KAWASAKI DISEASE

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HISTORY

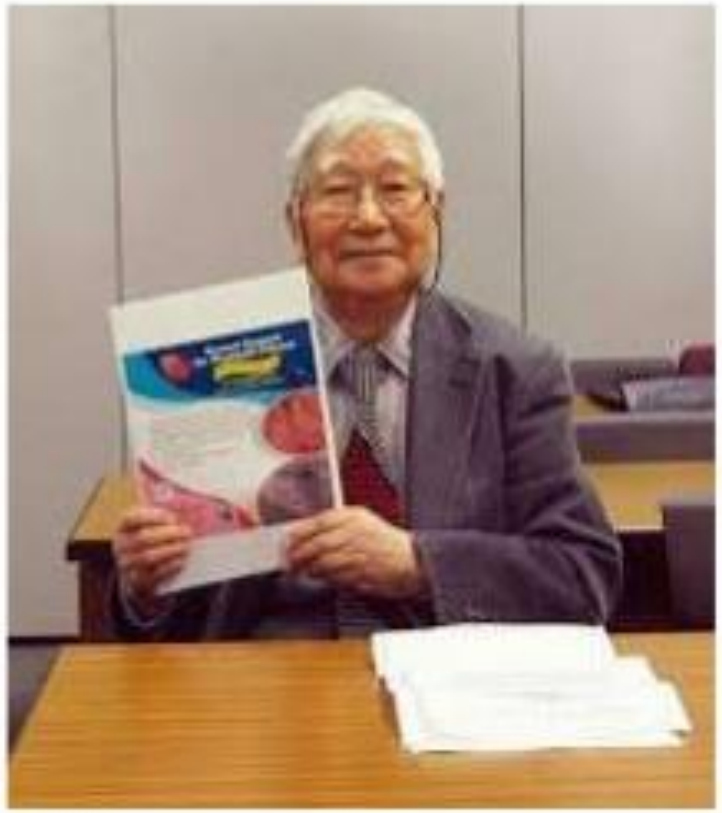
1967 - Tomisaku Kawasaki reports a series of 50 patients and establishes the clinical criteria for diagnosis (in Japanese)

1974 - first English language report of Kawasaki syndrome by Kawasaki

1976 - first series of American patients reported by Melish, Hawaii

1977 - landing and Larson establish that Kawasaki disease and infantile polyarteritis nodosa are pathologically indistinguishable

1988 - American academy of pediatrics endorses high does IVIG plus ASA as recommended therapy for Kawasaki disease



INTRODUCTION

- Also known as mucocutaneous lymph node syndrome and infantile polyarteritis nodosa.
- It is an acute febrile illness of childhood seen worldwide with the highest incidence occurring in Asian children.
- KD is a vasculitis affecting medium size vessels
- Coronary artery aneurysms or ectasia develop in 20% to 25% of untreated children & can lead to
  - ischemic heart disease or
  - sudden death

EPIDEMIOLOGY

- More prevalent in Japan and in children of Japanese ancestry (annual incidence of 112 cases per 100 000 children <5 years old)

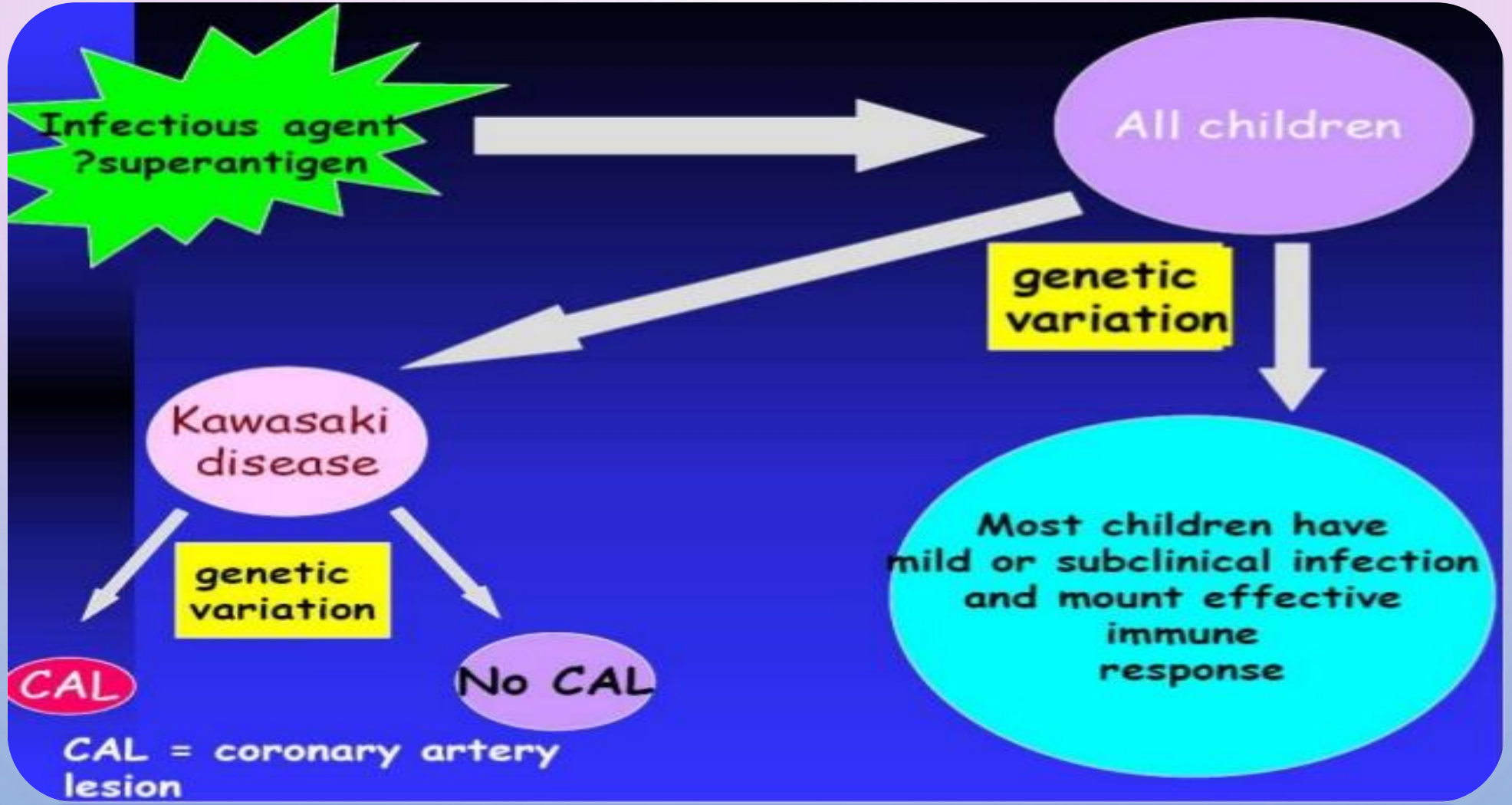
- Age of onset -
  - Peak age - 2 to 5 yrs
  - 80 - 85 % < 5 yrs
  - Rare > 18 yrs

ETIOLOGY & PATHOGENESIS

- Etiology of KD remains unknown, (although clinical and epidemiological features strongly suggest an infectious cause)

- Hypothesis - KD is caused by a ubiquitous infectious agent that produces clinically apparent disease only in certain genetically predisposed individuals, particularly Asians

- Its rarity in the first few months < 3m of life and in adults suggests an agent to which the adults are immune and from which very young infants are protected by passive maternal antibodies
- Little evidence exists of person-to-person transmission
- Hypothesis assumes that most infected children experience asymptomatic infection with only a small fraction developing overt clinical features of Kawasaki disease
- A genetic role in the pathogenesis of KD seems likely, as evidenced by the higher risk of KD in Asian children regardless of country of residence


Infectious agent
?superantigen
All children
genetic variation
Kawasaki disease
genetic variation
CAL
No CAL
Most children have mild or subclinical infection and mount effective immune response
CAL = coronary artery lesion

PATHOLOGY

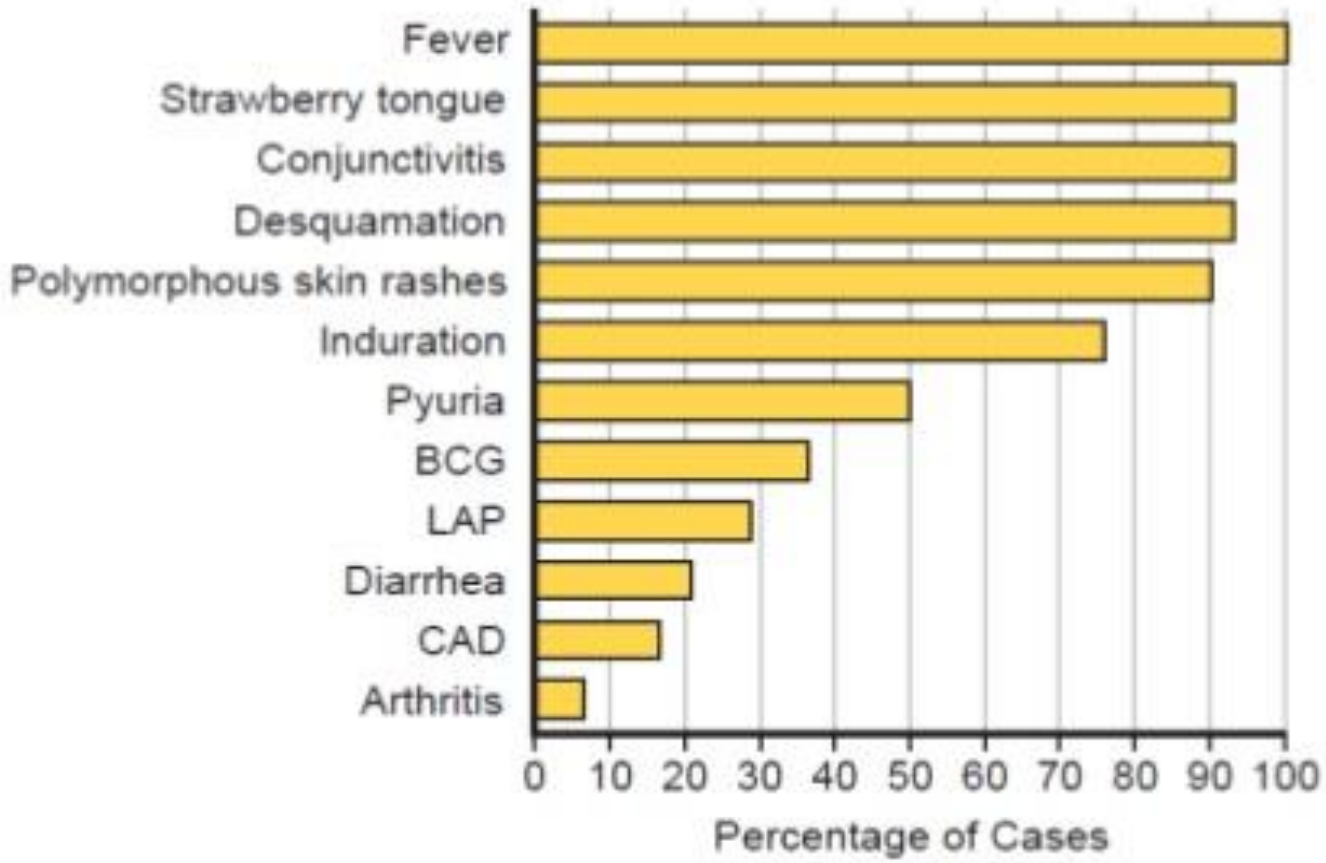
- KD is a vasculitis that predominantly affects the medium-size arteries.
- The coronary arteries are the most commonly involved, although other arteries, such as the popliteal and brachial arteries, can also develop dilation.

- A 3-phase process to the arteriopathy of KD are
- 1st phase - neutrophilic necrotizing arteritis in the 1st 2 wk of illness Saccular aneurysms may form from this arteritis.
- 2nd phase – subacute/chronic vasculitis driven by lymphocytes, plasma cells, and eosinophils, which may last weeks to years and results in fusiform aneurysms.

- 3rd phase - smooth muscle cell myofibroblasts develop which causes progressive stenosis. Thrombi may form in the lumen and obstruct blood flow.

Clinical Features

- Prolonged fever – usually > 5 days duration
- At least 4 of the following 5 features
- 1 – bilateral nonexudative conjunctival injection with limbal sparing
- 2 – erythema of the oral and pharyngeal mucosa with strawberry tongue and red, cracked lips
- 3 – edema and erythema of the hands and feet
- 4 – polymorphic rash usually truncal
- 5 – nonsuppurative cervical lymphadenopathy, usually unilateral, with node size >1.5 cm

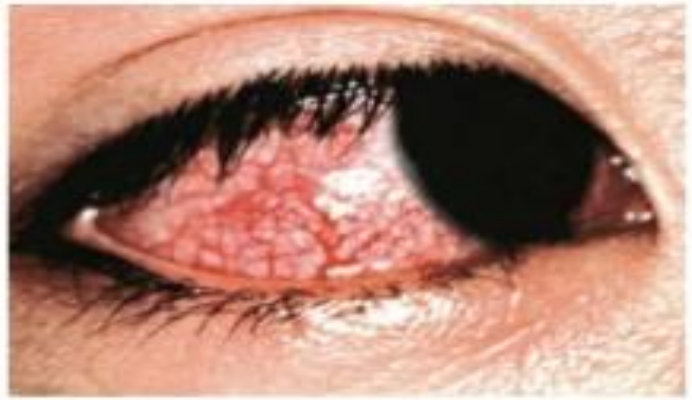

Fever
Strawberry tongue
Conjunctivitis
Desquamation
Polymorphous skin rashes
Induration
Pyuria
BCG
LAP
Diarrhea
CAD
Arthritis
0 10 20 30 40 50 60 70 80 90 100
Percentage of Cases

Fever in KD

- Fever is characteristically high (≥38.3°C [101°F]), unremitting, and unresponsive to antibiotics.
- The duration of fever without treatment is generally 1-2 wk, but may persist for 3-4 wk.
- Defervescence within 1-2 days of treatment with IVIG

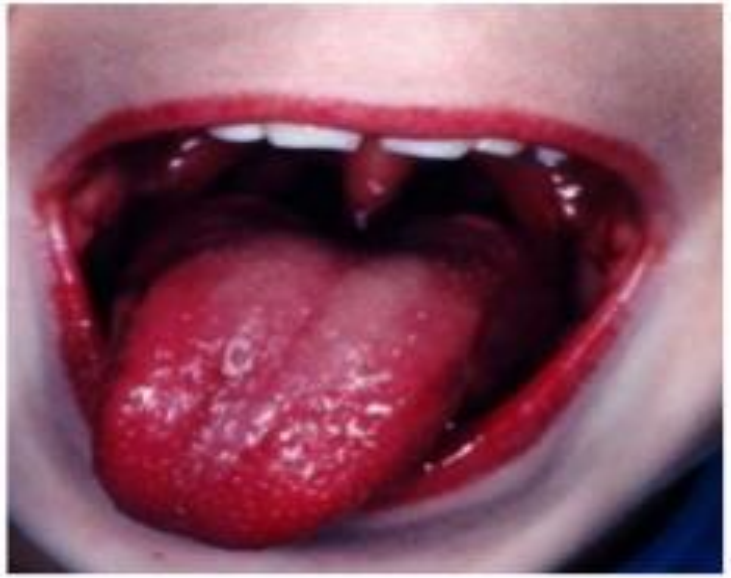
Conjunctivitis in KD

- Begins shortly after the fever
- Resolves promptly - may have disappeared by presentation
- Non-purulent conjunctival injection
- Bulbar conjunctivitis with limbic sparing
- Anterior uveitis may occur (in up to 80%)



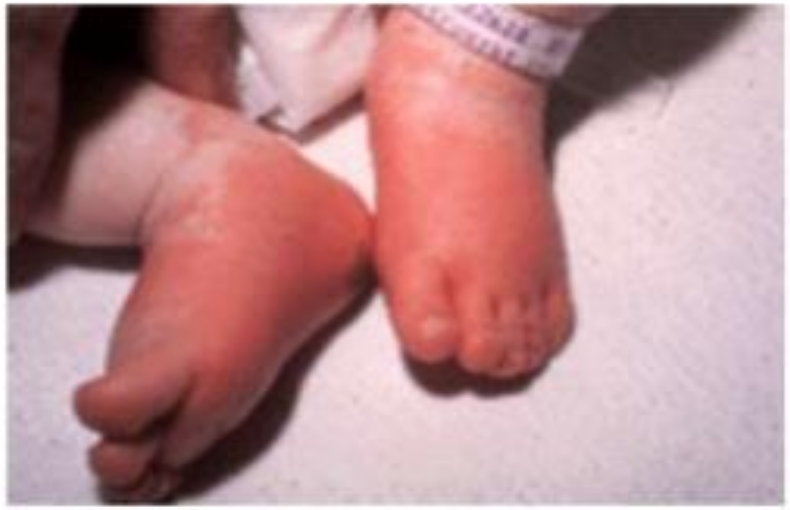
Oropharyngeal changes

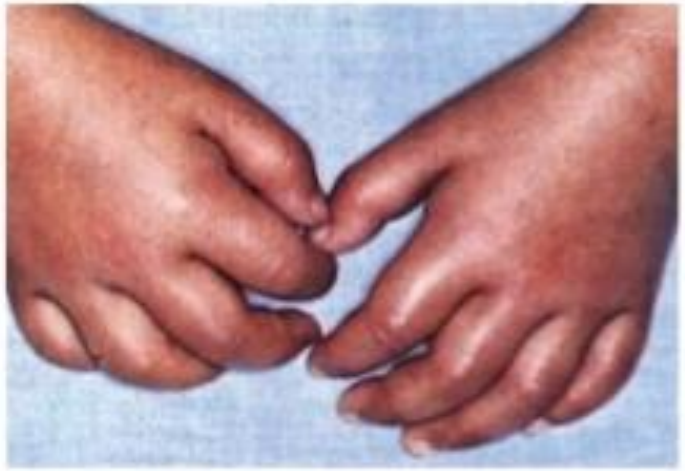
- Erythema, dryness, swelling and peeling of lips - lipstick sign
- Lips may bleed
- Erythema of oropharyngeal mucosa
- Strawberry tongue
- No Koplik's spots or oral ulceration or exudates in KD

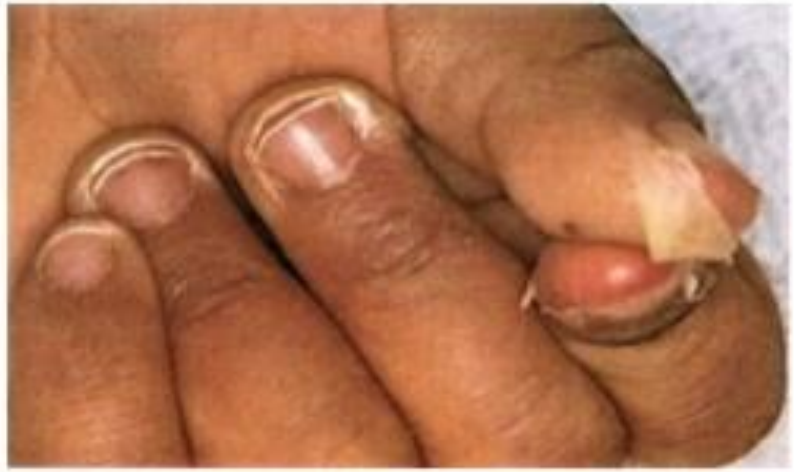


Changes in the extremities

- Oedema of hands and feet, especially in infants
- Peeling of fingers and toes (often periungual) is NOT a feature of the acute presentation
- Peeling of hands and feet in sub acute phase (1-2 weeks)
- Beau's lines in nails; occasionally nail is lost

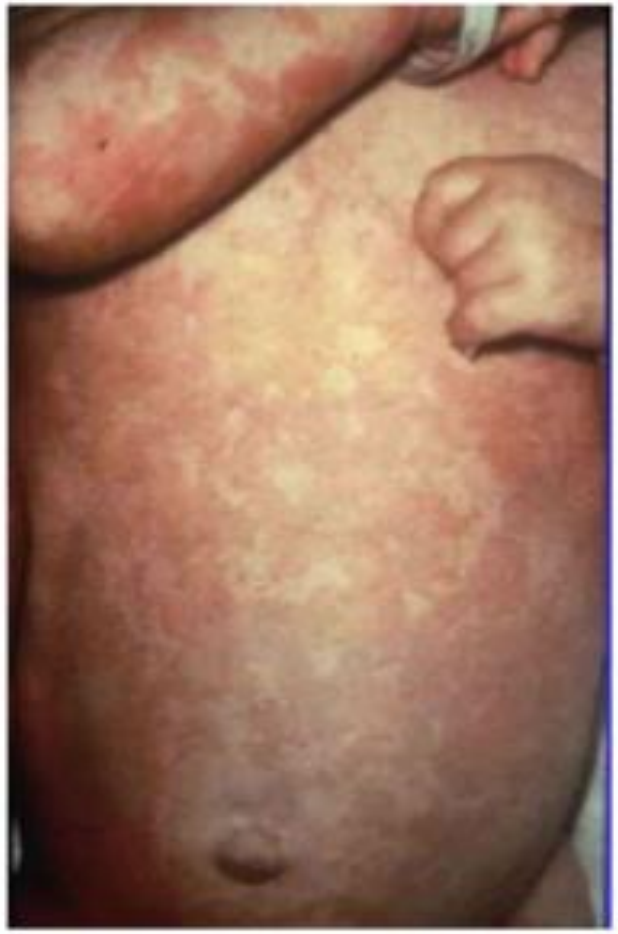


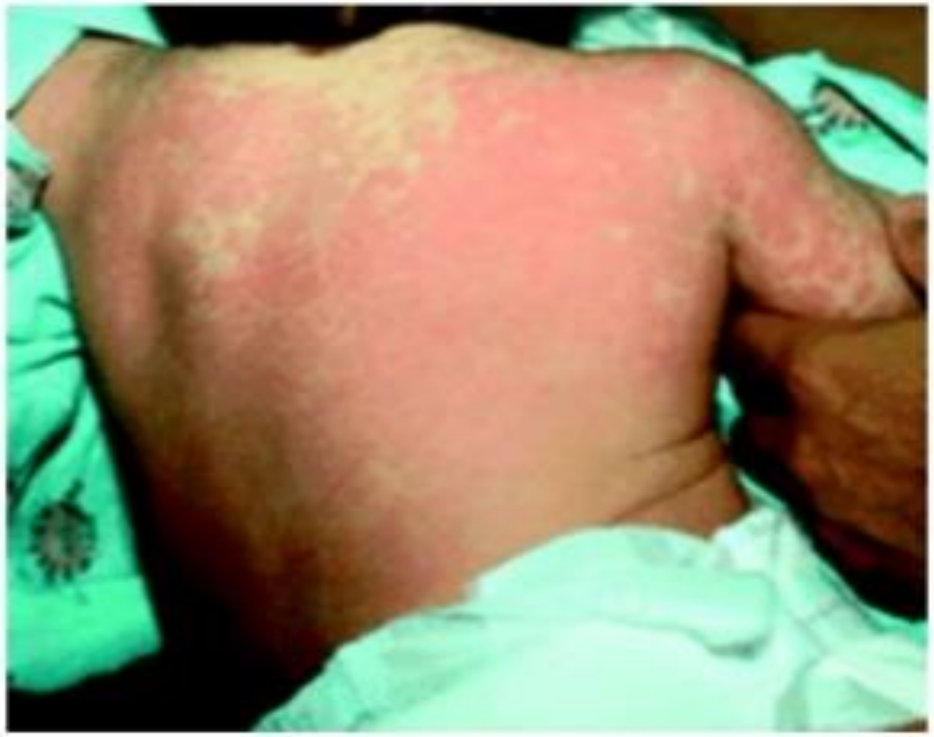




Polymorphous rash

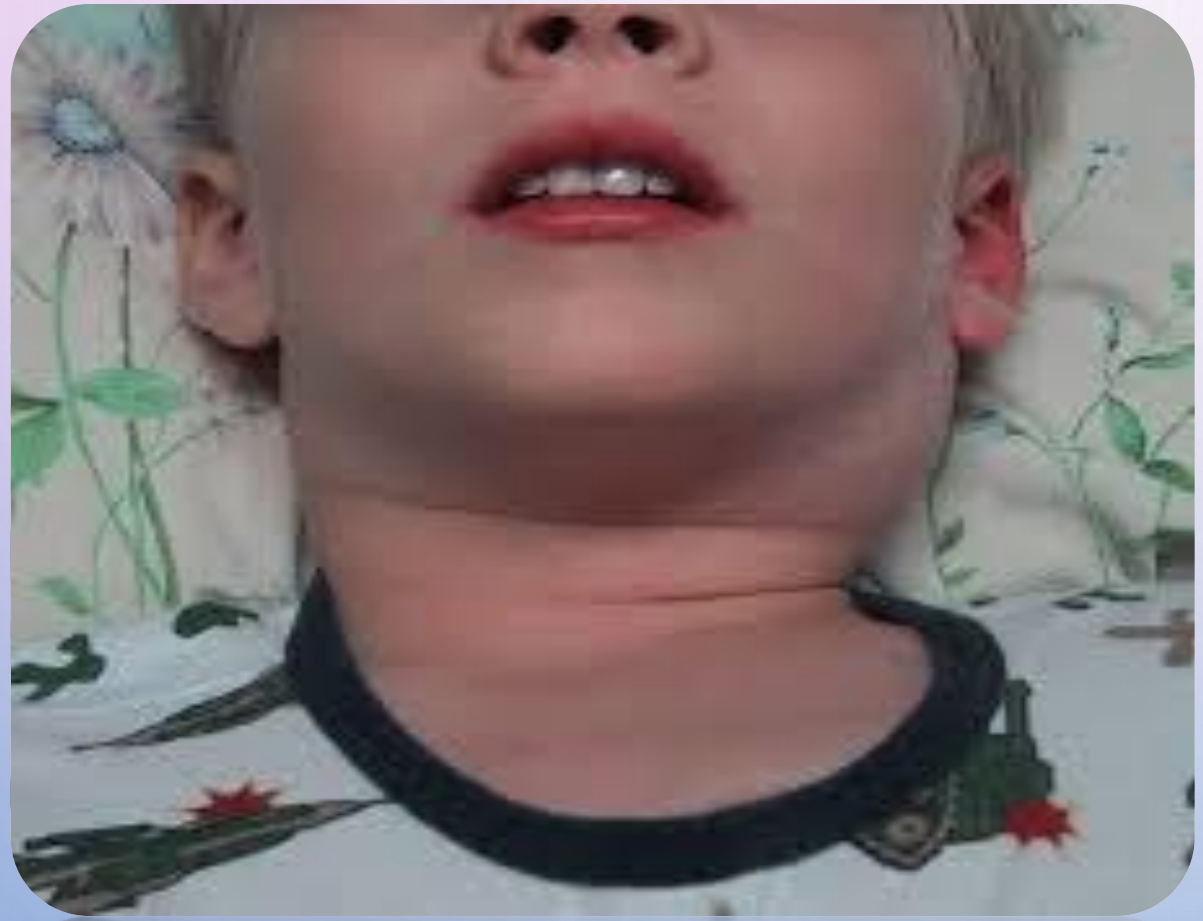
- Generally occurs with onset of fever and fades within a week
- Morbilliform rash or erythematous plaques at flexor creases
- Erythema and desquamation of the inguinal/perineal area Occurs early (desquamation of hands and feet is a later sign)
- The presence of - petechiae or purpura, vesicles or bullae, crusting, pruritis - search for an alternative diagnosis





Lymphadenopathy in KD

- 50-80% of cases
- >1.5cm, usually more obvious
- May be unilateral single node
- May be erythematous, but non-fluctuant and no pus



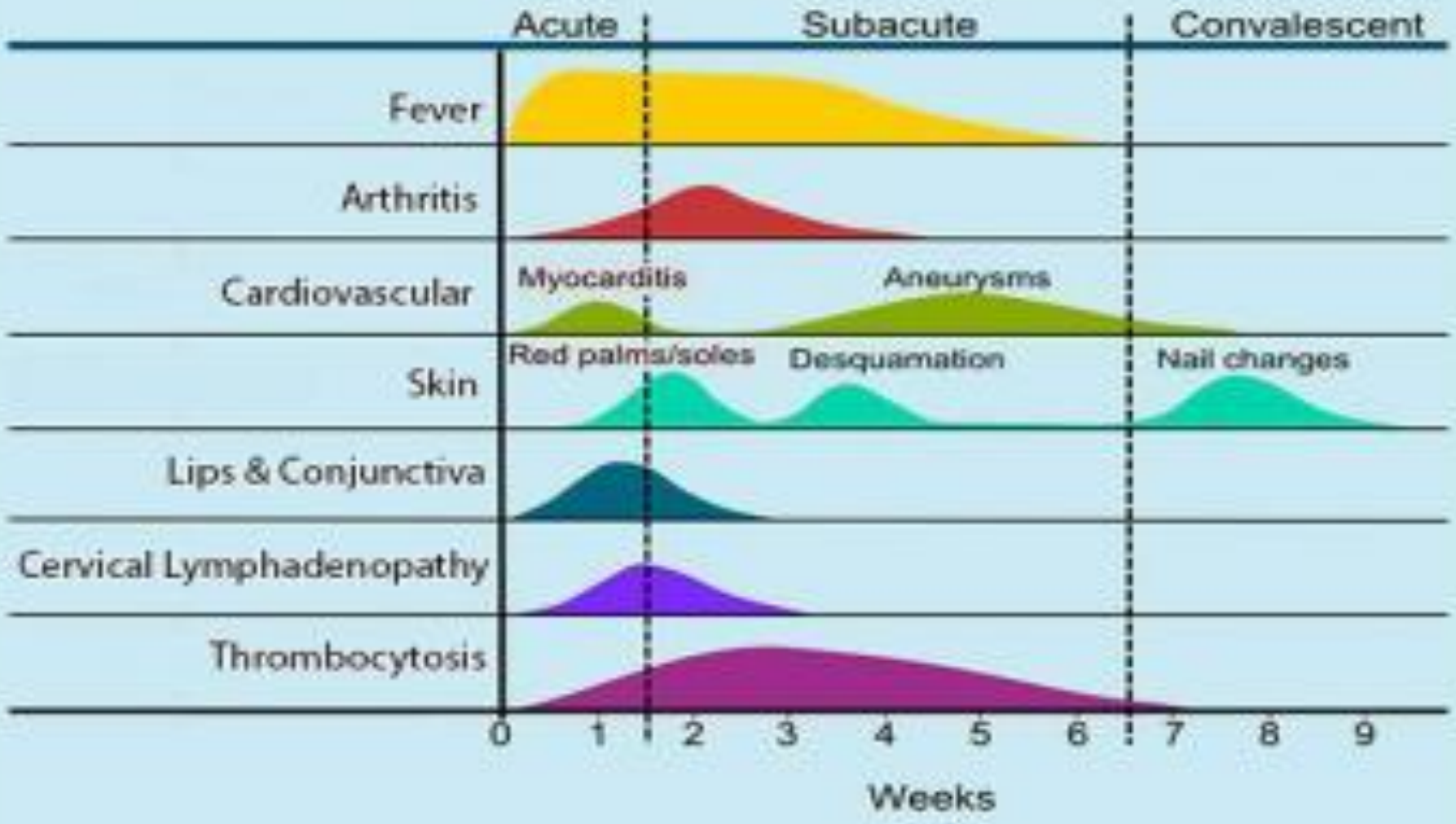
Other clinical features or KD

- Irritability
  - Aseptic meningitis (~25%) (CSF - ↑ lymph's, N glucose/protein)
  - Arthritis - probably less common since IVIG treatment
  - Hydrops of the gallbladder (RUQ pain, seen on USS)
  - Sterile pyuria, urethritis and diarrhoea
  - Pulmonary infiltrates or pneumonitis
- Inflammation at site of BCG scar
  - *Cross-reactivity of T cells in KD patients between specific epitopes of Mycobacterial and human heat shock proteins*

Clinical phase of KD

1. Acute febrile phase - characterized by fever and the other acute signs of illness and usually lasts 1-2 wk.
2. Subacute phase - is associated with desquamation, thrombocytosis, the development of CAA, the highest risk of sudden death, it lasts about 3 wk.
3. Convalescent phase - begins when all clinical signs of illness have disappeared and continues until the ESR returns to normal, typically about 6-8 wk after the onset of illness.

Clinical manifestations of Kawasaki Disease



Lab Investigations

1) TLC - ↑
2) Hb - ↓
3) Plt - N in 1st wk , ↑in 2nd & 3rd wk
4) ESR - ↑
5) CRP - ↑
6) SGOT & SGPT - ↑
7) Pus cells in urine - ↑
8) CSF pleocytosis - can be +

Table 191.1 | Clinical and Laboratory Features of Kawasaki Disease

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 wk 2 and 3
- Polymorphous exanthem
- Bilateral bulbar conjunctival injection without exudate
- Erythema and cracking of lips, strawberry tongue, and/or erythema of oral and pharyngeal mucosa
- Cervical lymphadenopathy (>1.5 cm diameter), usually unilateral

Exclusion of other diseases with similar findings‡

These features do not have to occur concurrently.

OTHER CLINICAL AND LABORATORY FINDINGS

Cardiovascular System

Myocarditis, pericarditis, valvular regurgitation, shock
Coronary artery abnormalities
Aneurysms of medium-sized noncoronary arteries
Peripheral gangrene
Aortic root enlargement

Respiratory System

Peribronchial and interstitial infiltrates on chest radiograph
Pulmonary nodules

Musculoskeletal System

Arthritis, arthralgias (pleocytosis of synovial fluid)

Gastrointestinal Tract

Diarrhea, vomiting, abdominal pain
Hepatitis, jaundice
Hydrops of gallbladder
Pancreatitis

Central Nervous System

Extreme irritability
Aseptic meningitis (pleocytosis of cerebrospinal fluid)
Facial nerve palsy
Sensorineural hearing loss

Genitourinary System

Urethritis/meatitis, hydrocele

Other Findings

Desquamating rash in groin
Retropharyngeal phlegmon
Anterior uveitis by slit-lamp examination
Erythema, induration at bacille Calmette-Guérin inoculation site

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 wk 1§
Sterile pyuria
Elevated serum transaminases
Elevated serum γ-glutamyl transpeptidase
Pleocytosis of cerebrospinal fluid
Leukocytosis in synovial fluid

- Cardiac involvement

a. Myocarditis – manifests as tachycardia disproportionate to fever, along with diminished left ventricular systolic function.

b. Cardiogenic shock (KD shock syndrome) – with markedly diminished left ventricular function

c. Pericarditis with a small pericardial effusion can also occur during the acute illness.

d. Mitral regurgitation – in 10-25% of patients

e. CAA develop in up to 25% of untreated patients in the 2nd to 3rd wk of illness.

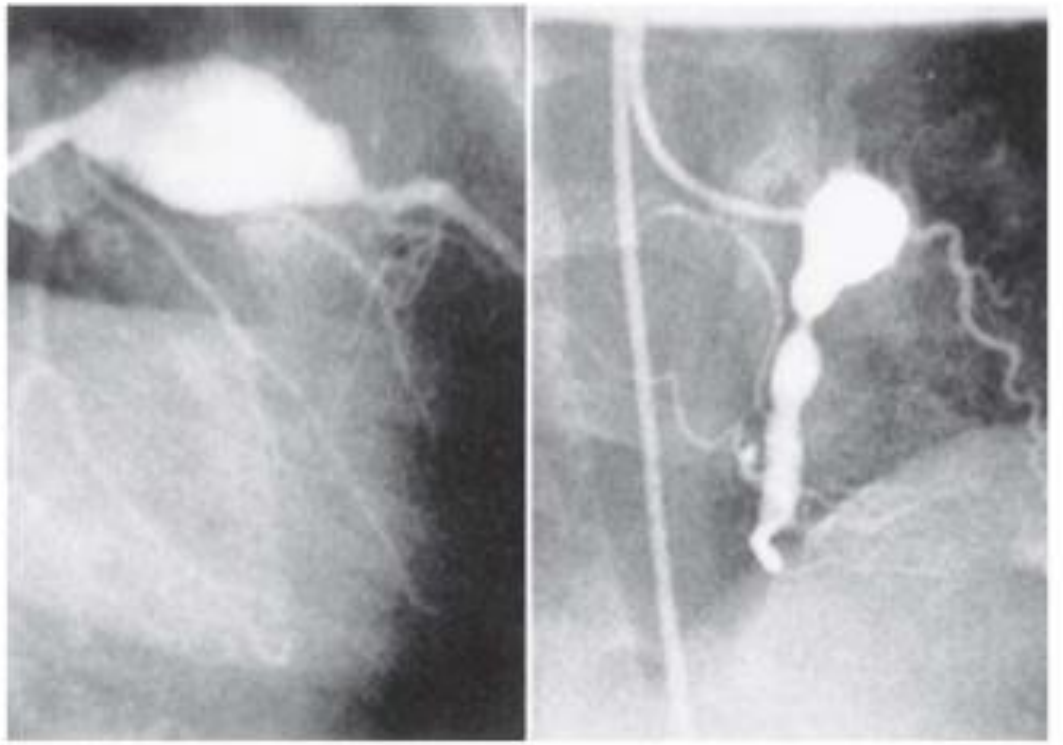
Coronary angiogram

Demonstrating giant aneurysm

of the left anterior descending coronary artery (LAD) with obstruction

and giant aneurysm of the right coronary artery (RCA) with an area of

severe narrowing in 6 yr old boy.



9) 2 D Echo - lack of normal tapering of the vessels

- Body surface area–adjusted coronary artery dimensions in the 1st 10 days of illness appear to be good predictors of involvement during early follow-up.

-Aneurysms have been defined with use of absolute dimensions by the Japanese Ministry of Health and are classified as

i. small (<5 mm internal diameter)
ii. medium (5-8 mm internal diameter)
iii. giant (>8 mm internal diameter).

- coronary artery dimensions, adjusted for BSA , provide a more accurate assessment of the size of RCA or LAD as compared with expected population norms.
- A *z* score ≥ 2.5 (ie, a coronary dimension that is ≥ 2.5 SDs above the mean for BSA) is expected to occur in 0.6% of the population without KD.
- *A z* score ≥ 3.0 in 1 of these segments would be expected to occur in 0.1% of the population without KD.

The AHA *z*-score classification system is as follows:

1. No involvement: always <2

2. Dilation only: 2 to <2.5; or if initially <2, a decrease in *z* score during follow-up ≥1

3. Small aneurysm: ≥2.5 to <5

4. Medium aneurysm: ≥5 to <10, and absolute dimension <8 mm

5. Large or giant aneurysm: ≥10, or absolute dimension ≥8 mm

- Echocardiography

I. *at diagnosis*

II. *again after 2-3 wk of illness.*

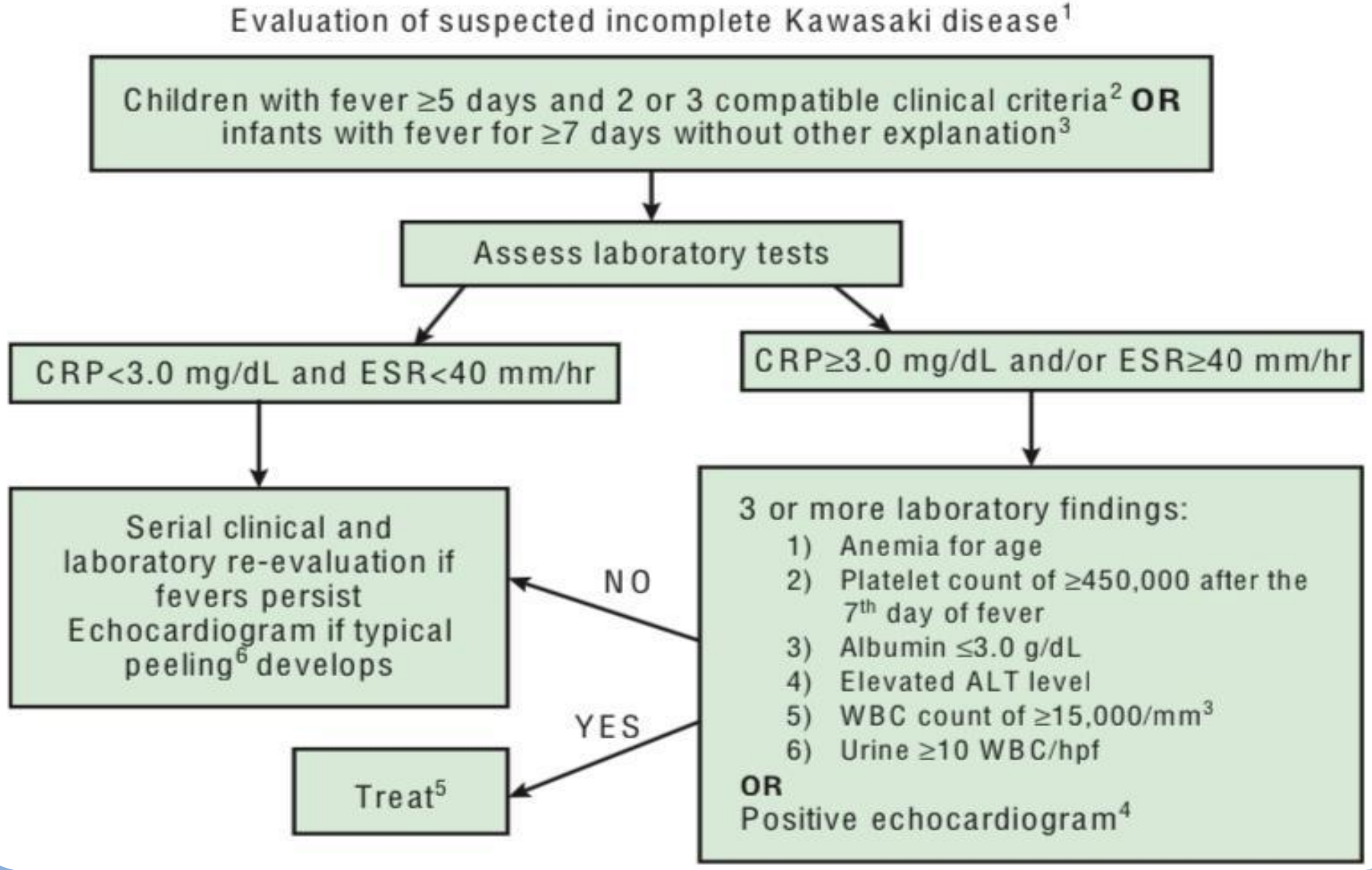
III. *If the results are normal, a repeat study should be performed 6-8 wk after onset of illness.*

Atypical and Incomplete KD

Incomplete KD – they have less then 4 clinical criteria along with fever

Atypical KD – patients who have a problem, such as renal impairment, that generally is not seen in Kawasaki disease.

- Incomplete KD is more common in young infants
- They have high risk of developing CAD
- Incomplete KD should be considered in all children with unexplained fever for 5 days associated with 2 or 3 of the principal clinical features of KD
- ECHO should be considered in any infant aged 6 months with fever of 7 days' duration, lab evidence of systemic inflammation, and no other explanation for the febrile illness.


Evaluation of suspected incomplete Kawasaki disease[1]
Children with fever ≥5 days and 2 or 3 compatible clinical criteria[2] OR infants with fever for ≥7 days without other explanation[3]
Assess laboratory tests
CRP<3.0 mg/dL and ESR<40 mm/hr
CRP≥3.0 mg/dL and/or ESR≥40 mm/hr
Serial clinical and laboratory re-evaluation if fevers persist
Echocardiogram if typical peeling[6] develops
NO
YES
3 or more laboratory findings:
1) Anemia for age
2) Platelet count of ≥450,000 after the 7th day of fever
3) Albumin ≤3.0 g/dL
4) Elevated ALT level
5) WBC count of ≥15,000/mm3
6) Urine ≥10 WBC/hpf
OR
Positive echocardiogram[4]
Treat[5]

Echocardiography is considered positive for purposes of this algorithm if any of 3 conditions are met:

z score of left anterior descending coronary artery or right coronary artery ≥2.5;

coronary artery aneurysm is observed;

or ≥3 other suggestive features exist, including decreased left ventricular function, mitral regurgitation, pericardial effusion, or *z* scores in left anterior descending coronary artery or right coronary artery of 2-2.5.

Table 191.2 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 ± retropharyngeal phlegmon
Meningococcemia
Urinary tract infection

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

OTHER
Toxic shock syndromes
Serum sickness
Staphylococcal scalded skin syndrome
Macrophage activation syndrome
Drug hypersensitivity reactions
Stevens-Johnson syndrome
Aseptic meningitis

Treatment

- Acute stage : - IVIG 2 gm/kg over 10 – 12 hrs

  - 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/day once daily orally until 6-8 wk after illness onset if normal coronary findings throughout course

- Long term therapy for patient with CAA : -
- 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

Table 191.3 | Treatment of Kawasaki Disease

ACUTE STAGE

Intravenous immune globulin 2 g/kg over 10-12 hr
and
Aspirin 30-50 mg/kg/day or 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

- IVIG-resistant KD : - occurs in 15% of patients
- Defined by persistent or recrudescent fever 36 hr after completion of the initial IVIG infusion.
- Patients with IVIG resistance are at increased risk for CAA.
- another dose of IVIG at 2 g/kg is administered to patients with IVIG resistance.
- TNF inhibitors, including infliximab and etanercept, have also been given for the treatment

Table 191.4 Treatment Options for IVIG-Resistant Patients With Kawasaki Disease

AGENT	DESCRIPTION	DOSE
MOST FREQUENTLY ADMINISTERED		
IVIG: 2nd infusion	Pooled polyclonal IG	2 g/kg IV
IVIG + prednisolone	IVIG + corticosteroid	IVIG: 2 g/kg IV + prednisolone 2 $mg \cdot kg^{-1} \cdot d^{-1}$ IV divided every 8 hr until afebrile, then prednisone orally until CRP normalized, then taper over 2-3 wk
Infliximab	Monoclonal antibody against TNF-α	Single infusion: 5 mg/kg IV given over 2 hr
ALTERNATIVE TREATMENTS		
Cyclosporine	Inhibitor of calcineurin-NFAT pathway	IV: 3 $mg \cdot kg^{-1} \cdot d^{-1}$ divided every 12 hr PO: 4-8 $mg \cdot kg^{-1} \cdot d^{-1}$ divided every 12 hr Adjust dose to achieve trough 50-150 ng/mL; 2 hr peak level 300-600 ng/mL
Anakinra	Recombinant IL-1β receptor antagonist	2-6 $mg \cdot kg^{-1} \cdot d^{-1}$ given by subcutaneous injection
Cyclophosphamide	Alkylating agent blocks DNA replication	2 $mg \cdot kg^{-1} \cdot d^{-1}$ IV
Plasma exchange	Replaces plasma with albumin	Not applicable

Poor prognostic markers

i. young age,
ii. male gender
iii. persistent fever,
iv. poor response to IVIG,
v. laboratory abnormalities - neutrophilia, thrombocytopenia, transaminitis, hyponatremia, hypoalbuminemia, elevated CRP levels.
vi. Asian and Pacific Islander race and Hispanic ethnicity

Complications

- small solitary aneurysm – aspirin should be continued indefinitely
- larger or numerous aneurysms – may require the addition of other antiplatelet agents or anticoagulation (pediatric cardiologist)
- Acute thrombosis – thrombolytic therapy
- *Reye syndrome* - d/t long-term aspirin therapy

- should receive annual influenza vaccination to reduce the risk of Reye syndrome.

- MMR and varicella vaccinations should generally be deferred until 11 mo after IVIG administration as IVIG interfere with immune response.

- All children with a history of KD should be counselled regarding

a. heart-healthy diet
b. adequate amounts of exercise
c. tobacco avoidance, and
d. Intermittent lipid monitoring.

Questions

One of the diagnostic criteria of Kawasaki disease is:

- a.Purulent conjunctivitis.
- b.Fever for at least 15 days.
- c.Fissured lips.
- d.Vesicular rash on the extremities.

Lymphadenopathy of Kawasaki disease is characterized by:

- a.Usually unilateral.
- b.Less than 1.5 cm in diameter.
- c.Commonly axillary.
- d.Very tender.

Laboratory results in Kawasaki disease may include:

- a.Thrombocytosis.
- b.Sterile pyuria.
- c.Neutrophilia.
- d.Hypoalbuminemia.
- e.All of the above.

Echocardiography is indicated in Kawasaki disease:

- a.At onset and then weekly thereafter.
- b.At diagnosis, 2 weeks and then 6 weeks after onset.
- c.At diagnosis, 2 months and then 6 months after onset.
- d.Only if there are ECG changes.

Intravenous immunoglobulin (IVIG) is given as follows:

- a.400 mg/kg over 10-12 hours.
- b.Two g/kg over 10-12 hours.
- c.One g/kg/day for 5 days.
- d.400 mg/kg/day for 10 days.


Thank you
for your
patience listening