Connective tissue diseases

Dr. Dhikra Nabil

Connective tissues

Two proteins:

1. Collagen: tendons, ligaments, skin, cornea, cartilage, bone, and blood vessels.
2. Elastin: ligaments and skin

Connective tissue diseases

- Rheumatoid Arthritis(RA)
- Scleroderma
- Granuolomatosis with polyangiitis
- Chrug- Strauss syndrome
- Systemic Lupus Erythematosus (SLE)
- Microscopic polyangiitis(MPA)
- Polymyositis/ dermatomyositis
- Mixed Connective Tissue Disease (MCTD)
- Undifferentiated connective tissue diseases

Causes

- Genetics
- Environmental

Arthritis

- Swelling or effusion, or presence of two of the following:
  - Limitation of range of motion
  - Tenderness or pain of motion
  - Increased heat in the joint
- A manifestation of several disorders

Review of system in the differential diagnosis of childhood joint pain and swelling

Dermatologic	SLE	Malar rash and hair loss
	Dermatomyositis	Gottron's papules
	Systemic JIA	Evanescent pink macular rash
	HSP	Lower extremity purpuric lesions

Ophthalmologic	Oligoarthritis or psoriatic JIA	Asymptomatic chronic anterior uveitis
	Enthesitis related arthritis	Acute symptomatic uveitis (pain, redness)
	Kawasaki disease	Conjunctival injection without discharge
	Sjogren's syndrome	Dry eyes with keratitis
Oral	SLE	Painless oral ulcers on palate
	Behcet Disease	Large extremely painful oral ulcers

Respiratory	CF or immunodeficiency	Recurrent pneumonia
	Wegener's granulomatosis	Destructive upper tract lesions
	SLE or systemic JIA	Pleuritis
	SLE or scleroderma	Interstitial lung disease
	Churg-Strauss syndrome	Eosinophilic pneumonia
Cardiovascular	ARF or endocarditis	New heart murmur
	SLE, systemic JIA, or ARF	Pericarditis
	SLE or scleroderma	Raynaud phenomenon
	Takayasu arteritis	Absent pulses

Gastrointestinal	IBD, SLE, or vasculitis	Weight loss or poor growth
	IBD	Diarrhea and abdominal pain
	Reactive arthritis	Preceding infectious gastroenteritis
	HSP	Intermittent colicky abdominal pain
Genitourinary	Gonococcal arthritis	Pustular urethritis or cervicitis
	Reactive arthritis	Non-gonococcal urethritis
	Behcet disease or IBD	Large painful genital ulcerations

Hematologic	SLE or hemoglobinopathy (eg, SCD)	Hemolytic anemia
	SLE	Pancytopenia
	Bleeding disorders	Hemarthrosis
Neurologic	SLE	Seizures and psychosis
	SLE or fibromyalgia	Difficulty concentrating
	SLE, vasculitis, or hypercoagulability	Stroke
	Vasculitis	Asymmetric polyneuropathy
	Dermatomyositis and polymyositis	Proximal muscle weakness

Classification of childhood arthritis

- American College of Rheumatology (ACR)
- European League Against Rheumatism (EULAR)
- International League of Associations for Rheumatology (ILAR)

Rheumatic diseases

defined by the constellation of results of the physical examination, autoimmune marker and other serologic tests, tissue pathology, and imaging.

-JIA

-SLE

- JUVENILE DERMATOMYOSITIS

Juvenile Idiopathic Arthritis (JIA)

Juvenile Idiopathic Arthritis (JIA)

- Is a common, rheumatic disease of children and a major cause of chronic disability.
- It is characterized by a synovitis of the peripheral joints manifesting in soft tissue swelling and effusion.

JIA classification

- **Systemic onset JIA (SoJIA)**

  arthritis with fever and rash.

- **Oligoarthritis**

  < 5 joints in the first 6 months of illness.

- **Polyarthritis**

  > 4 joints in the first 6 months of illness.

Psoriatic arthritis	Arthritis and psoriasis, or arthritis and at least 2 of the following: 1. Dactylitis‡ 2. Nail pitting§ and onycholysis 3. Psoriasis in a 1st-degree relative
Enthesitis-related arthritis	Arthritis and enthesitis,‖ or arthritis or enthesitis with at least 2 of the following: 1. Presence of or a history of sacroiliac joint 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 inflammatory bowel disease, Reiter syndrome, or acute anterior uveitis in a 1st-degree relative
Undifferentiated arthritis	Arthritis that fulfills criteria in no category or in ≥2 of the above categories.

- Eighteen-month-old girl with arthritis in her right knee. Note the flexion contracture of that knee.

Criteria for the Classification of Juvenile Rheumatoid Arthritis
Age at onset: <16 yr
Arthritis (swelling or effusion, or the presence of 2 or more of the following signs: limitation of range of motion, tenderness or pain on motion, increased heat) in ≥1 joints
Duration of disease: ≥ 6 wk
Onset type defined by type of articular involvement in the 1st 6 mo after onset:
Polyarthritis: ≥5 inflamed joints
Oligoarthritis: ≤4 inflamed joints
Systemic disease: arthritis with a characteristic intermittent fever
Exclusion of other forms of juvenile arthritis

ETIOLOGY.

- Unknown etiology
- Autoimmune disease AND Genetic susceptabilty factors
- Environmental (infection,trauma,and stress).
- Possible external triggers include viruses (parvovirus B19, rubella, Epstein-Barr virus),
- Host hyperreactivity to specific self antigens (type II collagen), and enhanced T-cell reactivity to bacterial or mycobacterial heat shock proteins.

EPIDEMIOLOGY.

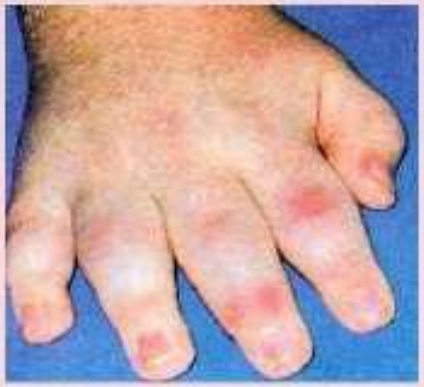
- **Describe in all races and geographical areas**
- **The incidence of JRA is ≈13.9/100,000 children/yr among white children ≤15 yr of age, with a prevalence of ≈113/100,000 children.**
- **Female predominance 2:1**

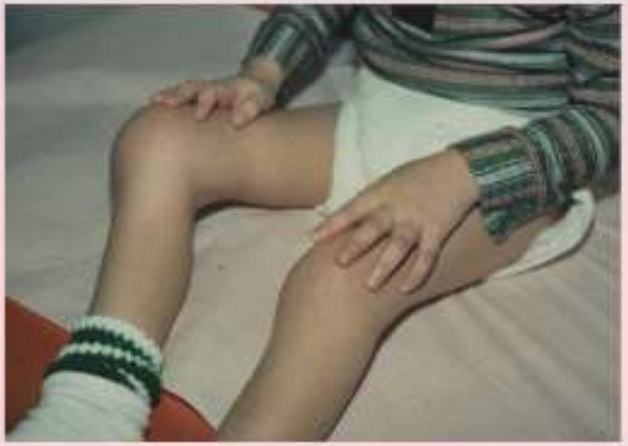
CLINICAL MANIFESTATIONS

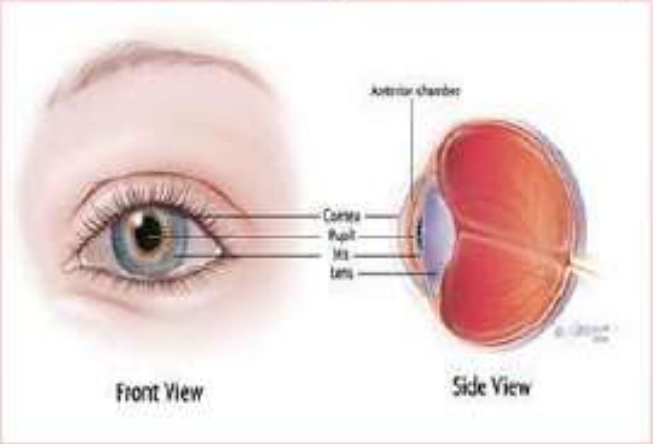
Initial symptoms

- **subtle or acute**
- **morning stiffness**
- **easy fatigability, particularly after school in the early afternoon**
- **joint pain**
- **joint swelling**
- **Joint stiffness**
- **limp**
- **Restriction of movement**
- **Eye symptoms**
- **Systemic manifestation .**

Clinical Manifestations of JRA

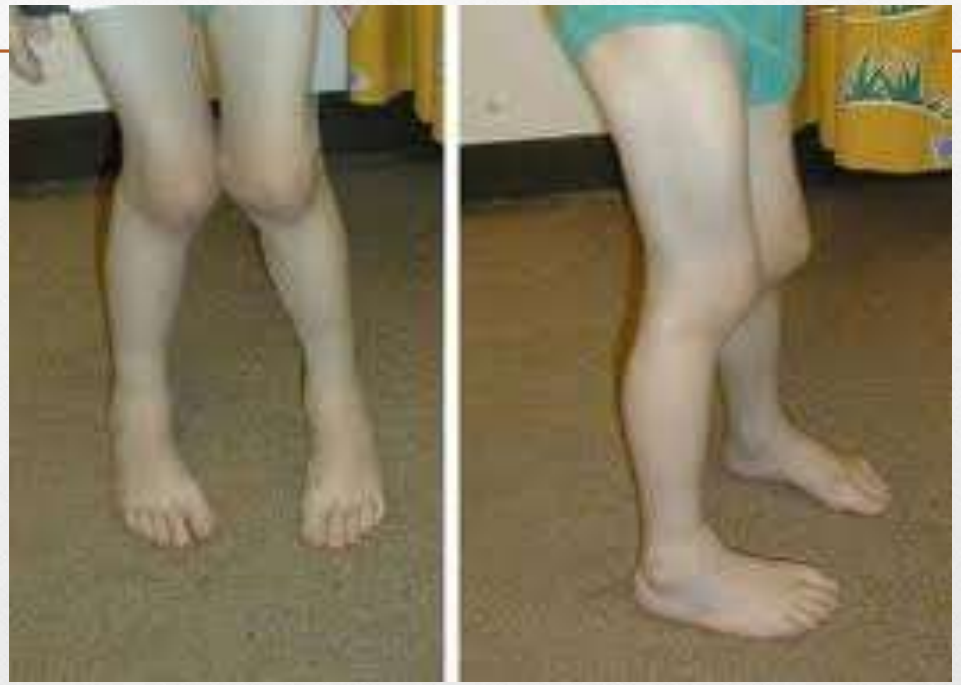






Oligoarthritis (pauciarticular disease)

- Persistent vs. extended
- predominantly affects the joints of the lower extremities, such as the knees and ankles .
- Isolated involvement of upper extremity large joints is not characteristic of this type of onset.
- Involvement of the hip is almost never a presenting sign of JRA.

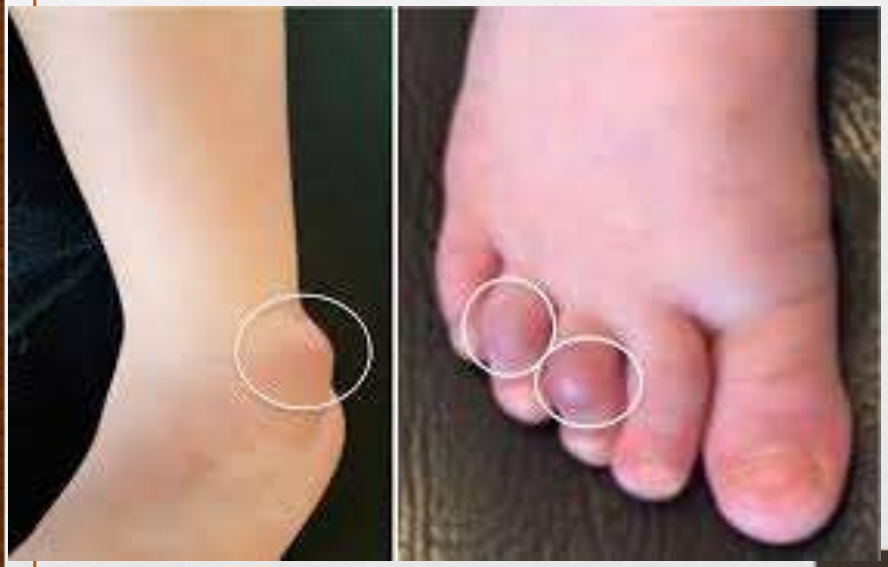


Polyarthritis

- is generally characterized by involvement of both large and small joints of both upper and lower extremities .
- As many as 20–40 joints may be affected in the more severely involved child, although inflammation of only ≥5 joints is required as a criterion for classification of this type of onset.
- Rheumatoid factor (+ve / –ve)

- **Rheumatoid nodules on the extensor surfaces of the elbows and over the Achilles tendons, while unusual, are associated with a more severe course**
- **Micrognathia reflects chronic temporomandibular joint disease.**
- **Cervical spine involvement of the apophyseal joints occurs frequently with a risk of atlantoaxial subluxation and potential neurologic sequelae.**


© Jere Mammino, DO



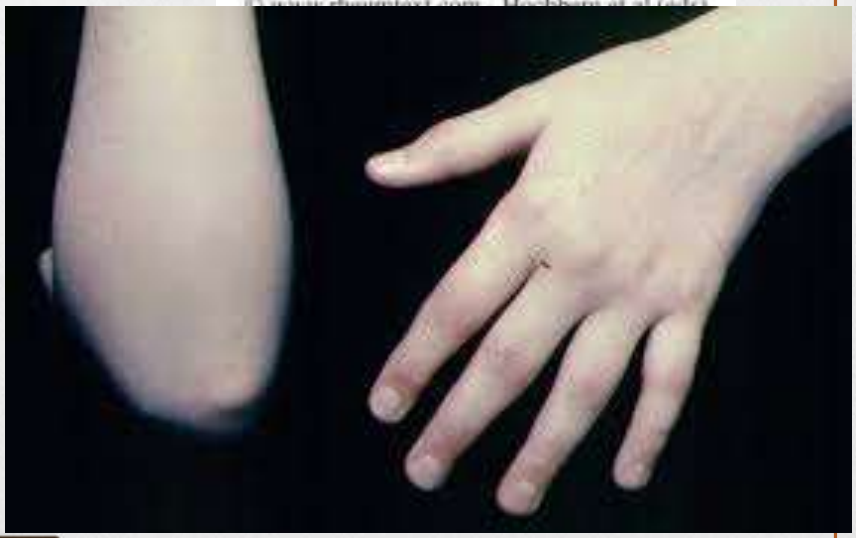
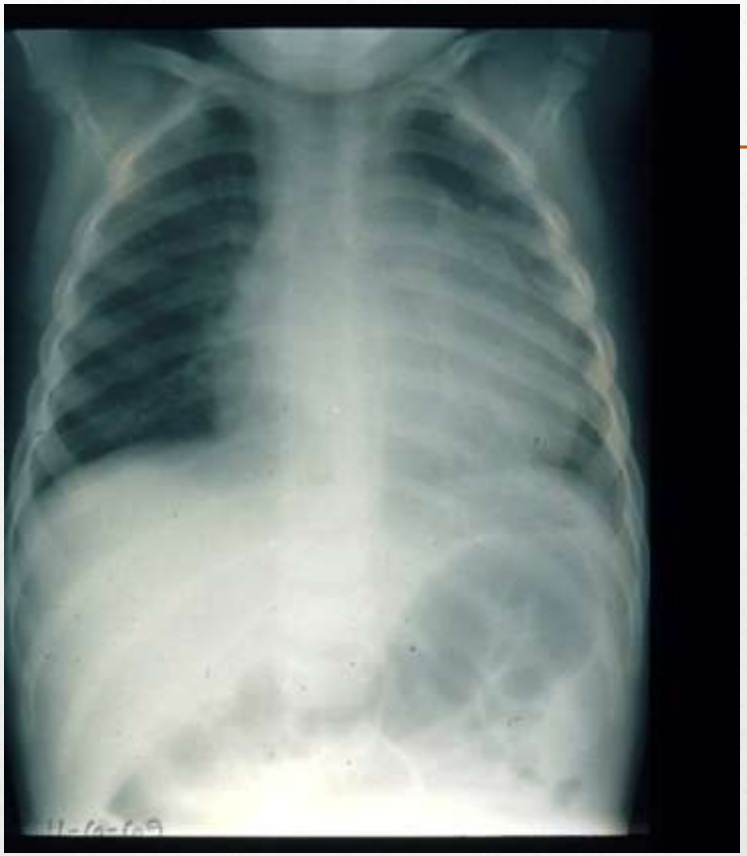


Table 1: Systemic JIA ILAR Classification Criteria[1]

1. Fever ≥2 weeks, quotidien in pattern (≥39°C at least once a day and returns to ≤37°C), documented daily for ≥3 days

2. Arthritis in ≥1 joint (for ≥6 weeks)

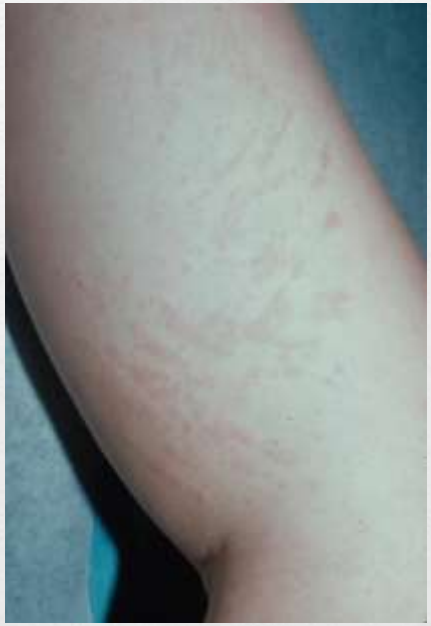
3. At least one of the following:
   - >Evanescent erythematous rash;
   - >Generalized lymph node enlargement;
   - >Hepatomegaly and/or splenomegaly; or
   - >Serositis

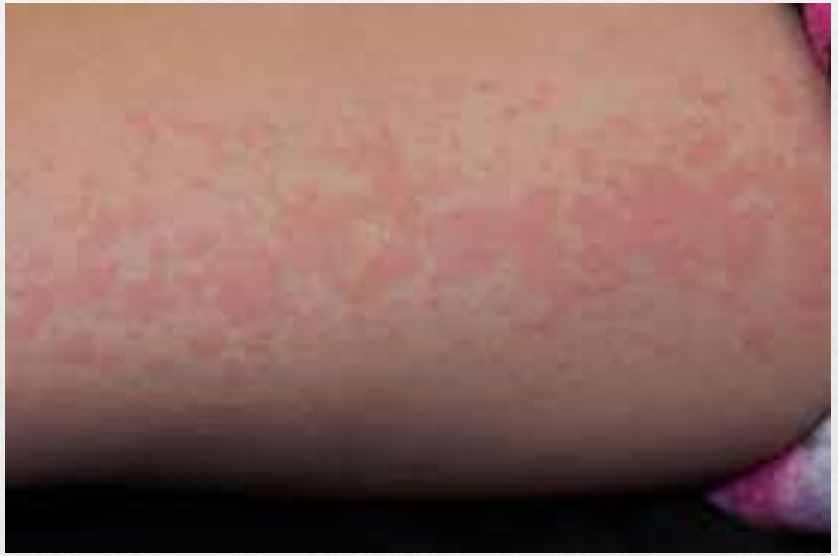


- Child with pericardial effusion due to systemic onset juvenile idiopathic arthritis (JIA).
- serositis (pericarditis)

Systemic juvenile idiopathic arthritis (JIA) rash

- Salmon-colored, erythomatous non pruritic macules





DIAGNOSIS

- **Based on a history compatible with inflammatory joint disease and a physical examination that confirms the presence of arthritis**
- **No one pathognomonic finding**
- **The classic intermittent fever , the typical rash and objective arthritis highly suggestive of systemic-onset JRA.**

Laboratory abnormalities

- elevated erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP),
- leukocytosis,
- thrombocytosis,
- anemia of chronic disease.
- anti-cyclic citrullinated peptide (CCP) antibody has very high specificity for rheumatoid arthritis may detected before RF (poor prognosis)
- Carriage of HLA27 antigen is associated with increased risk of developing enthesitis –associated arthritis
- ANA is associated with increased risk of iridocyclitis in pt with oligoarthritis
- RF is positive only in 5% of pt when polyarticular disease occur after 8 yrs of age

	Systemic onset JIA	Pauciarticular onset JIA	Polyarticular onset JIA
Percent of JIA patients	10 to 15	50	30 to 40
Sex	F = M	F > M	F > M
Age	any <17 years	peak 2 to 3 years, rare >10	peaks 2 to 5, 10 to 14 years
Joints	any	large joints, but rarely hips	any, rare to start in hip
Fever, rash, lymphadenopathy, hepatosplenomegaly	yes	no	no
Uveitis	rare	20 percent, esp ANA +	less frequent

	Systemic onset JIA	Pauciarticular onset JIA	Polyarticular onset JIA
Laboratory abnormalities			
- Leukocytosis	marked	no	no
- Anemia	marked	no	mild
- Elevated ESR	marked	mild	mild
- ANA	absent	low titer common	low titer common in younger
- Rheumatoid factor	rare	absent	10 to 20 percent in those >10 years
Destructive arthritis	>50 percent	rare	>50 percent
Disease modifying drugs	commonly used	rarely used	commonly used

Differential diagnosis of joint pain or swelling in children

- Trauma
- Irritable hip and transient synovitis
- septic arthritis and osteomyelitis,
- Infection: bacterial ,viral ,Lyme disease
- Hematologic: leukemia ,bleeding diatheses, and hemoglobinopathies
- Tumor: Musculoskeletal neoplasia (eg, osteosarcoma), lymphoma, and neuroblastoma
- Leg-Calve- Perthes disease
- Slipped capital femoral epiphysis

Diagnosis of JIA requires the exclusion of all the above diagnoses.

Management

- **Remissions and relapses**
- **No cure but treatable**
- **Relieve pain ,reduce inflammation ,preserve joint function ,maintain normal growth and development**

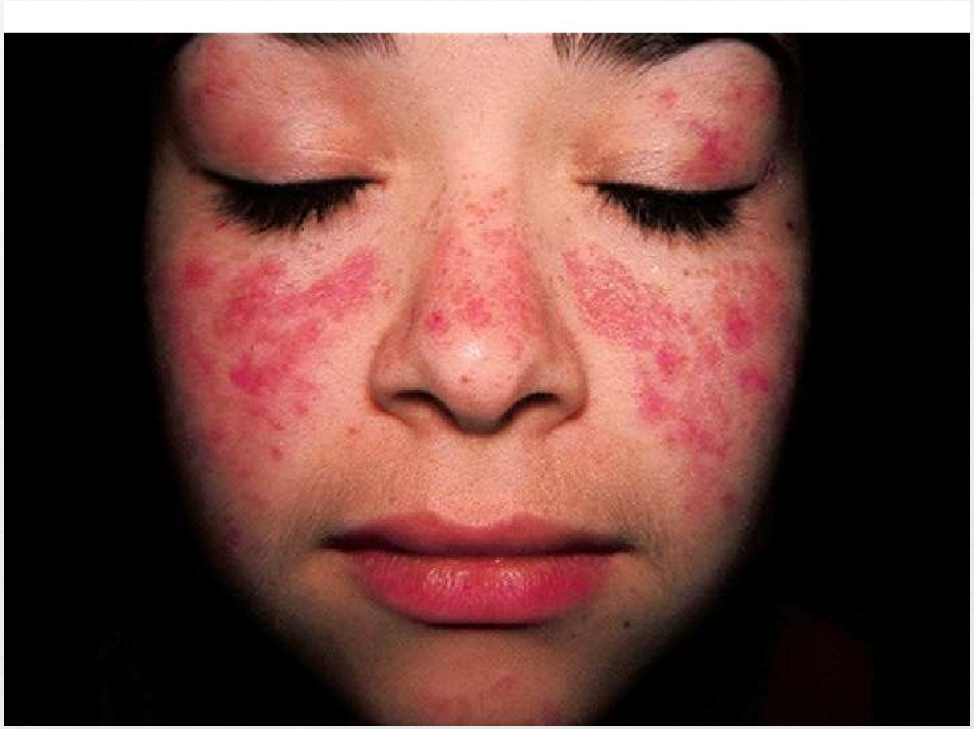
Management

- **Screen for uveites by periodic slit-lamp ophthalmologic examinations of all patients**
- **Require multidisciplinary team (MDT) approach**
  - **dietary evaluation and counseling to ensure appropriate calcium, vitamin D, protein, caloric intake;**
  - **physical and occupational therapy.**
  - **A social worker**

Medical management

- Nonsteroidal anti-inflammatory drugs (NSAIDs) : Ibuprofen ,Naproxen ,Piroxicam
- Disease modifying anti rheumatic drugs (DMAR)
  - Under supervision of rheumatologist
  - methotrexate the safest, most efficacious, and least toxic given once weekly
  - azathioprine and cyclophosphamide, are reserved for the few children who do not respond to less aggressive therapy.
- Joints steroid injections
- Corticosteroid : oral or IV methyleprednisolone
  - Toxicity :-
    - Cushing syndrome, growth retardation, and osteopenia
- TNF-α blockers :block the immune protein TNF etanercept infliximab

Systemic Lupus Erythematosus (SLE) in children



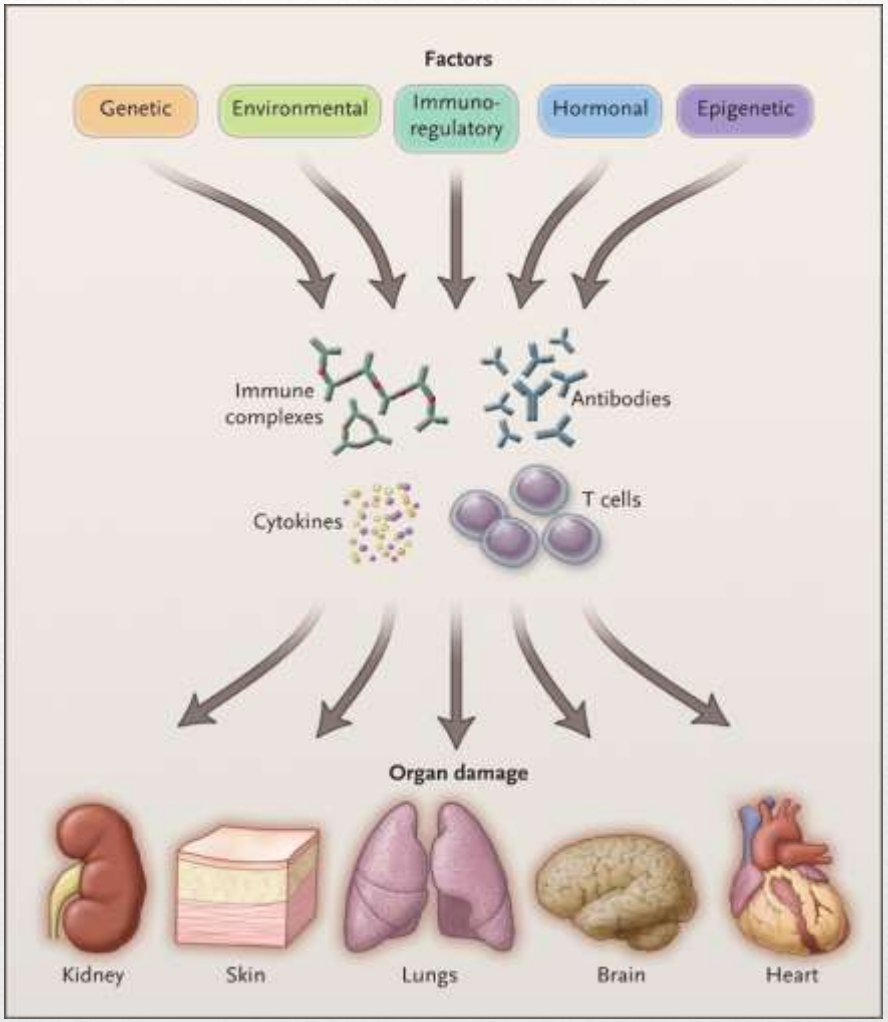
- Systemic lupus erythematosus (SLE) in children is fundamentally the same disease as in adults with similar etiology, pathogenesis, clinical manifestations, and laboratory findings.
- However, the care of children and adolescents with SLE is very different from that of adults because of the impact of the disease and its therapy on physical and psychological growth and development.

Systemic lupus erythematosis

- A chronic inflammatory multi-systemic autoimmune disease characterized by widespread inflammation of blood vessel and connective tissue
- The primary pathology is of persistent polyclonal B-cell stimulation resulting in autoantibody production with wide spread tissue antibody production ,with the widespread tissue deposition of immune complex

- The pathogenesis of SLE remains largely unknown, but several genetics, hormonal and environmental factors.
- Prevalence of SLE in children and adolescents (1-6/100,000) .
- More among African-Americans, Asians, Hispanics, Native Americans, and Pacific Islanders for both adult and pediatric populations.
- SLE predominantly affects females

Overview of the Pathogenesis of Systemic Lupus Erythematosus



American College of Rheumatology Criteria for the Diagnosis of Systemic Lupus Erythematosus (SLE)

Table 1. American College of Rheumatology Criteria for the Diagnosis of Systemic Lupus Erythematosus (SLE).*

Criterion	Definition
Malar rash	A rash on the cheeks and nose, often in the shape of a butterfly
Discoid rash	A rash that appears as red, raised, disk-shaped patches
Photosensitivity	A reaction to sunlight that causes a rash to appear or get worse
Oral ulcers	Sores in the mouth
Arthritis	Joint pain and swelling of two or more joints
Serositis	Inflammation of the lining around the lungs (pleuritis) or inflammation of the lining around the heart that causes chest pain, which is worse with deep breathing (pericarditis)
Kidney disorder	Persistent protein or cellular casts in the urine
Neurologic disorder	Seizures or psychosis
Blood disorder	Anemia (low red-cell count), leukopenia (low white-cell count), lymphopenia (low level of specific white cells), or thrombocytopenia (low platelet count)
Immunologic disorder	Positive test for anti–double-stranded DNA, anti-Sm, or antiphospholipid antibodies
Abnormal antinuclear antibodies	Positive antinuclear-antibody test

* Four of the 11 criteria are needed for the formal diagnosis of SLE.

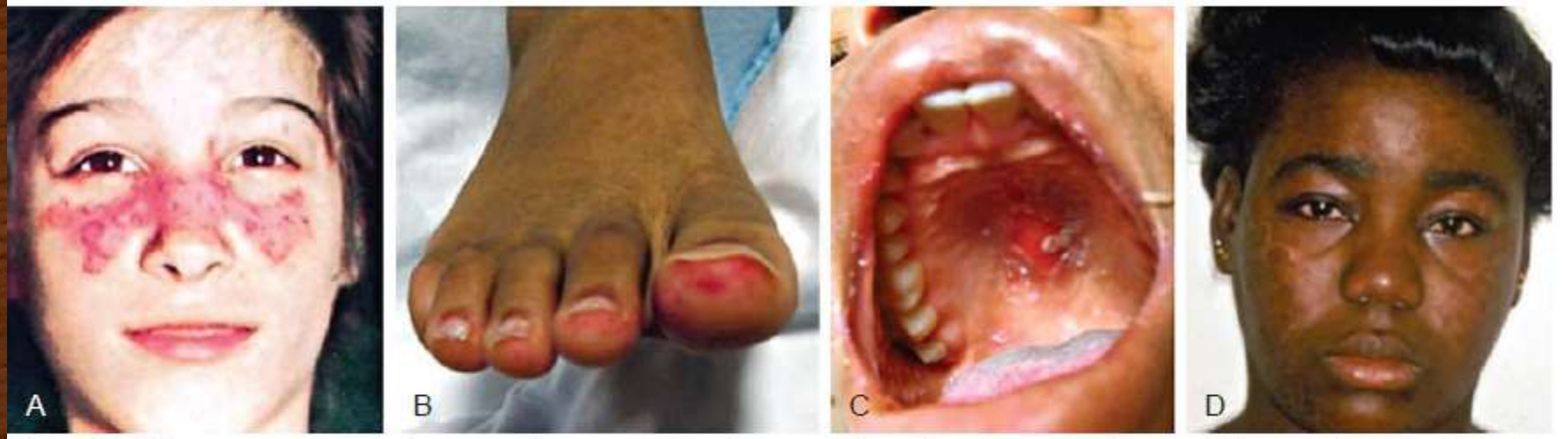


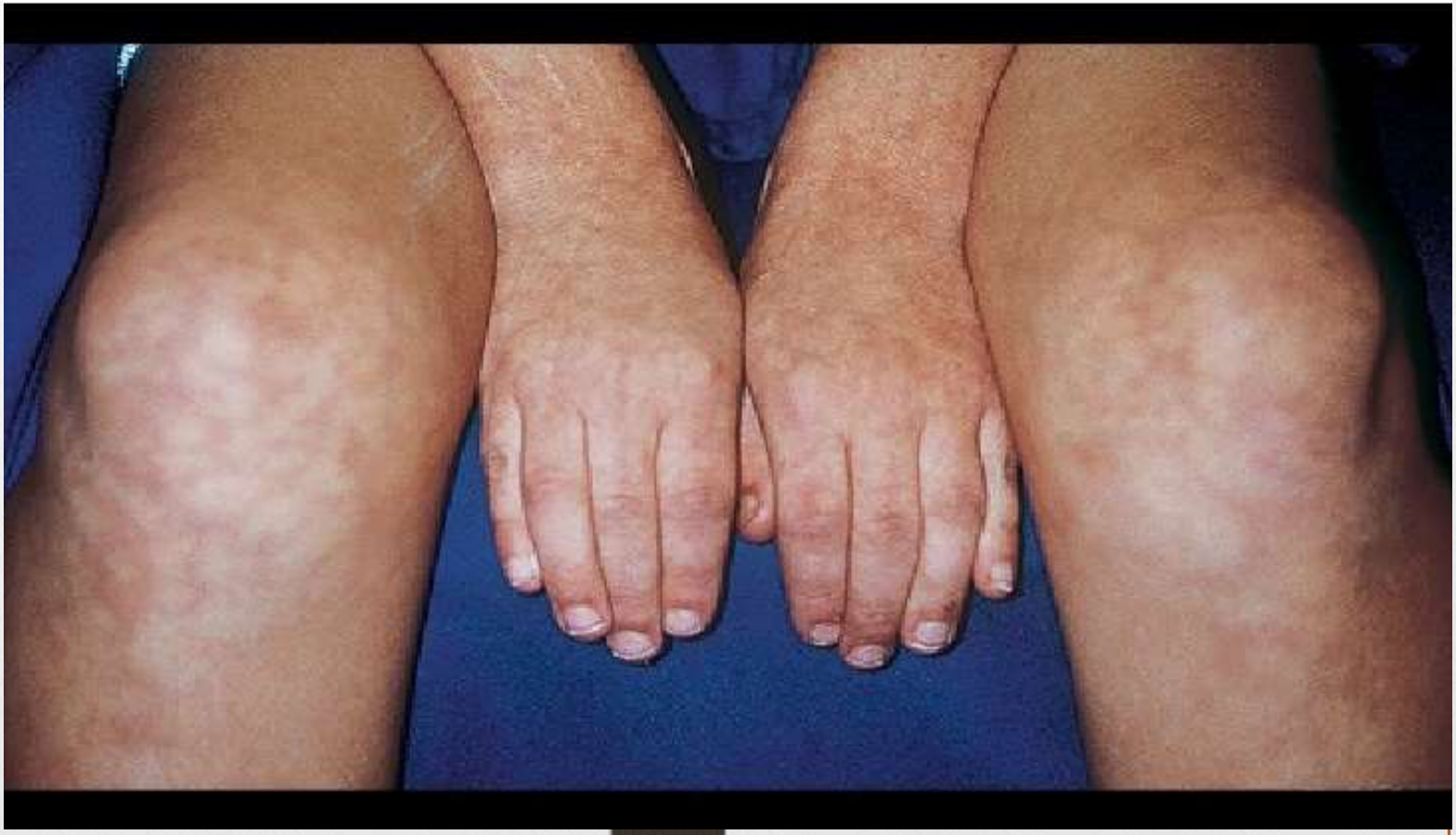
Figure 158-1 Mucocutaneous manifestations of SLE. **A,** Malar rash; **B,** vasculitic rash on toes; **C,** oral mucosal ulcers; **D,** discoid rash in malar distribution.

Signs and symptoms

- The disease can affect a wide range of organ systems
- Generalized symptoms such as fever , weight loss , and malaise are common
- Other common signs and symptoms include fever ,anorexia ,Raynauds phenomenon , vasculitis , chorea, neuropathy, depression, and cognitive changes

Livedo reticularis

A mottled purplish discoloration of the skin



Laboratory findings

- Complete blood counts
  - Leukopenia ,anemia ,thrombocytopenia
- 15% coombs test- positive
- ESR frequently elevated
- CRP with active SLE is normal but elevated may be due to infectious causes especially bacterial infection
- Urine analysis for proteinuria and hematuria

Laboratory findings

- **Complements :- C3& C4** are frequently reduced due to increased consumption
- **ANA** is positive in 95-100% of patients usually at titer 1:320 or above
- **Anti double -strand DNA** sensitive and specific , raised particularly in lupus nephritis
- **Anti-smith antibody** are specific for lupus and are related to CNS involvement, positive in only 30% ,lack sensitivity as diagnostic test
- **Antiphospholipid antibodies** found in approximately 50-60% of pediatric SLE patients , increase risk of thrombosis
- **Anticardiolipin antibodies** are detected in up to 50% of children with lupus ,associated with episode of arterial and venous thrombosis

Autoantibodies Found in Systemic Lupus Erythematosus Antibody Manifestation

- Coombs antibodies : Hemolytic anemia
- Antiphospholipid antibodies :Antiphospholipid antibody syndrome : Lupus anticoagulant ,Coagulopathy
- Antithyroid antibodies : Hypothyroidism
- Antiribosomal P antibody : Lupus cerebritis

Treatment

- Mild SLE:
  - NSAID
  - Hydroxychloroquine
- Moderate SLE
  - High-dose glucocorticoids
  - Mycophenolate mofetil
- Sever SLE
  - Cyclophosphamide
  - Prednisone

Neonatal lupus

Figure 158-3 Neonatal lupus syndrome. Typical rash, often photosensitive with a malar distribution, appearing as annular plaques with erythema and scaling. *(Reproduced, with written parental permission, from Pain C, Beresford MW: Neonatal lupus syndrome,* Paediatr Child Health *17:223–227, 2007.)*

- Results from the passive transfer of maternal immunoglobulin G autoantibodies to the fetus.
- The vast majority of are associated with maternal anti-Ro and anti-La antibodies

Clinical manifestations of neonatal lupus

- Characteristic annular or macular rash typically affecting the face (especially the periorbital area), trunk, and scalp

  Typically appears within the 1st 6 wk of life after exposure to ultraviolet light and lasts 3-4 mo.

- Infants may also have cytopenias and hepatitis,
- Congenital heart block is the most feared complication.
- Conduction system abnormalities range from prolongation of the PR interval to complete heart block, with development of progressive cardiomyopathy

Course and prognosis

- Cutaneous and hematological manifestations are reversible
- Congenital heart block is permanent
- Hepatic fibrosis is occasional
- Some risk of SLE in teenage or adult year

Management:

- Symptomatic for transient manifestations
- Heart block may need pace maker

Juvenile dermatomyositis (JDM)and Polymyositis

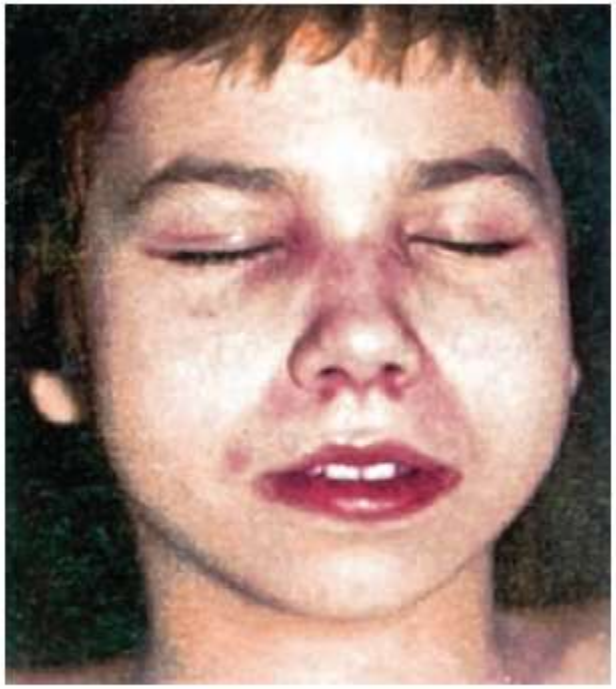


Figure 159-1 The facial rash of juvenile dermatomyositis. There is erythema over the bridge of the nose and malar areas with violaceous (heliotropic) discolorations of the upper eyelids.

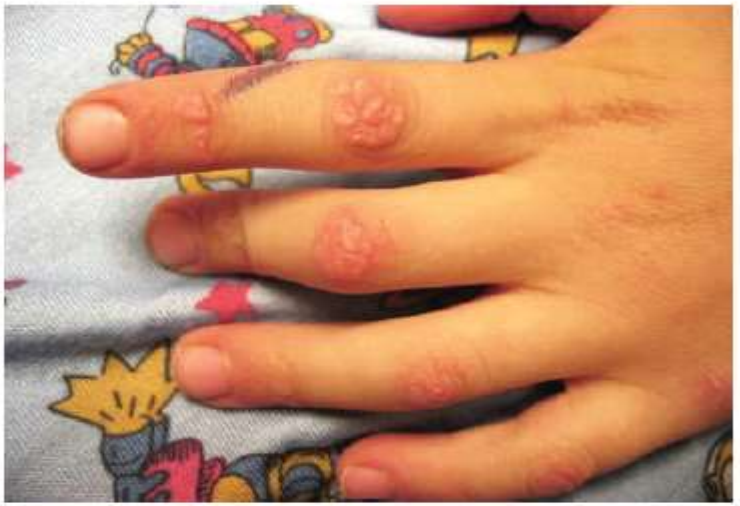


Figure 159-2 The rash of juvenile dermatomyositis. The skin over the metacarpal and proximal interphalangeal joints may be hypertrophic and pale red (Gottron papules).

- Non –suppurative myositis with characteristic skin rash and vasculitis
- Girls more than boys
- Peak incidence 4-10 yrs of age
- juvenile polymyositis involves direct T-cell invasion of muscle fibers similar to that seen in adult polymyositis ,accounts 3-6% of cases.

CLASSIFICATION AND DIAGNOSTIC CRITERIA

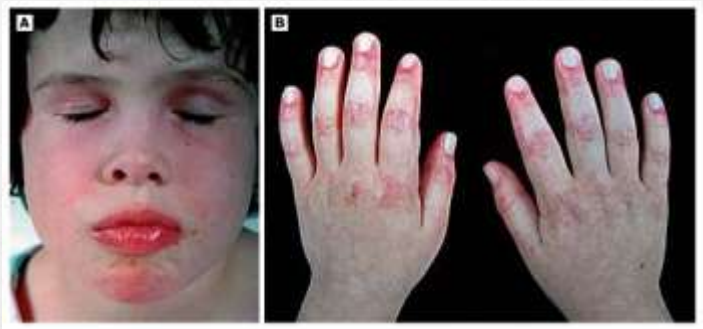
- Classic rash plus 3 of the following:

1. Weakness
2. Muscle enzyme elevation
3. Electromyographic changes
4. Muscle biopsy

CLASSIFICATION AND DIAGNOSTIC CRITERIA

- Characteristic cutaneous changes :-
  - heliotrope dermatitis (reddish-purple rash on the upper eyelids with periorbital edema) and
  - Gottron's papules (erythematous, papulosquamous eruption over the dorsal surfaces of the knuckles)
- Symmetrical weakness of the proximal muscles

Clinical images of typical juvenile dermatomyositis



- A) Heliotrope discoloration of the eyelids, and malar or facial erythema and
- (B) scaly, red rash on the knuckles with Gottron's papules.

- Elevation of the serum level of one of the muscle enzymes
  - Creatine kinase (CK)
  - Lactate *dehydrogenase (LDH)*
  - AST
  - Aldolase
- ANA positive in some
- **Electromyography:** useful to distinguish myopathic from neuropathic causes of muscle weakness (myopathy vs. denervation)

Muscle biopsy

- Is indicated in cases of myositis without the pathognomonic rash.
- Muscle biopsy displaying fiber necrosis and inflammation, small vessel occlusive vasculitis

Magnetic resonance imaging

- MRI scan of quadriceps muscle can be used in equivocal cases to confirm the presence of inflammatory myositis

Treatment

- Suppression of inflammatory response and prevention of the loss of muscle function and joint range of motion
- Assessment of the ventilatory effort and swallowing
- Corticosteroids prednisone or pulse methylprednisolone
- Methotrexate
- In severe cases cyclosporine or cyclophosphamide
- For skin manifestation :Hydroxychloroquine and intravenous immunoglobulin

Prognosis

- Variable
- Usually good with adequate treatment
- Recurrent rate 10-20%
- Small percent develop extensive muscle wasting ,severe contracture and wide spread calcinosis
- Dermatomyositis in children is not associated with increase risk of cancer as in adult

Familial Mediterranean Fever
FMF

FMF

- Autosomal recessive.
- Brief acute self-limited episodes of fever and polyserositis.
- Have irregular intervals.
- Associated with the development of amyloidosis.

Etiology

- Responsible gene: on short arm of chr. 16p13.3(MEFV)
- More than 70 mutations, the most common ones:
  - M694V (20-67% of cases, full penetrance, if homozygous; more sever and higher risk of amyloidosis))
  - V726A (7-35%, milder disease, less amyloidosis)
  - M694I
  - M680I
  - E148Q(low penetrance, very mild)

Epidemilogy

- Primarily among ethnic groups of Mediterranean origin (Sephardic Jews, Turks ,Armenians, Arabs)
- The carrier frequency is estimated to be 1 in 5 persons
- Onset : 65% before 5 years, 90% before 20 years, may present as early as 6 months of age

Pathogenesis

- The exact pathogenesis of acute episodes is unknown.
- FMF mutations lead to a gain-of-function and IL-1B-dependent inflammation, with a gene dosage effect.
- These results explains why:
  - many heterozygous carriers of FMF mutations have biochemical evidence of inflammation
  - As many as 30% of symptomatic FMF patients have only one demonstrable mutation
  - IL-1 inhibitors have a therapeutic effect in FMF

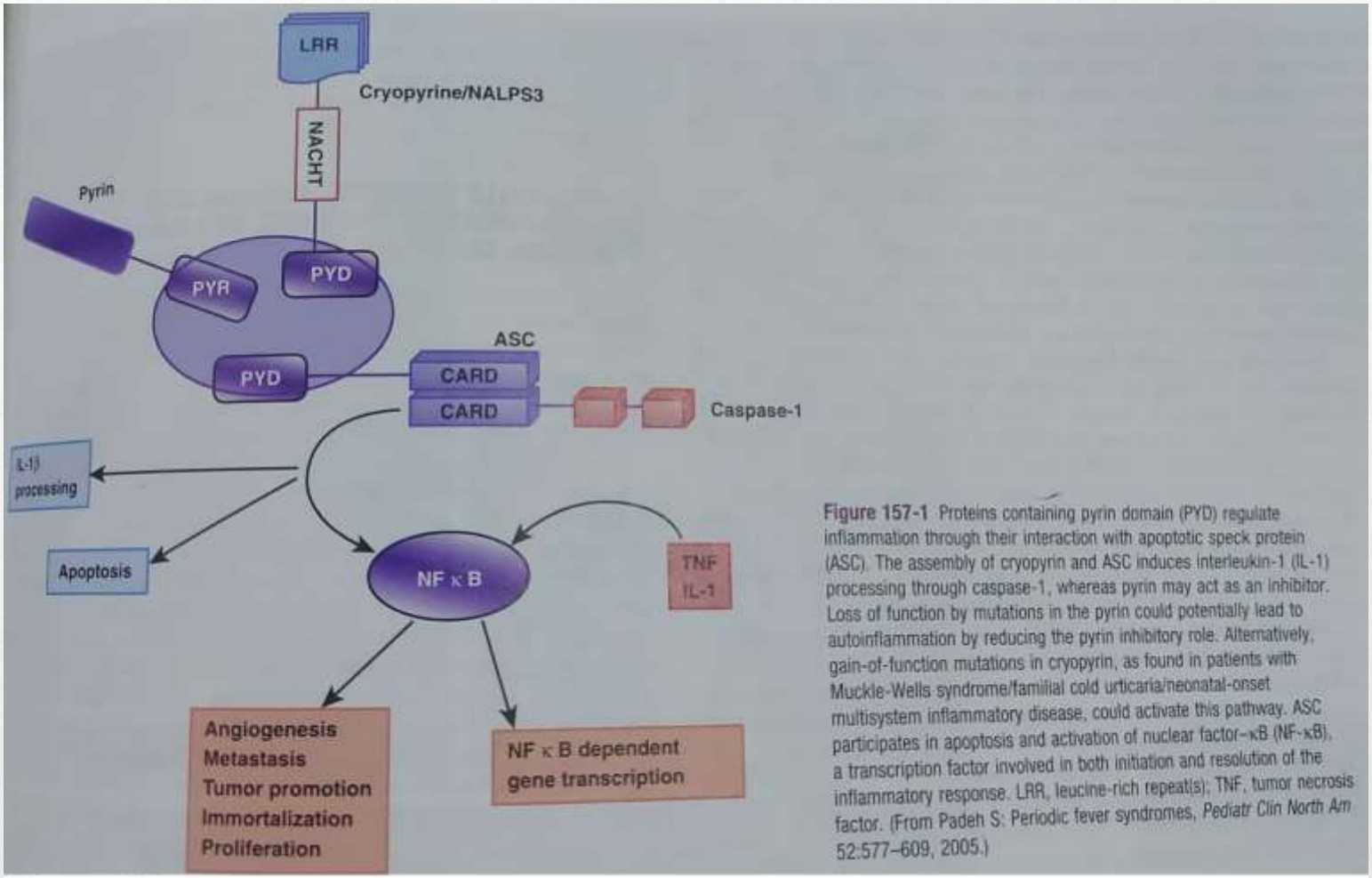


Figure 157-1 Proteins containing pyrin domain (PYD) regulate inflammation through their interaction with apoptotic speck protein (ASC). The assembly of cryopyrin and ASC induces interleukin-1 (IL-1) processing through caspase-1, whereas pyrin may act as an inhibitor. Loss of function by mutations in the pyrin could potentially lead to autoinflammation by reducing the pyrin inhibitory role. Alternatively, gain-of-function mutations in cryopyrin, as found in patients with Muckle-Wells syndrome/familial cold urticaria/neonatal-onset multisystem inflammatory disease, could activate this pathway. ASC participates in apoptosis and activation of nuclear factor–κB (NF-κB), a transcription factor involved in both initiation and resolution of the inflammatory response. LRR, leucine-rich repeat(s); TNF, tumor necrosis factor. (From Padeh S: Periodic fever syndromes, *Pediatr Clin North Am* 52:577–609, 2005.)

Clinical manifestations

- fever plus 1 or more:
- Pleuritic chest pain, sterile peritonitis ;sever abdominal pain), arthritis , rash.
  - Pleural pain20%: typically unilateral
  - Abdominal pain 90%: generalized or localized to one quadrant
  - Arthritis or arthralgia 85% : in large joints, large neutrophil-rich effusion, nonerosive, nondestructive
  - Erysipeloid erythematous rash overlies the ankles and dorsum of foot

Other clinical findings(Rare)

- Scrotal pain; inflammation of tunica vaginalis testis(acute scrotum)
- Pericaditis
- Febrile myalgia
- Exercise-induced myalgia (common in children)
- Association with other forms of vasculitis(ex. HSP 5% of pediatric cases)
- Splenomegaly
- Neurological involvement

FMF episodes

- May be triggered by menses, stress, infections, surgery
- Acute episodes last 1-4 days
- Between flares: symptom-free with persistent elevation of inflammatory markers
- Attack frequency :from weekly to 1-2 flares/year

Diagnosis

- Clinical manifestations plus genetic testing
- *Clinically:*

  Duration, recurrence, documentation of fever, characteristic serositis, synovitis, erysipeloid rash, responsiveness to daily colchicine prophylaxis, absence of other causative factor.

- *Genetic testing is diagnostic*

Treatment

- Attacks can be prevented by prophylaxis daily oral colchicine
- 20-30 % shows improvement(decrease number and severity of attacks)
- 5-10% no response
- Biological treatment: like IL-1 inhibitor Anakinra is good for cases not responding to colchicine

Colchicine

- Reduce the frequency of acute attack
- Decrease development of amyloidosis
- May produce partial regression in amyloidosis
- Untreated amyloidosis will end in renal failure within 3-5 years
- GI side effects reduce the compliance
- Toxic effect: Acute myopathy, BM hypoplasia
- Safe during pregnancy to mother and fetus, and during lactation
- No effect on male or female fertility

Complications and prognosis

- Renal amyloidosis: 30-50% of children, 75% of adult
- Manifestation of serum amyloidosis A (SAA):

  Proteinuria, nephrotic syndrome, renal failure.

  Transplantation may be required
- Mortality from FMF usually results from the complications of renal failure and amyloidosis:

  Infections, thromboembolism, uremia.
- Others: joint contracture, abdominal adhesion, impairments in social development.

Amyloidosis

- Serum AA : acute phase reactant: deposit most commonly in : kidney, GI, lungs, spleen,, testes, thyroid. Adrenals.
- Rarely cardiac amyloidosis may develop
- Macroglossia and neuropathy NOT seen in amyloidosis of FMF
- Diagnosis confirmed by rectal or renal biopsy
- Might proceed overt FMF attacks, due subclinical manifestations

Amyloidosis

- Risk factors:
- Homozygousity of M694V
- Polymorphism of serum AA gene
- Non compliance with colchicine
- Male gender
- Positive FHX of AA amyloid
- Country of origin

Kawasaki disease

Kawasaki disease (KD)

- Acute febrile illness of childhood
- Leading cause of acquired heart disease in children in the developed countries
- Vasculitis, coronary arteries

Etiology

- Unknown
- Epidemiologic and clinical features support the infection origin with a genetic role in the pathogenesis

Epidemiology

- 80% less than 5 years(median age 2-3 years)
- More among patient of Asian and pacific islander background.

Pathology

- Vasculitis of medium-sized arteries
- Edema of endothelial and smooth muscle cells , with intense inflammatory infiltration of the vascular wall initially with PMN cells then by macrophages, lymphocytes(CD8+T cell), plasma cells.
- IgA plasma cells prominent in inflammatory infiltrate
- In sever vessels, all layers are affected with destruction of internal elastic lamina.
- Weakness of vessel wall lead to the aneurysm
- Thrombi may be formed and lead to blood flow obstruction
- Arterial stenosis and occlusion occurs due to progressive vascular wall fibrosis

Clinical manifestation

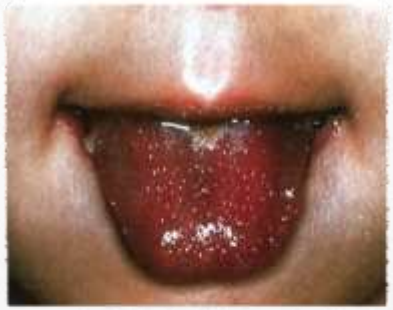
EPIDEMIOLOGIC CASE DEFINITION (CLASSIC CLINICAL CRITERIA)*

Fever persisting at least 5 days†

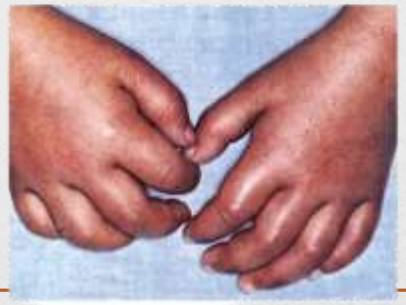
Presence of at least 4 principal features:

- Changes in extremities:
  - Acute: Erythema of palms, soles; edema of hands, feet
  - Subacute: Periungual peeling of fingers, toes in weeks 2 and 3
- Polymorphous exanthem
- Bilateral bulbar conjunctival injection without exudate
- Changes in lips and oral cavity: erythema, lip cracking, strawberry tongue, diffuse injection of oral and pharyngeal mucosa
- Cervical lymphadenopathy (>1.5 cm diameter), usually unilateral

Exclusion of other diseases with similar findings‡



155-3



166-4 Inflammatory edema of

- Other associated symptoms might occur 10 days prior to the diagnosis
- Respiratory 30% or GI 65% symptoms
- Irritability; reflect aseptic meningitis
- Mild hepatitis
- Hydrops gallbladder
- Urethritis, meatitis with sterile pyurea
- Arthritis, arthralgia

OTHER CLINICAL AND LABORATORY FINDINGS

Cardiovascular findings:
- Congestive heart failure, myocarditis, pericarditis, valvular regurgitation
- Coronary artery abnormalities
- Aneurysms of medium-size noncoronary arteries
- Raynaud phenomenon
- Peripheral gangrene

Musculoskeletal system:
- Arthritis, arthralgias

Gastrointestinal tract:
- Diarrhea, vomiting, abdominal pain
- Hepatic dysfunction
- Hydrops of gallbladder

Central nervous system:
- Extreme irritability
- Aseptic meningitis
- Sensorineural hearing loss

Genitourinary system:
- Urethritis/meatitis

Other findings:
- Erythema, induration at bacille Calmette-Guérin inoculation site
- Anterior uveitis (mild)
- Desquamating rash in groin

Cardiovascular involvement

- Cardiac involvement is the most important manifestation
- Tachycardia out of proportion to fever, with diminished left ventricular systolic function which rarely might lead to shock
- Pericarditis with pericardial effusion can occur
- Mitral regurge in 25% at presentation
- Coronary artery aneurysm in 25% of untreated patient within 2-3 weeks
- Aneurysm in other arteries (axillary, popliteal, iliac…)

Phases of Kawasaki disease

- **<u>In the absence of treatment:</u>**
- **Acute febrile phase(1-2 wks):**

  Fever plus acute signs of the illness
- **Subacute phase(for 2 weeks):**

  Desquamation, thrombocytosis, coronary aneurysms

  Highest risk of sudden death if aneurysms developed
- **Convalescent phase(6-8 wks):**

  Begins when all clinical signs of KD disappeared

  Continues until ESR is normal

LABORATORY FINDINGS IN ACUTE KAWASAKI DISEASE

Leukocytosis with neutrophilia and immature forms
Elevated erythrocyte sedimentation rate
Elevated C-reactive protein
Anemia
Abnormal plasma lipids
Hypoalbuminemia
Hyponatremia
Thrombocytosis after week 1[§]
Sterile pyuria
Elevated serum transaminases
Elevated serum gamma glutamyl transpeptidase
Pleocytosis of cerebrospinal fluid
Leukocytosis in synovial fluid

*Patients with fever at least 5 days and <4 principal criteria can be diagnosed with Kawasaki disease when coronary artery abnormalities are detected by 2-dimensional echocardiography or angiography.

[†]In the presence of ≥4 principal criteria, Kawasaki disease diagnosis can be made on day 4 of illness. Experienced clinicians who have treated many patients with Kawasaki disease may establish diagnosis before day 4.

[‡]See differential diagnosis (Table 166-2).

Echocardiogram

- At diagnosis then after 2-3 weeks of illness
- If normal, repeat 6-8 weeks after onset of illness
- If abnormal echo or recurrent symptoms, more frequent echo needed
- If no coronary abnormality, repeat echo and do lipid profile in 1 year, then cardiologic follow up every 5 years

Diagnosis

- **Classic KD:** fever for at least 4 days and at least 4 of 5 of the other principle characteristics of the illness
- **Atypical or incomplete KD:** persistent fever but with fewer than 4 of the characteristics
- Incomplete cases high in infants and have higher risk to develop coronary artery abnormalities

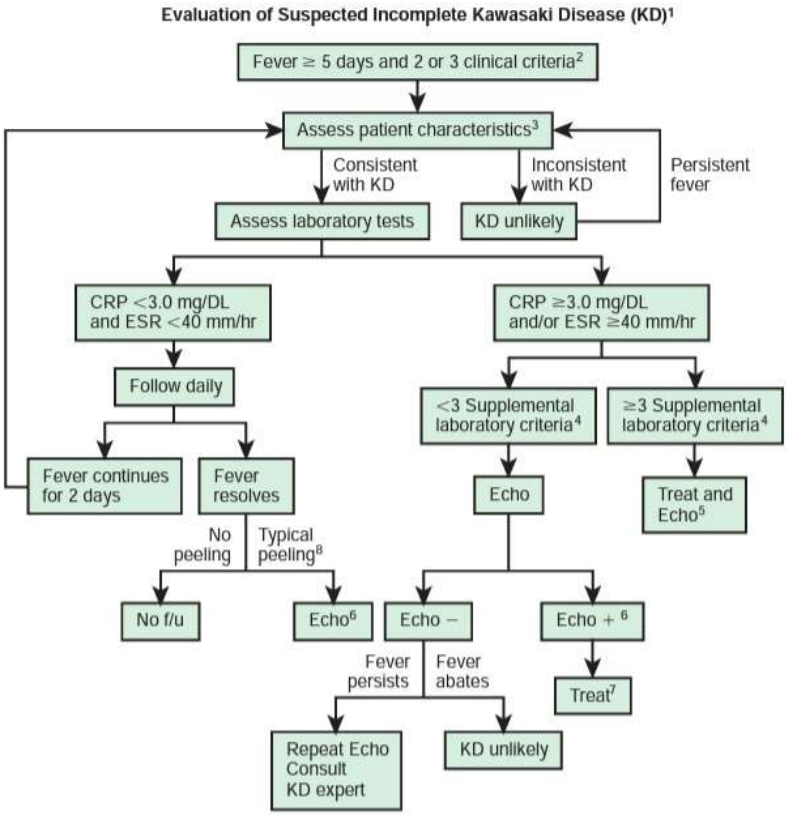


Figure 166-8 Algorithm for evaluation of suspected incomplete Kawasaki disease (KD). (1) In the absence of a gold standard for diagnosis, this algorithm cannot be evidence based, but rather represents the informed opinion of the expert committee. Consultation with an expert should be sought anytime assistance is needed. (2) Infants ≤6 mo old on day ≥7 of fever or later without other explanation should undergo laboratory testing and, if evidence of systemic inflammation is found, given an echocardiogram (Echo), even if they have no clinical criteria. (3) Patient characteristics suggesting KD are listed in Table 166-1. Characteristics suggesting disease other than KD include exudative conjunctivitis, exudative pharyngitis, discrete intraoral lesions, bullous or vesicular rash, and generalized adenopathy. Consider alternative diagnoses (see Table 166-2). (4) Supplemental laboratory criteria include albumin ≤3.0 g/dL, anemia for age, elevation of alanine aminotransferase, platelet count after 7 days ≥450,000/mm^3, white blood cell count ≥15,000/mm^3, and urine white blood cell count ≥10/high-power field. (5) Can treat before performing echocardiogram. (6) Echocardiogram findings are considered positive (Echo+) for purposes of this algorithm if any of 3 conditions are met: *z* score of left anterior descending coronary artery (LAD) or right coronary artery (RCA) ≥2.5; coronary arteries meet Japanese Ministry of Health criteria for aneurysms; ≥3 other suggestive features exist, including perivascular brightness, lack of tapering, decreased left ventricle (LV) function, mitral regurgitation, pericardial effusion, or *z* scores in LAD or RCA of 2-2.5. (7) If echocardiogram findings are positive, treatment should be given to children within 10 days of fever onset and to those beyond day 10 with clinical and laboratory signs (C-reactive protein [CRP], erythrocyte sedimentation rate [ESR]) of ongoing inflammation. (8) Typical peeling begins under nail beds of fingers and then toes. Echo−, negative echocardiogram findings; f/u, follow-up. *(From Newburger JW, Takahashi M, Gerber MA, et al: Diagnosis, treatment, and long-term management of Kawasaki disease,* Pediatrics *114:1708–1733, 2004.)*

Table 166-2 Differential Diagnosis of Kawasaki Disease

VIRAL INFECTIONS
- Adenovirus
- Enterovirus
- Measles
- Epstein-Barr virus
- Cytomegalovirus

BACTERIAL INFECTIONS
- Scarlet fever
- Rocky Mountain spotted fever
- Leptospirosis
- Bacterial cervical lymphadenitis
- Meningococcemia

RHEUMATOLOGIC DISEASE
- Systemic-onset juvenile idiopathic arthritis
- Behçet disease

OTHER
- Toxic shock syndromes
- Staphylococcal scalded skin syndrome
- Drug hypersensitivity reactions
- Stevens-Johnson syndrome

Treatment

Table 166-3	Treatment of Kawasaki Disease

ACUTE STAGE

- Intravenous immunoglobulin 2 g/kg over 10-12 hr
  and
- Aspirin 80-100 mg/kg/day divided every 6 hr orally until patient is afebrile for at least 48 hr

CONVALESCENT STAGE

- Aspirin 3-5 mg/kg once daily orally until 6-8 wk after illness onset if normal coronary findings throughout course

LONG-TERM THERAPY FOR PATIENTS WITH CORONARY ABNORMALITIES

- Aspirin 3-5 mg/kg once daily orally
- Clopidogrel 1 mg/kg/day (maximum: 75 mg/day)
- Most experts add warfarin or low-molecular-weight heparin for those patients at particularly high risk of thrombosis

ACUTE CORONARY THROMBOSIS

- Prompt fibrinolytic therapy with tissue plasminogen activator or other thrombolytic agent under supervision of a pediatric cardiologist

Complications

- Coronary artery aneurisms
- Acute thrombosis
- Reyes syndrome : patient should receive annual influenza vaccine
- Delay in life-attenuated vaccines for 11 months, due IVIG interfere with immune response

Prognosis

- Majority of cases return to normal health
- Acute KD recurs in 1-3%
- 50% of coronary artery aneurysm regress to normal by 1-2 years, but thickness of myointimal wall and function might be affected.
- Giant aneurysms: unlikely to resolve, lead to thrombosis and stenosis
- Might need coronary artery bypass grafting or heart transplantation
- Occurrence of atherosclerotic heart diseases in adulthood is unclear

THANK YOU