiency.

Specific examples

1. Severe combined immunodeficiency (SCID)

- Is the **most serious form of PID.** It is a **pediatric emergency.**

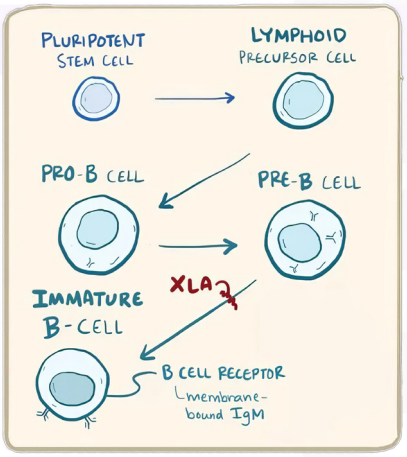
SCID may present with one or more of the following features;

- Neonatal sepsis
- Failure to thrive
- Persistent diarrhea
- Pneumonia
- Persistent oral thrush
- Disseminated BCG infection
- Persistent lymphopenia (ALC < 2800 X103/uL) with low or absent lymphocyte subsets.

Omenn syndrome

- A characteristic form of SCID that presents with generalized erythroderma, lymphadenopathy, hepatosplenomegaly, and elevated serum IgE.

2. X-linked agammaglobulinemia (Bruton disease)



Characterized by:

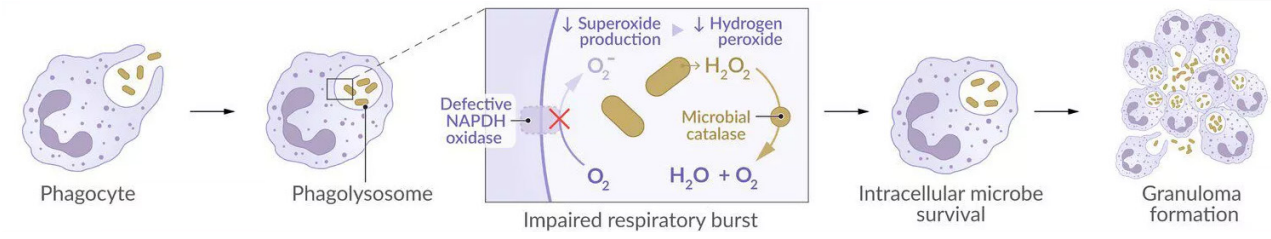
- **Small lymphoid tissues**
- **Low B cell** number (CD19)
- **Absent or very low** serum IgM, IgG and IgA
- **Increased susceptibility to infection** with entero-viruses (polioviruses, coxsachieviruses, and echoviruses)
- **High risk of post vaccination paralytic polio** with live-oral polio vaccine.

3. Chronic granulomatous disease (CGD)

- Due to **defective intracellular killing** of bacteria.
- Inherited as **autosomal recessive** (AR) or **X-linked**.

CGD is characterized by: Deep seated infection (granulomata) in liver, lungs, lymph nodes or bones due to staphylococcal infection (catalase-positive organisms), Candida or Aspergillus species.

The neutrophil oxidative burst can be assessed by the nitroblue tetrazolium (NBT) test or the dihydrorhodamine (DHR) test.

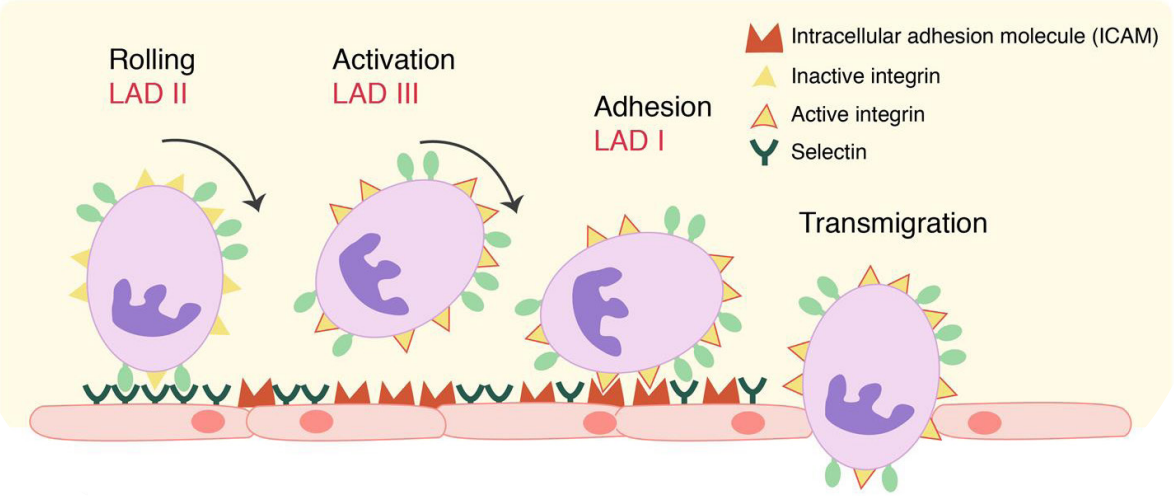


4. Leukocyte adhesion defect (LAD)

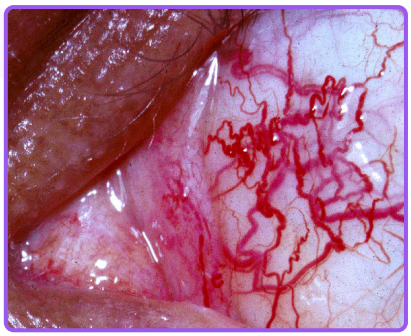
- An **autosomal recessive (AR)** disorder
- Involving the **common ß chain of the integrin molecule** that is essential for the leukocyte adhesion at site of infection.

The characteristic clinical features include:

- Delayed separation of umbilical stump
- Recurrent staphylococcus and gram negative bacterial infections
- Peri-rectal and peri-anal abscesses
- Absence of pus at sites of infection
- Severe dental affection
- Defective wound healing
- Disfiguring scars after trauma
- Marked leukocytosis (20,000 x 10^3/uL)
- Absent or very low expression of CD18/ CD11 on leukocytes.



5. Ataxia telangiectasia (AT)



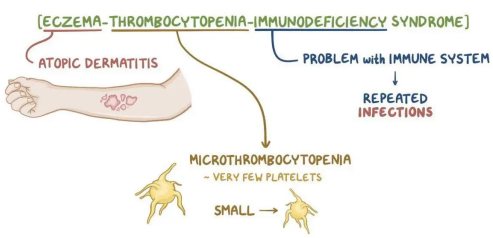
Is characterized by:

- Progressive cerebellar ataxia
- Ocular and/or facial telangiectasia
- Recurrent respiratory infections
- Low serum IgA
- High serum alpha fetoprotein
- Increased radiation induced chromosomal breakage in cultured cells.
- There is **high risk of leukemia and lymphomas** (10-15% of patients).

6. Wiskott-Aldrich syndrome (WAS)

Characterized by:

- Congenital thrombocytopenia with small platelets
- Recurrent infections and eczema.
- There is increased IgE and IgA, with low IgM.



7. DiGeorge syndrome (DS)

- Results from **deletion of chromosome 22q11.2.**

Characterized by:

- Absent thymus Cardiac defect
- Hypocalcemia
- **Dysmorphic facial features** (hypertelorism, long filtrum, fish-like mouth, small receding mandible and deformed ear auricle)
- Mental delay
- Lymphopenia (mainly T-cell deficiency).

8. Hyper IgE syndrome

Characterized by:

- Recurrent invasive infections and pneumatoceles due to staphylococcal pneumonia **(diagnostic feature).**
- Atypical eczema
- Skin abscesses
- Coarse facial features
- Delayed shedding of milk teeth
- Scoliosis
- **High serum IgE (> 800 IU/L).**

Work-up of PID

High index of suspicion

History

Age at onset of symptoms
Site and type and severity of infections
Allergies, autoimmunity
Number of hospital admissions
Response to treatment
Vaccine complications
Family history, consanguinity

Physical examination (General, Local)
Growth parameters, different systems affection

Exclude causes of 2ry immunodeficiency

Laboratory investigations

Laboratory evaluation of suspected cases

Principles:

- Use **age-matched reference values** to avoid misinterpretation of results
- Tests should be **repeated at least two times one week apart** before you consider diagnosis
- Check if there is **ongoing infections or medications received**, may cause abnormal immunological tests (e.g. anticonvulsant drugs may cause neutropenia, hypogammaglobulinemia).

A. Start with simple basic tests that are available in every health center and hospital.

1. Complete blood count (CBC) with differential: (NOT percentages)

- **Absolute neutrophil count (ANC)** for neutropenia (< 500 x 10^3/L) neutrophilia (> 20,000 X103/L).
- **Absolute lymphocyte count (ALC)** for lymphopenia (< 3000 x 10^3/L at birth & < 2800 X10^3/L in infancy). **In case of lymphopenia, exclude HIV infection.**
- **Platelet count** including mean platelet volume (MPV), needed for Wiskott-Aldrich syndrome (WAS).

2. Serum immunoglobulin levels (IgM, IgG, IgA and IgE).

3. Mantoux test (MT) to detect **mycobacterial infection.**

4. Blood culture.

Suspect T cell defect (combined immunodeficiency) when:

- ALC< 3000 x 10^3/uL at birth
- 2800 x 10^3/uL during infancy

B. According to results of the initial laboratory test

One or more of specific immunological tests (done at a specialized PID center):

1. Basic protocol for in vitro determination of lymphocyte subpopulations and function

A. Absolute count of lymphocyte subpopulations (NOT percentages)

- CD3 +
- CD3+/CD4+
- CD3+/CD8+
- CD19+
- CD56 and/or CD16
- Pan T lymphocytes
- Helper-T lymphocytes
- Cytotoxic T lymphocytes
- B lymphocytes
- NK cells

B. T cell function

- **Mitogens:** Phytohemagglutinin (PHA) test
- **Antigens:** Tetanus antibodies after booster vaccination, intradermal candida test

2. Determination of granulocyte function (Oxidative burst and flow cytometry)

- Flow cytometric analysis using dihydrorhodamine test (DHR)
- Nitroblue tetrazolium test (NBT)
- Immunophenotyping (CD18, CD11)

3. Complement assay

- Measurement of specific components (C1q, C4, C2, , factor I, factor H, properdin)
- Functional assay (complement hemolytic assay; CH50)

4. Genetic studies

Form an essential part of the investigation and management of PID, and include:

- Cytogenetics (deletion, translocation)
- 22q11 micro deletions (FISH-fluorescent in situ hybridization)
- Prenatal diagnosis
- Carrier detection

Management

Early diagnosis & treatment of PIDs saves lives, prevents morbidity, and improves QoL.

Treatment for IEI aims to:

- Minimize infection frequency, severity, and complications
- Prevent complications of underlying disease
- Correct the immunodeficiency where possible.

General management

- **Early referral** to specialized center.
- **Diet:** Failure to thrive.
- **General management:** Germ-free environment, isolation.
- **Antibiotics:** in acute illness and as prophylaxis.
- **Careful use of blood and blood products:** Avoid whole blood transfusion in combined immunodeficiency, for **fear of GVHD.**
- **Avoid live vaccines:** BCG, OPV, rota virus, measles, MMR, yellow fever and oral typhoid.

Specific treatment

- **Immunoglobulin G (IVIG) replacement therapy** for those who do not produce functional immunoglobulins e.g. for **Predominantly antibody defects**
- **GM-CSF** temporarily for **severe congenital neutropenia till HSCT**
- **Immune reconstitution by haematopoietic stem cell transplant (HSCT)** to cure the immunological defect by inserting healthy haematopoietic progenitors into the host bone marrow that will in turn produce a functional immune system **(curative therapy e.g. for combined and phagocyte disorders; SCID requires HSCT as early as possible).**
- Specific treatments aimed at the **molecular defect** are being developed
- **Gene therapy** is a promising avenue of research with treatments aimed at single gene defects.

Prognosis of PID

The fate of children with PID rests on three pillars:

- Timely recognition (Early diagnosis offers better prognosis)
- Adequate therapy and follow up
- The nature of the underlying disease

Precautions that should be considered in suspected/diagnosed cases

- Give only irradiated cytomegalovirus (CMV) negative blood and blood products in any suspected case or proven T-cell defect Do not immunize with BCG, or live virus vaccines such as MMR, oral polio vaccine (OPV), varicella and rota virus.
- PID patients can be given killed vaccines like DPT, HAV and conjugate vaccines (Hib, Typhoid, HBV and Pneumococcal).
- Treat infections aggressively with antibiotics, antiviral and antifungal agents.
- Before you give intravenous immunoglobulin (IVIG), save serum sample for later analysis.
- Do not delay referral of suspected cases to a specialized center until you obtain laboratory results that support your suspicion.

Secondary Immunodeficiency Disorders

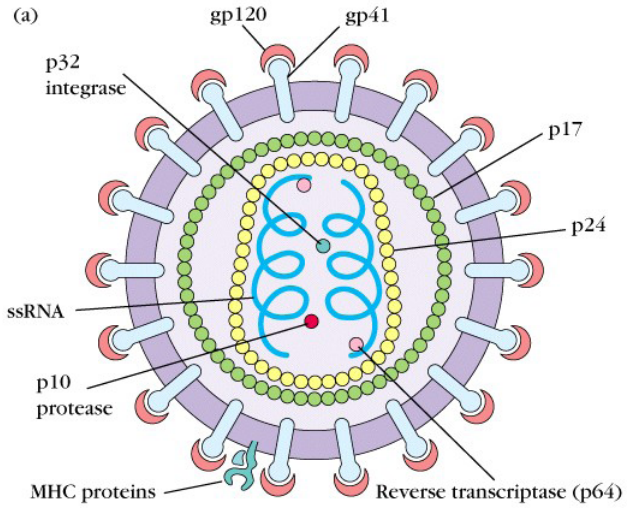
Causes of secondary immunodeficiency:

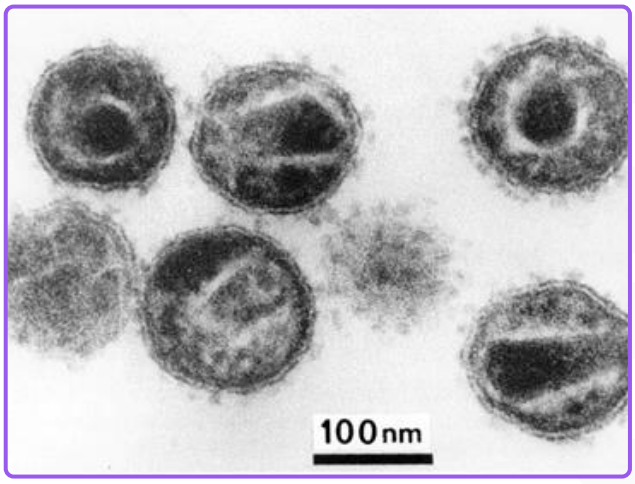
- **Infections:**
  - Viral infections (HIV, CMV, EBV, rubella)
  - Chronic bacterial infection (TB)
  - Parasitic infestation (malaria, leishmania).
- Prematurity/old age.
- Malignancy (lymphoma/leukemia)
- Drugs (captopril, gold salts, carbamazepine, phenytoin, penicillamine, sulfasalazine, antimalarial, steroid and cytotoxic drugs)
- Radiation/Toxins.
- Protein-calorie malnutrition
- Chronic renal failure.
- Protein losing enteropathies.
- Metabolic diseases (eg; Diabetes mellitus).
- Excessive burn.
- Transfusion therapy/Plasmapheresis
- Splenectomy

Human Immunodeficiency Virus (HIV) & Acquired Immunodeficiency Syndrome (AIDS)

Structure of HIV

- HIV-1 is a member of the Retroviridae family (Lentivirus genus); HIV-1 genome is single stranded RNA (ssRNA).





Transmission

Sexual contact.

Blood transfusion.

Vertical transmission:

- **Intrauterine (30%)**
- **Intrapartum** (highest percentage of transmission **70%**)
- **Postpartum** (**breast-feeding risk:** 28% of infants born to mothers who acquire infection while nursing versus 18% of infants born to HIV infected mothers before pregnancy)

Risk Factors influencing vertical transmission

- Preterm delivery (< 34 weeks gestation).
- Birth weight < 2500gm.
- Ruptured membranes > 4hr.
- Vaginal delivery.
- Low maternal antenatal CD4 count.
- High maternal viral load (> 50,000 copies/ml)

How does HIV affect the immune system?

- HIV specifically **attacks the T helper (CD4) cells**
- HIV antibodies produced by the immune system are unable to overcome the infection
- Over time, HIV progressively weakens the immune system; The individual becomes immunodeficient.
- The weak immune system can no longer effectively defend the body against opportunistic organisms.

Immunological derangements with HIV infection

B-cells

- Polyclonal activation
- Hypergammaglobulinemia
- Loss of specific Ab responses

CD4

- Depletion
- Impaired functions
- Impaired cytokines function
- Opportunistic infections

CD8: Impaired cytokine responses and cytolytic activity.

NK

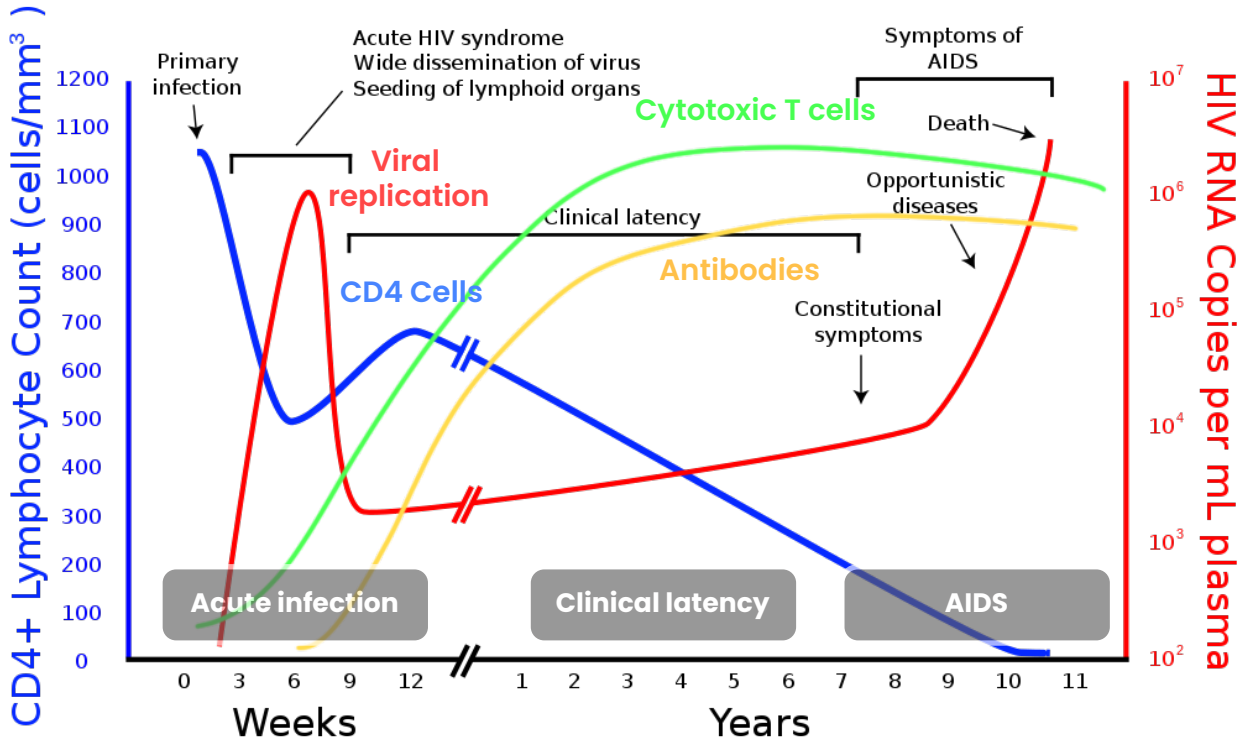
Neutrophils

Monocytes

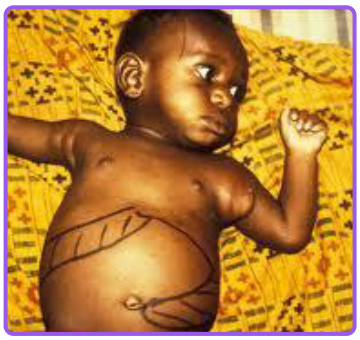
Thymus

Bone marrow

Stages of HIV infection



Clinical Picture



- Failure to thrive, oral candidiasis, chronic diarrhea
- Recurrent infection (opportunistic organisms)
- Lymphopenia (mainly T helper cells)
- Generalized lymphadenopathy
- Hepatosplenomegaly
- Progressive developmental delay
- Lymphoid interstitial pneumonitis (LIP), Pneumocystis pneumonia (PCP)
- Parotitis, cardiomyopathy, chronic hepatitis, nephropathy and malignancies.

Laboratory tests

Lymphopenia with hypergammaglobulinemia

- **High blood viral load (HIV-RNA)** by PCR. It is sensitive for **early diagnosis and follow up.**
- **Low T helper (CD4) cell count**
- **High T suppressor (CD8) cell** **specific for HIV.**
- **Specific HIV antibodies** such as anti-p24, anti-envelope Abs (Not helpful in recent HIV infection)

Treatment

There is no curative treatment.

- Treatment provides **control of infection and offers a better quality of life.**
- **Prognosis with treatment is better**
- **Life-long treatment with a combination of antiretroviral drugs** including zidovudin, didanosine, abacavir, lamivudine.
- **Antimicrobial drugs** (Prophylaxis and treatment).

Highly active anti-retroviral therapy (HAART): A combination of 3 or 4 drugs

- **Reverse transcriptase inhibitors:** Nucleoside & Non-nucleoside analogues
- **Protease inhibitors**
- **Adjuvant drugs:** IL-2, hydroxyurea, G-CSF and L-acetyl carnitine

END.

Questions

1. Which statement is false in the management of anaphylaxis?

A. Antihistamines may improve urticaria and itching but are not life saving
B. Hypotension is treated by saline 0.9% infusion
C. Absorption of subcutaneous epinephrine is too slow to save the patient's life
D. Beta blockers are used to treat hypertension in patients with anaphylaxis
E. The dose of epinephrine is 0.01 mg/kg body weight per dose

D

2. The mainstay of treatment of atopic dermatitis is:

A. Oral antibiotics
B. Topical corticosteroids
C. Systemic glucocorticoids
D. Epinephrine
E. All of the above

B

3. The following are true about urticaria/angioedema except:

A. It is a common allergic disorder in children
B. Not caused by local contact with allergens
C. Food allergy is a common cause
D. It is usually a self-limiting condition.
E. Oral antihistamines are the main stay of therapy.

B

4. Clinical manifestations of anaphylaxis include:

A. Flushing, urticaria or angioedema
B. Hypotension
C. Respiratory distress
D. Abdominal cramps
E. All of the above

E

5. The following statement is true about childhood allergic rhinitis:

A. Symptoms are intermittent and never persistent
B. Symptoms include paroxysmal sneezing, and nasal itching
C. Dark circles under the eyes are have no relation to its pathology
D. The child with allergic rhinitis rarely develops asthma
E. Systemic steroids are the main line of therapy

B

6. The following statement is true about allergy diagnosis:

A. Specific IgE assay can diagnose cell-mediated allergic reactions
B. Total IgE is usually elevated in atopic persons but may be elevated in other conditions
C. Skin prick testing is not sensitive in allergen detection
D. Challenge tests are safe but less accurate in allergen detection.
E. History taking is of limited role in guiding allergy diagnosis

B

7. One of the following statements is true about septic arthritis:

A. Staph. aureus is the most commonly incriminated organism
B. It is more common in males with a peak age >5 years
C. It is polyarticular in over 90% of cases
D. Blood culture and ESR usually reveals no abnormalities
E. Oral antibiotic therapy for 10 days is sufficient treatment

A

8. A 4-year old boy presented in the emergency room by his mother. Three days ago, he developed fever, rash over his legs and feet and abdominal pains with recurrent vomiting. On examination, his vital signs are normal. His abdomen is tender to palpation and he has a palpable purpuric rash on his feet and lower legs associated with diffuse non-pitting edema. The most appropriate next step for this patient is:

A. Administration of ibuprofen or paracetamol.
B. Urine analysis.
C. Blood culture.
D. Administration of systemic steroids.

D

9. In Kawasaki disease, all are true except:

A. Unexplained fever of more than 5 days' duration.
B. In acute phase, C-reactive protein is usually normal.
C. Bilateral non-suppurative conjunctivitis.
D. Pharyngeal injection, dry fissured lips, injected lips, and "strawberry" tongue.

B

10. All are clinical features of systemic lupus erythematosus except:

A. Photosensitivity.
B. Gottron papules
C. Alopecia.
D. Arthritis.

B

11. A 4-year old girl presented to your office by her mother. She has a daily recurring spiking fever associated with evanescent rash of 2 weeks duration. On examination, she has fever (39oC), with faint salmon-colored urticarial rash over the trunk. She has mild arthralgia of her knees and ankles. She has mild generalized lymphadenopathy and mild hepatosplenomegaly. The most appropriate initial investigation for this patient is:

A. Complete blood picture with differential count.
B. Bone marrow aspirate.
C. Serum Ferritin.
D. Rheumatoid factor

A

12. Patients with active dermatomyositis have all of the following except:

A. Bilateral, proximal and symmetrical muscle weakness .
B. Heliotrope discoloration around the eyes.
C. Normal muscle enzymes.
D. Skin rash over the face and cheeks.

C

13. Intravenous immunoglobulin is the main stay of treatment of which disease:

A. Henoch-Schonlein purpura.
B. Systemic onset juvenile idiopathic arthritis.
C. Kawasaki disease.
D. Selective immunoglobulin A deficiency.

C

14. The presence of failure to thrive together with post – vaccination disseminated BCG infection and marked lymphopenia can describe:

A. Selective IgA deficiency.
B. Severe combined Immunodeficiency.
C. Common variable immunodeficiency.
D. X-linked agammaglobulinemia.

B

15. Low B-cell count with absent all immunoglobulins (IgG,IgM,IgG) in a 7 months old infant can describe:

A. X-linked agammaglobulinemia.
B. DiGeorge Syndrome.
C. Chronic granulomatous disease.
D. Common variable immunodeficiency.

A

16. Increased susceptibility to Neisseria Meningitidis is found in which type of primary immunodeficiency (PID):

A. B-cell deficiency.
B. T-cell deficiency.
C. Phagocytic deficiency.
D. Complement deficiency.

D

17. Common variable immunodeficiency (CVID) is a primary immunodeficiency where there is a defect in:

A. Humoral immunity defect.
B. T-cell defect.
C. Phagocytic defect.
D. Non of the above.

A

18. Primary immunodeficiency(PID) should be suspected in all of the following except:

A. Multiple infections despite aggressive therapy.
B. Unusual infection site e.g. osteomyelitis, liver abscess
C. Infection by an opportunistic organism.
D. Delayed teething.

D

19. Leucocyte adhesion defect (LAD) is a primary immunodeficiency where the defect is sorted in:

A. Humoral immunity.
B. T-cell .
C. Phagocytes.
D. Combined B and T-cell defect.

C

20. Tuberculosis test or candida skin test can be used to show :

A. How well T-cell are functioning.
B. How well B-cell are functioning.
C. How well phagocytes are functioning.
D. Non of the above.

A

21. A 4-yr-old white girl has had a low-grade fever, intermittent crampy abdominal pain with emesis, and swollen knees for 3 days. There is a petechial rash on the lower extremity. The most likely diagnosis is:

A. Meningococcemia
B. Idiopathic Thrombocytopenia Purpura
C. Henoch-schonlein Purpura
D. SLE
E. Rocky Mountain Spotted Fever

C

22. Organisms associated with reactive arthritis include:

A. Shigella
B. Chlamydia trachomatis
C. Yersinia enterocolitica
D. Campylobacter jejuni
E. All of the above

E

23. A 12-yr-old presents with sneezing, clear rhinorrhea, and nasal itching. examination reveals boggy, pale nasal edema with a clear discharge. The most likely diagnosis is:

A. Foreign body
B. Vasomotor rhinitis
C. Neutrophilic rhinitis
D. Nasal Masto-cytosis
E. Allergic rhinitis

E

24. Useful test for evaluation of possible B-cell (antibody) deficiency include all of the following except:

A. Isohemagglutinins
B. Antibodies to tetanus
C. Flow cytometry for CD3 + T cells
D. Serum IgA level
E. Total IgG level

C

25. Primary immunodeficiency (PID) should be suspected in all of the following except:

A. Multiple infections despite aggressive therapy.
B. Unusual infection site e.g. osteomyelitis, liver abscess
C. Infection by an opportunistic organism.
D. Recurrent hospital admission due to asthma exacerbation.

D

26. A 9-yr-old girl reports that she has had difficulty combing her hair and walking up stairs for approximately 1 mo. Physical examination reveals a positive Gowers sign and a faint maculopapular rash over the metacarpophalangeal joints. The most appropriate laboratory study to order is:

A. Determination of erythrocyte sedimentation rate
B. Measurement of serum creatine kinase level .
C. Rheumatoid factor
D. Motor nerve conduction study
E. Assay for antinuclear antibodies

B

27. A 4-yr-old Middle Eastern boy presents with a history of brief acute episodes of fever and abdominal pain. The most likely diagnosis is:

A. Behçet syndrome
B. Sjogren syndrome
C. Juvenile dermatomyositis
D. Familial Mediterranean fever

D

28. Features of the complete DiGeorge syndrome include susceptibility to infection and:

A. Neonatal hypocalcemia
B. Anomalies of the great vessels
C. Graft versus host disease after blood transfusion with nonirradiated blood
D. Micrognathia
E. Onset of infections after age 12 mo.

E

29. All of the following are prominent features of Wiskott-Aldrich syndrome except:

A. Atopic dermatitis
B. Thrombocytopenia
C. Recurrent infections with encapsulated bacteria
D. Autosomal dominant
E. More frequent occurrence in males

D

CASE 1

13 year-old girl, She describes a two month history of general malaise and decreased energy. Her mother states that her daughter has felt "feverish" on and off for the last 2 months. She used to play soccer regularly, but she has stopped participating not only because she feels "too run down" but she has also been having pain and stiffness in her left knee. Last week when she was out in the sun with her classmates she developed a rash on her cheeks. with puffy eye lids.

Physical Exam: Vitals (tachypnea, hypertension) , Alopecia, Facial rash , Oral ulcers , Lymphadenopathy

Thorough respiratory and cardiovascular exam, Thorough GI exam, Complete detailed MSK for assessing arthritis

After you complete your exam you begin to think about further investigations.

1. Which tests would you like to send this patient for?

SLE Investigations:

Start with your more 'basic' workup

- CBC with diff, retics, Cr, Urea, ESR, CRP, urinalysis including microscopy, urine protein: creatinine ratio
- AST, ALT, albumin, INR, PTT (can have liver dysfunction in the form of acute autoimmune hepatitis and coagulation abnormalities)
- ANA, C3
- Consider infection (either DDx or trigger of a flare of SLE): Depending on the patients features -parvovirus, respiratory panel, CMV, EBV, blood and urine culture (consider)
- More extensive work-up: Anti ds DNA, Anti-phospholipid antibodies
- As symptoms indicate: CXR, ECG, echo
- Other investigations and consultations as necessary

2. How can you treat this case?

Treatment approach:

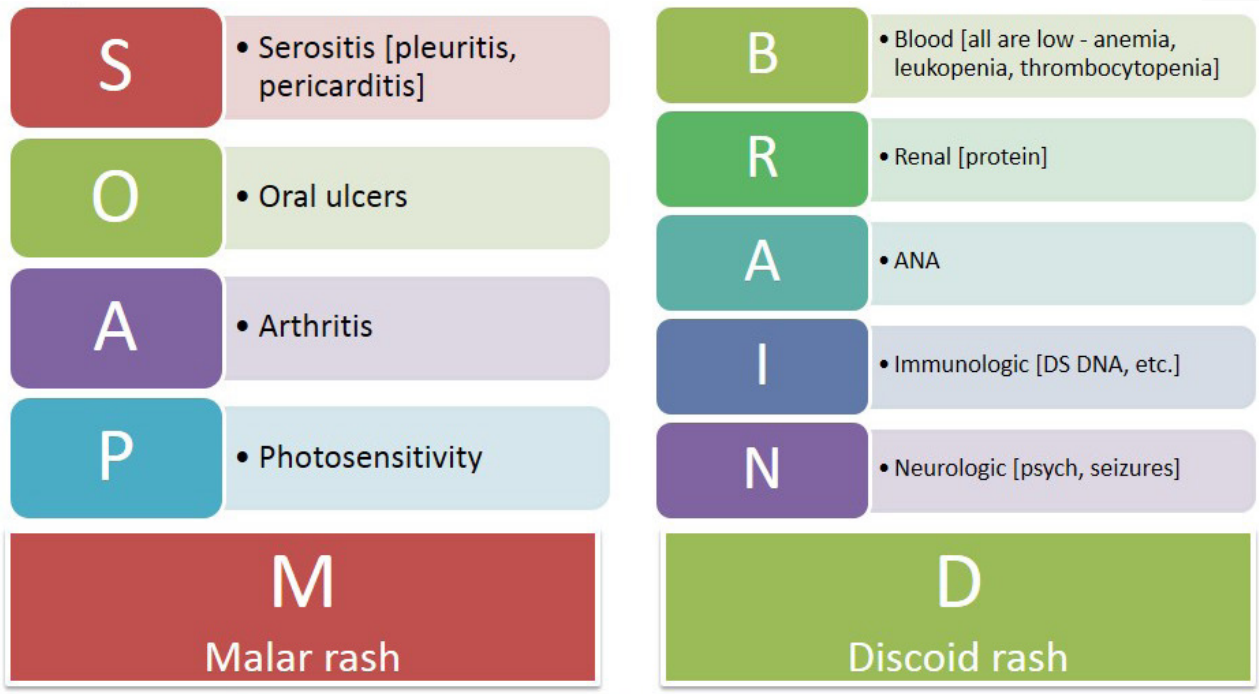
- Non-pharmacologic – sun protection is key to preventing rashes and avoiding flares
- Pharmacologic treatment (these would all be initiated in conjunction with advice from pediatric rheumatology)
  - A. Hydroxychloroquine (Plaquenil) for MSK and skin manifestation
  - B. NSAIDS (If no renal involvement)
  - C. Steroids (from low dose oral to high dose IV steroids)
  - D. biologic medications or cytotoxic drugs

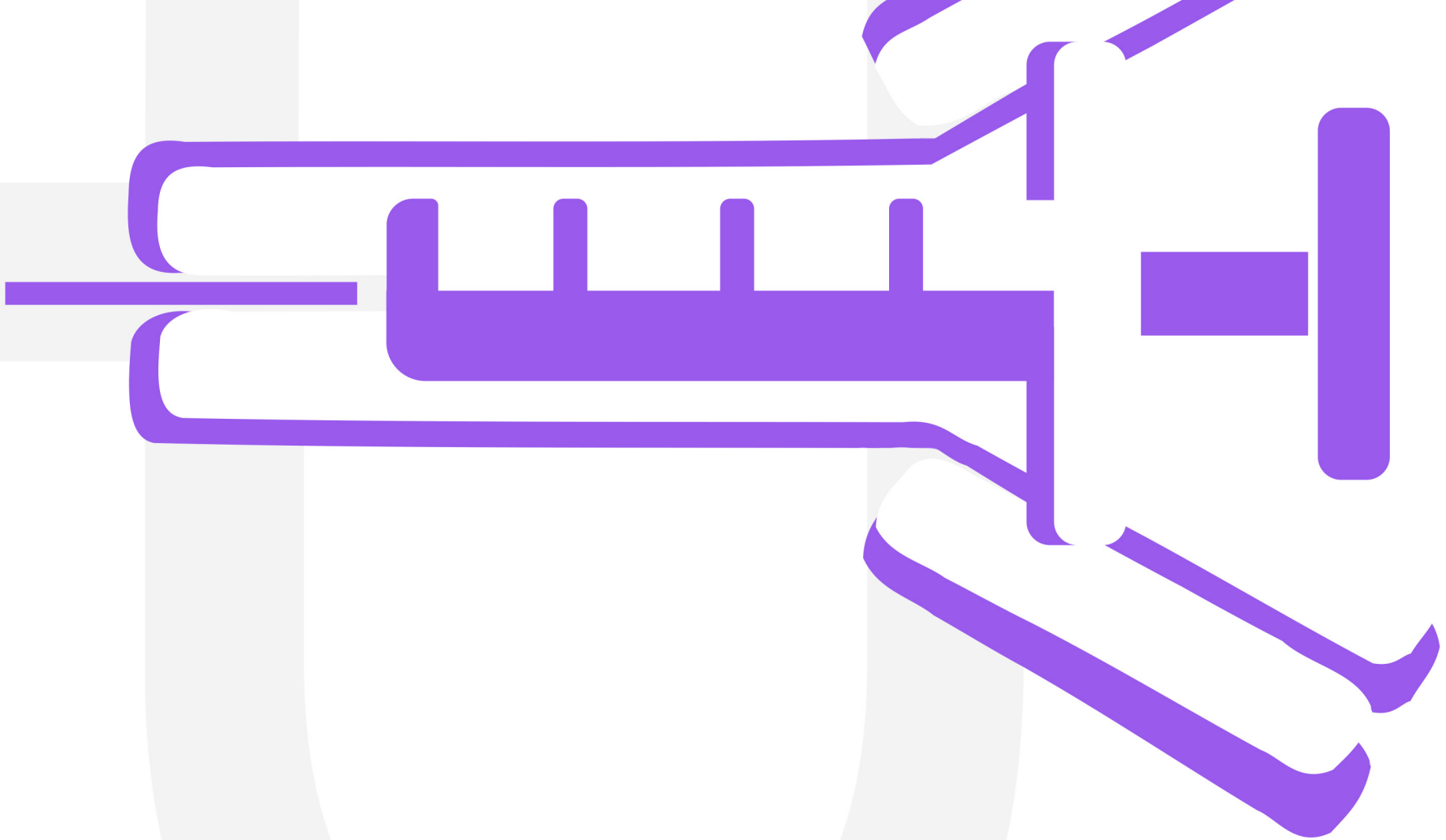
3. What are the classification criteria?

One needs to meet at least 4 of 11 ACR criteria.

11 criteria you can use a helpful pneumonic to remember them! The pneumonic is MD SOAP BRAIN

- M- Malar rash – erythematous rash over the malar eminences, a 'butterfly rash'. It can be flat or raised, and tends to spare the nasolabial folds
- D- Discoid rash – this is a raised, scaling and scarring rash. It is extremely rare in pediatric patients
- S- Serositis – literally means 'inflammation of a serous membrane'; most commonly involving the heart or lungs in SLE,
- O- Oral/Nasal ulcers – this ulceration is usually painless, and is often on the palate or nasal septum
- A- Arthritis – this is non-erosive arthritis involving two or more peripheral joints, tenderness, decreased range of motion, and effusion.
- P- Photosensitivity – rash from sun
- B– Blood abnormalities – hemolytic anemia (with reticulocytosis), leukopenia, lymphopenia and thrombocytopenia.
- R– Renal dysfunction – 6 classes of SLE nephritis range from asymptomatic to severe nephritic or nephrotic syndrome.
- A– ANA positive – This is anti-nuclear antibody. Essentially all patients with SLE are ANA positive.
- I– Immunologic – antibodies, including anti-ds-DNA, anti-Smith, anticardiolipin antibodies and lupus anticoagulant.
- N– Neurologic – Lupus can present with a wide array of central and/or peripheral signs and symptoms. This can be anything from headaches and difficulty concentrating to seizures and psychosis.





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