Kawasaki Disease Module

Clinical Features: *Dr Bhaskar Shenoy*

Incomplete or Atypical KD: *Dr. Pratap Kumar Patra*

Role of laboratory investigations and imaging : *Dr. Ankur Kumar Jindal*

TREATMENT: *Dr Priyankar Pal*

KAWASAKI DISEASE – CLINICAL FEATURES

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- Clinical Features
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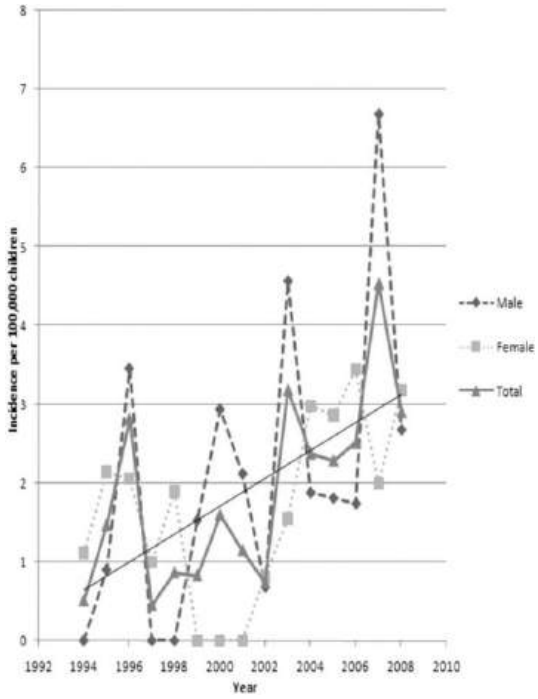
Epidemiology of Kawasaki disease at Chandigarh, India

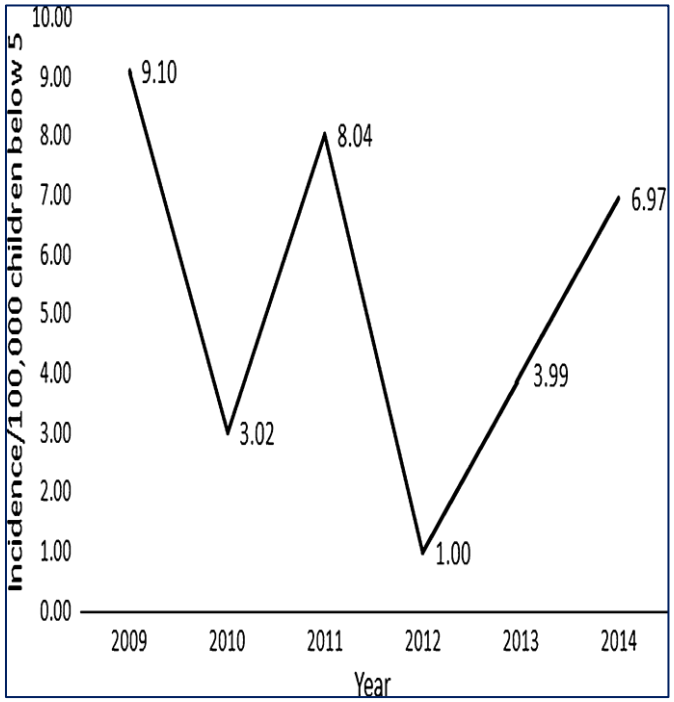
Between 1994 - 2008



Incidence of KD in children <15 at Chandigarh (1994 – 2008)

0.51/100,000 (1994) to 4.54/100,000 (2007)

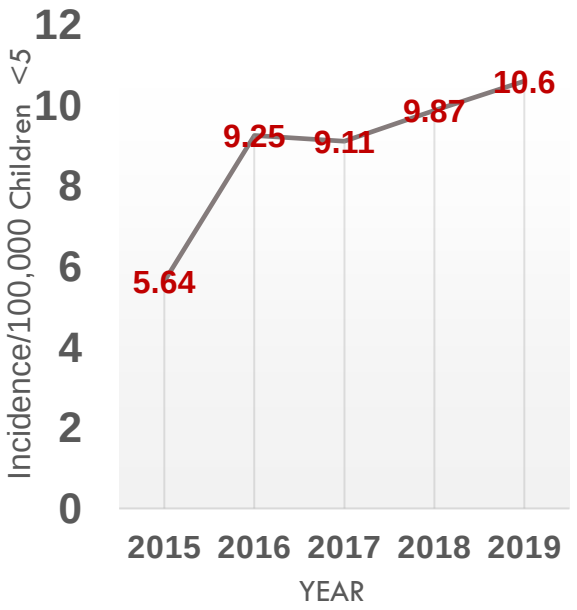
Between 2009 - 2014



Incidence of KD in children <5 at Chandigarh (2009-2014)

Mean incidence: ***5.35/100,000***

Between 2015 - 2019



Incidence of KD in children <5 at Chandigarh (2015-2019)

Mean incidence: ***8.89/100,000***

Singh S et al. Is Kawasaki disease incidence rising in Chandigarh, North India? ***Arch Dis Child. 2011***

Singh S, Bhattad S. Kawasaki disease incidence at Chandigarh, North India, 2009-2014. ***Rheumatol Int. 2016***

Incidence of Kawasaki disease among children in Chandigarh, India during 2015–2019: a trend analysis Pilania, Rakesh Kumar et al. The Lancet Regional Health - Southeast Asia, Volume 29, 100474

Kawasaki Disease
Mucocutaneous Lymph Node Syndrome

"A self-limited vasculitis of unknown etiology that predominantly affects children younger than 5 years. It is now the most common cause of acquired heart disease in children in the United States and Japan."

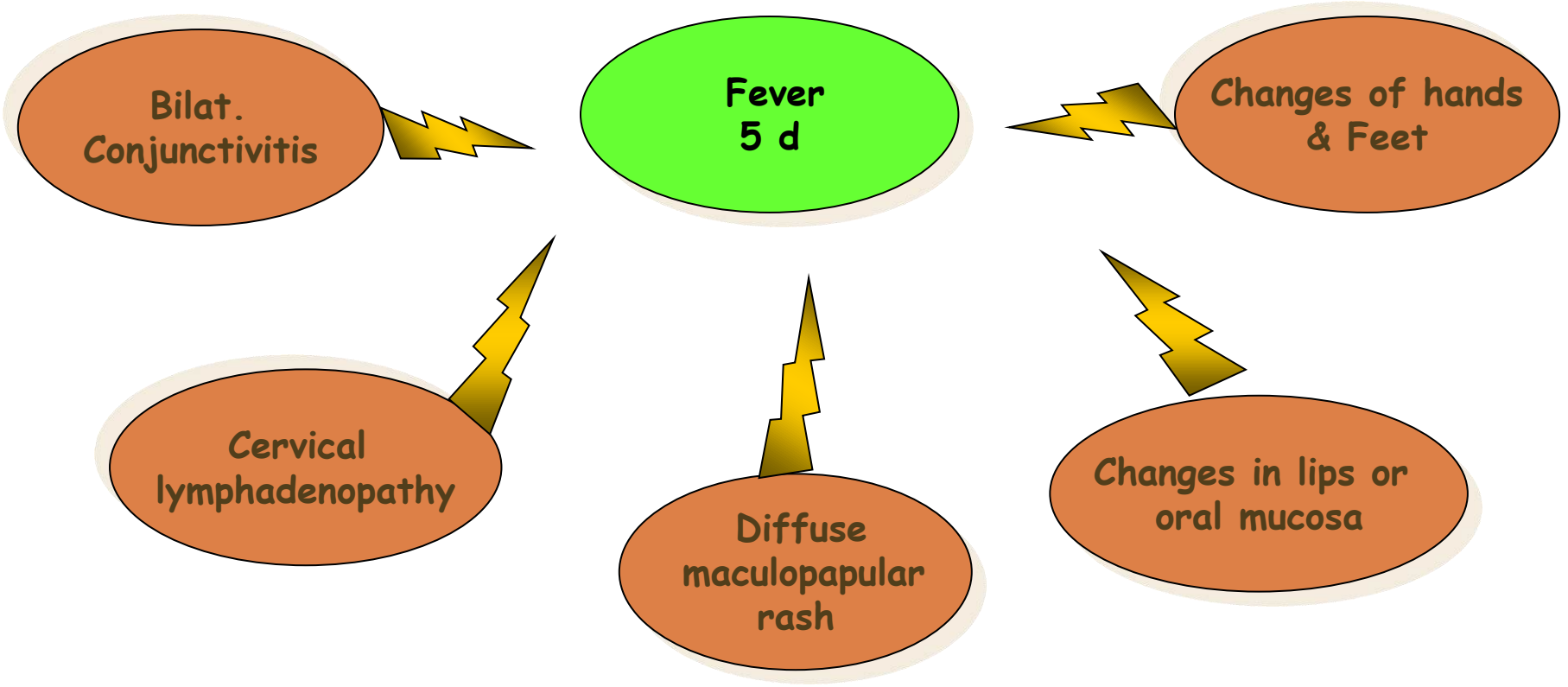
Jane Burns, MD*

*Burns, J. Adv. Pediatr. 48:157. 2001.

- Classical Kawasaki
- Incomplete Kawasaki
- Atypical Kawasaki

Criteria for diagnosis

(Classic Kawasaki)



Other Clinical Findings/Non classical features

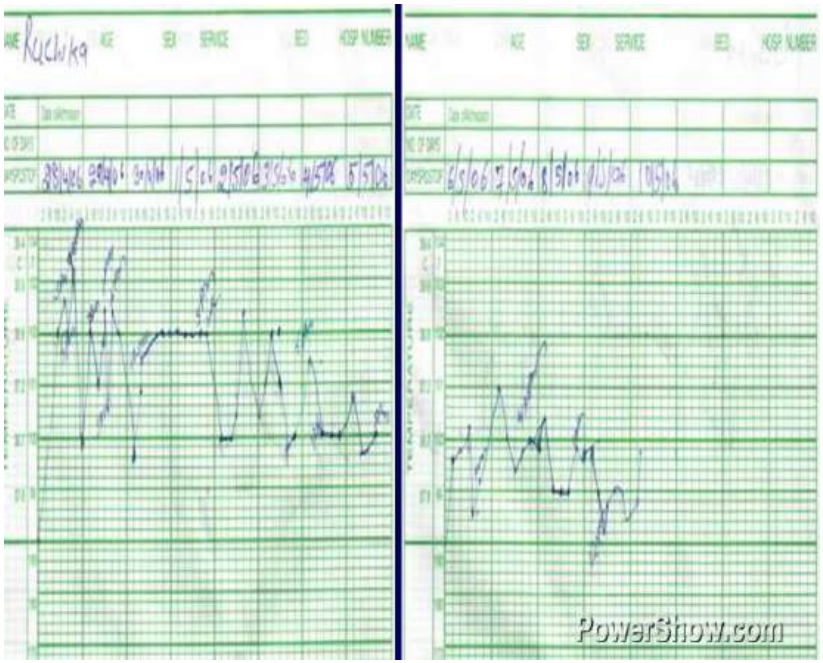
- Perianal or perineal desquamation is typically seen during the acute phase of KD, as early as day 6 of fever .
- Reactivation of BCG scar:
- Nervous system: Irritability is a common finding , marked in infants. It is usually out of proportion to the degree of fever and thought to be a manifestation of aseptic meningitis.

- Profound sensorineural hearing loss may be present. Facial palsy, though rare, has been well documented.
- Prolonged unexplained fever with extreme irritability may be the only clinical manifestation in many infants below 6 months of age without any of the principal clinical signs of KD.
- Gastrointestinal system: Diarrhea, vomiting, pain abdomen, hepatitis, pancreatitis and gallbladder hydrops .
- Genitourinary system: Urethritis/meatitis is a common feature in the acute phase presenting as sterile pyuria.
- Musculoskeletal system: Pain and swelling of interphalangeal joints may occur during the acute phase. Arthritis of large joints (knees and ankles) usually occur during the convalescent phase and is seen in 10-15% of cases.

- Respiratory system: Tachypnea, dyspnea, and cough may rarely be seen. Chest radiograph may reveal peribronchial or interstitial infiltrates.
- Cardiovascular: Pericarditis, myocarditis, valvular dysfunction, congestive heart failure, and peripheral gangrene.
- About 5% of children may present with cardiovascular collapse and shock that may be difficult to differentiate from toxic shock.
- KD shock is readily responsive to IVIg which helps in differentiating from a viral myocarditis.
- Beau lines: Transverse grooves in the nails can be noted 1-2 months after the onset of illness indicating a catabolic process in the preceding weeks.

Classical manifestations

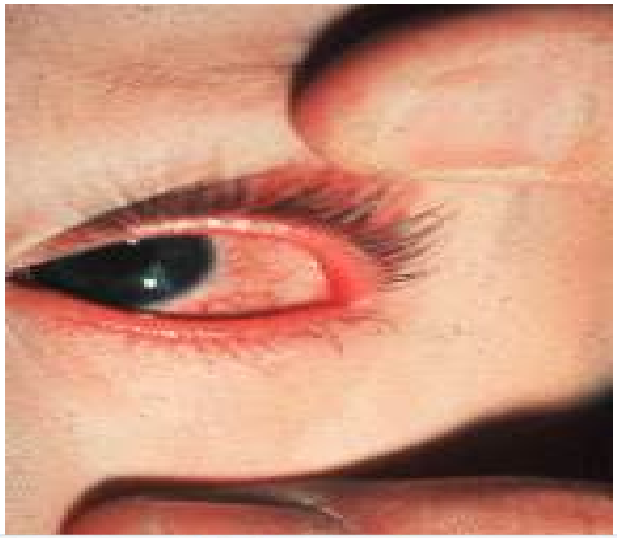
FEVER



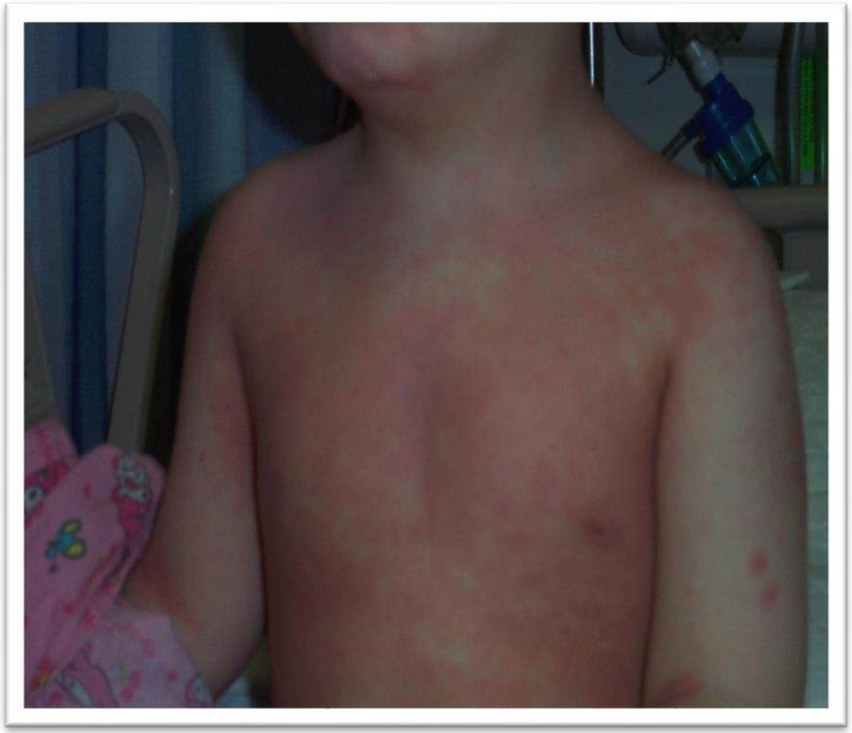
- Most common manifestation of KD
- High-spiking
- Peak temperatures>39°
- Without therapy, fever lasts a mean of 11 days but may last up to 4 weeks
- Usually resolves within 2 days of appropriate therapy

BULBAR CONJUNCTIVITIS

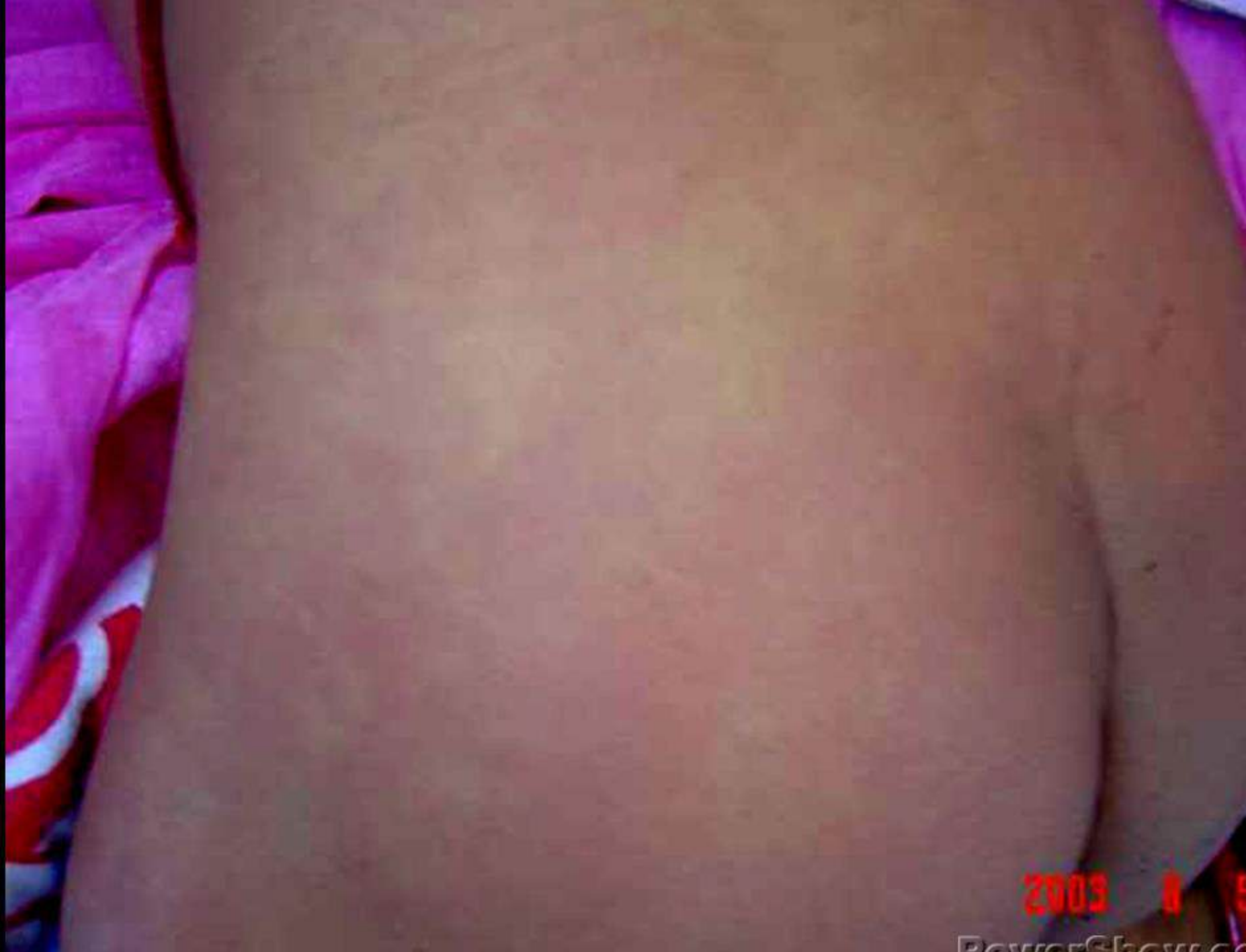
- Appears shortly after the onset of fever and is seen in 90% of patients
- Typically spares the limbus
- Painless and non-exudative
- Mild acute iridocyclitis or anterior uveitis may be seen on slit lamp exam



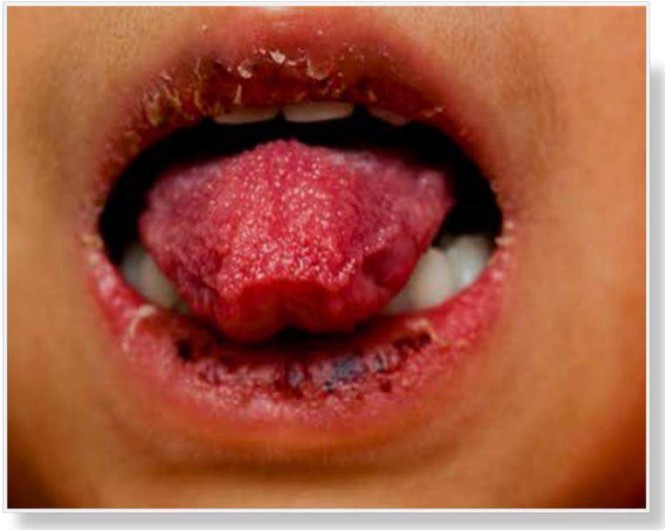
POLYMORPHOUS EXANTHEM

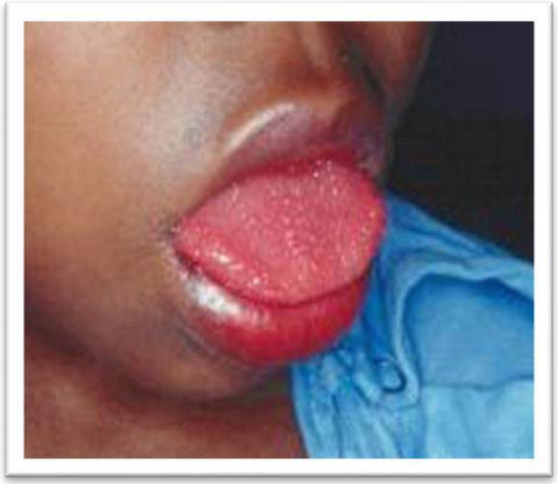


- Rash usually appears within 5 days of fever
- Rash usually involves the trunk and extremities
- Rash most commonly a diffuse maculopapular eruption, but may be urticarial, scarlatiniform, erythroderma.
- NEVER VESICULAR


2003

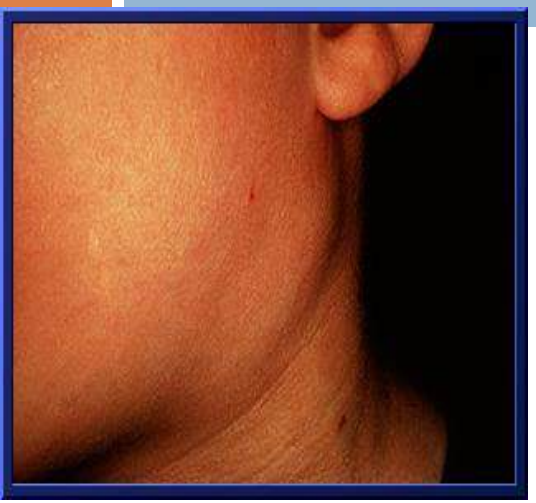
CHANGES IN THE LIPS AND ORAL CAVITY

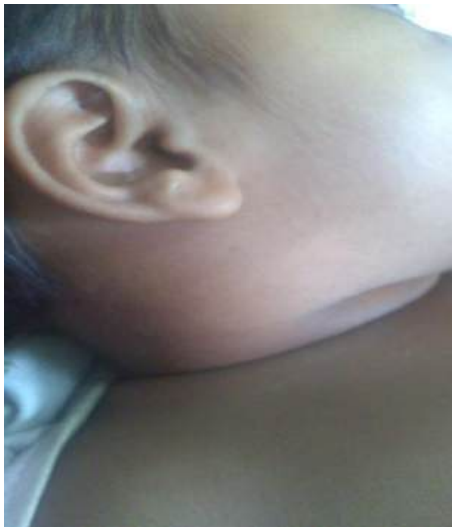




- Erythema, dryness, fissuring, peeling, cracking and bleeding of the lips
- “Strawberry tongue” with erythema and prominent papillae
- Diffuse erythema of the oral mucosa

CERVICAL LYMPHADENOPATHY



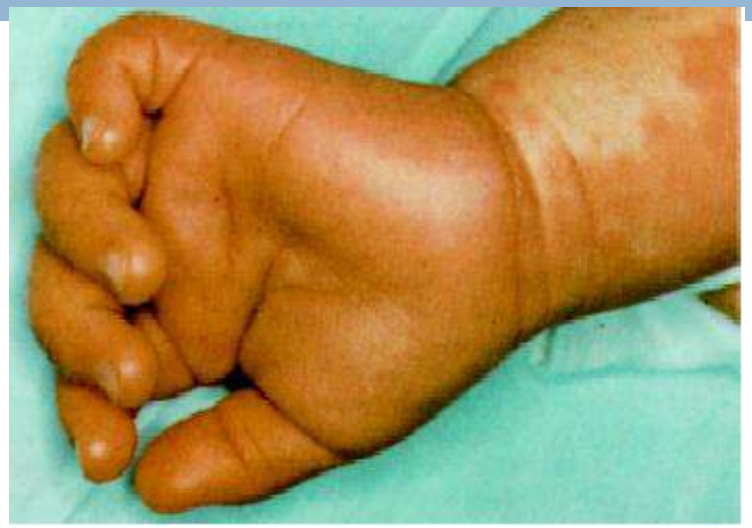


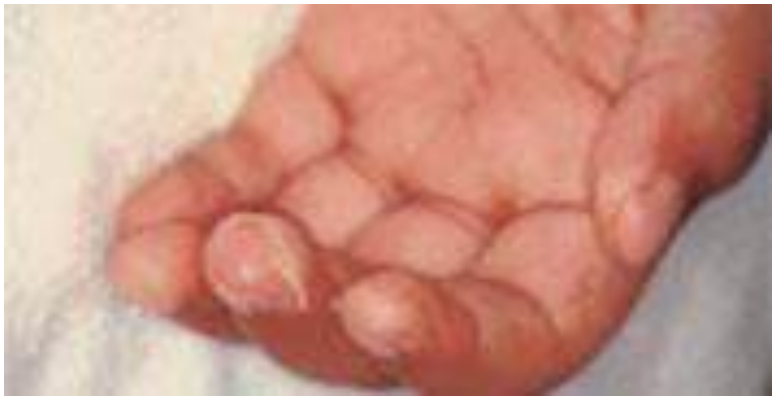
- Unilateral and confined to the anterior cervical triangle
- ≥ 1.5 cm in diameter

  (> 1 cm in infants)
- Firm and non-fluctuant

EXTREMITY CHANGES

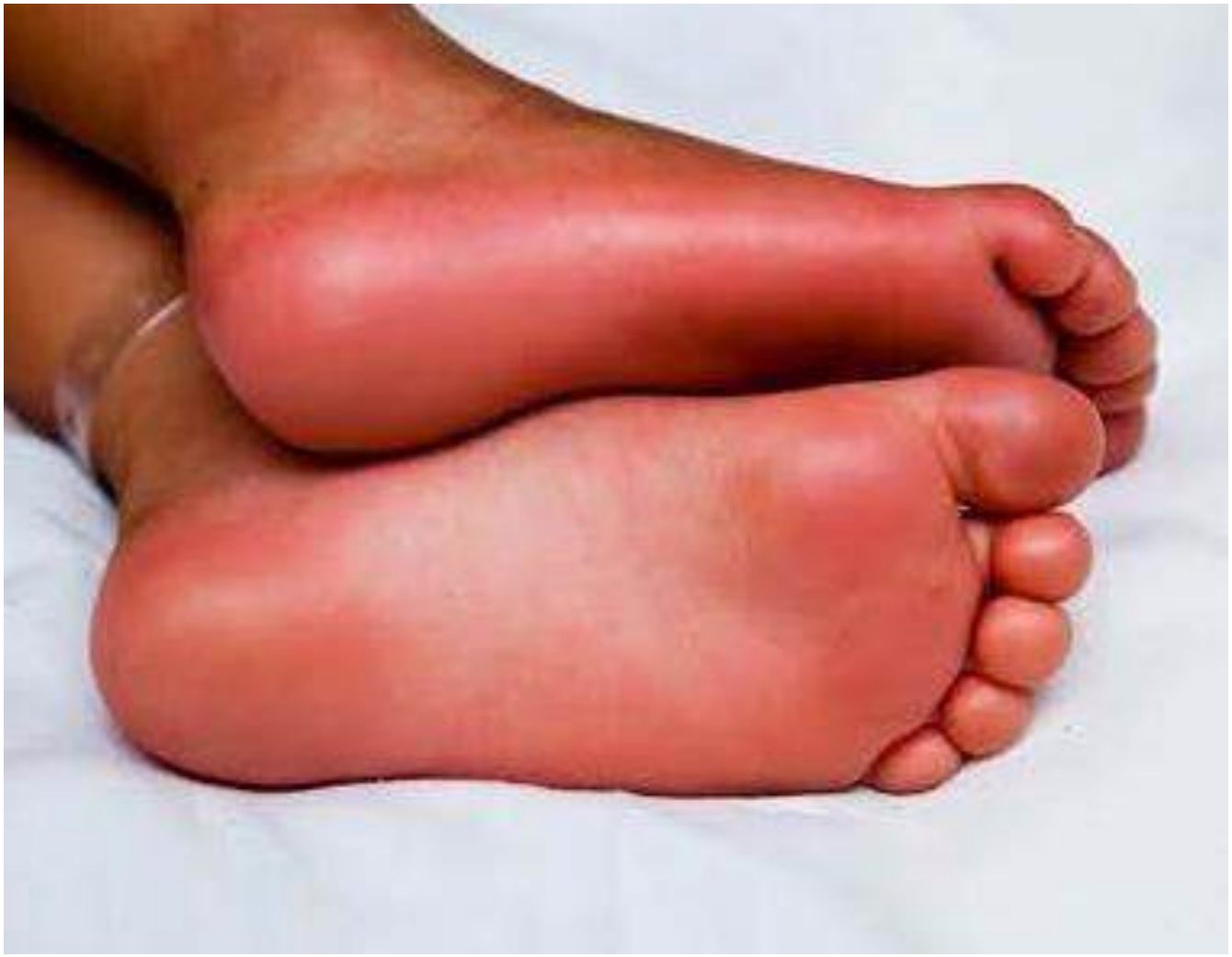
- Acute:
  - Erythema of the palms and soles and/or edema of the hands and feet
- Subacute (2-3 weeks):
  - Desquamation of the fingers and toes (70-98% of children)-



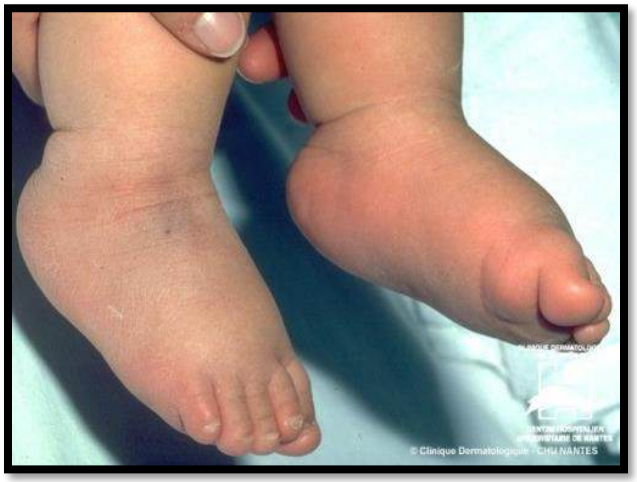


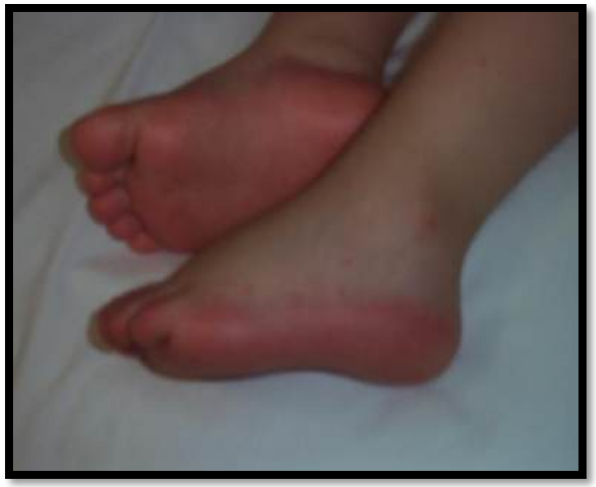
Typical Periungual Desquamation

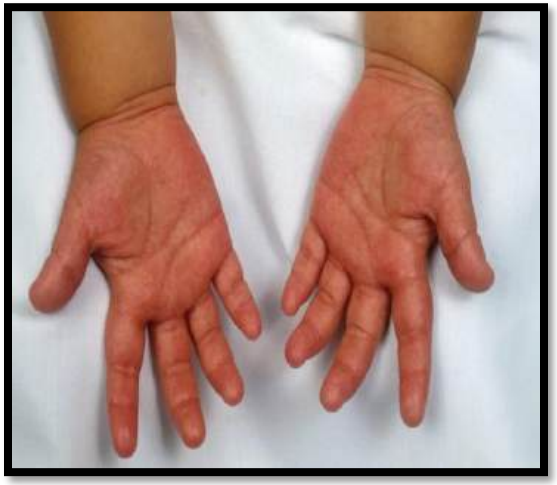
RED PALMS AND SOLES

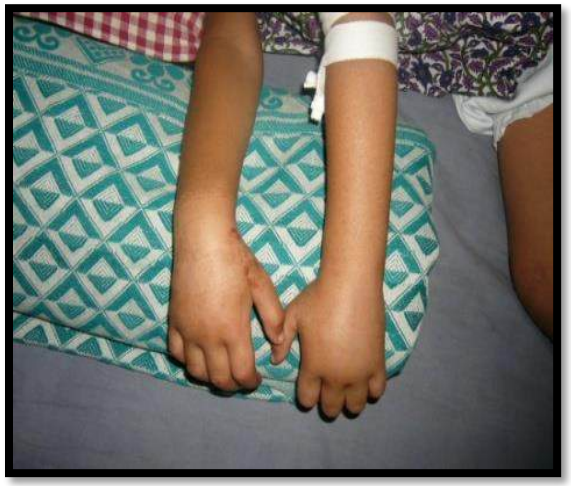


EDEMA AND ERYTHEMA OF HANDS & FEET

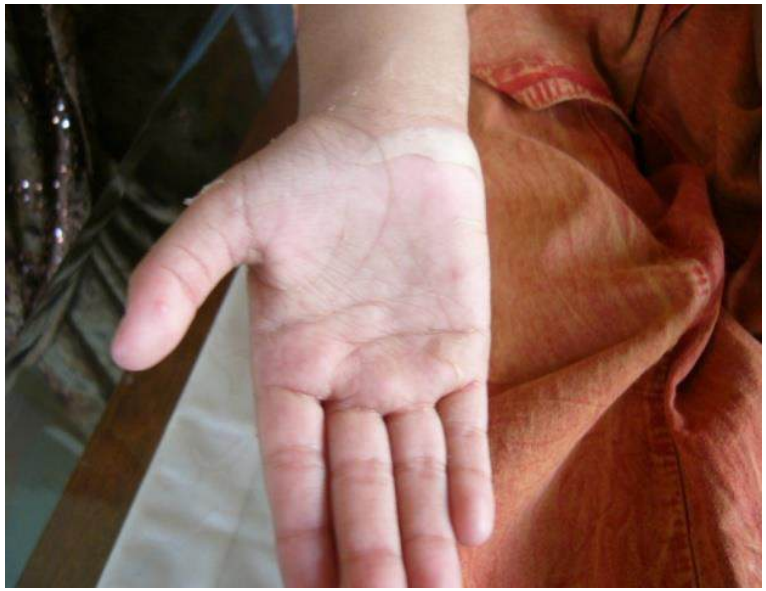


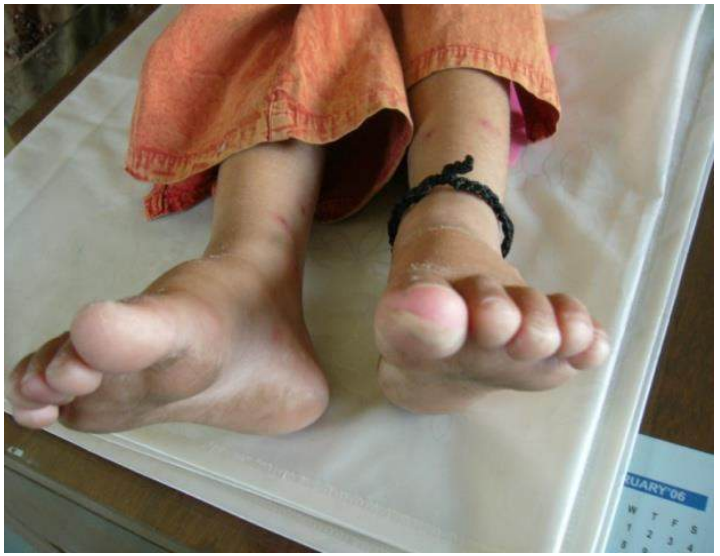


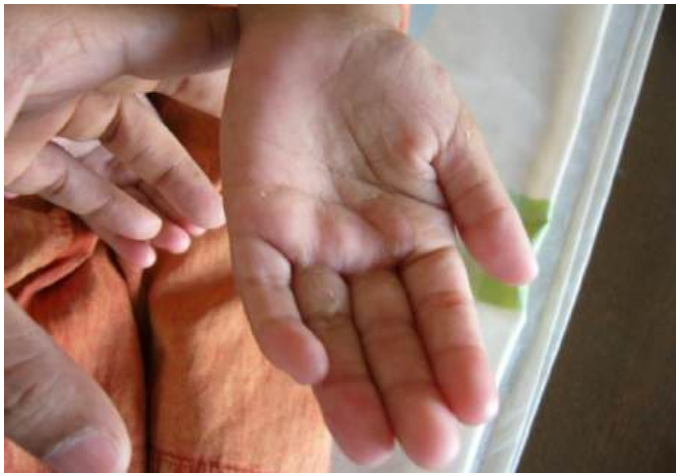




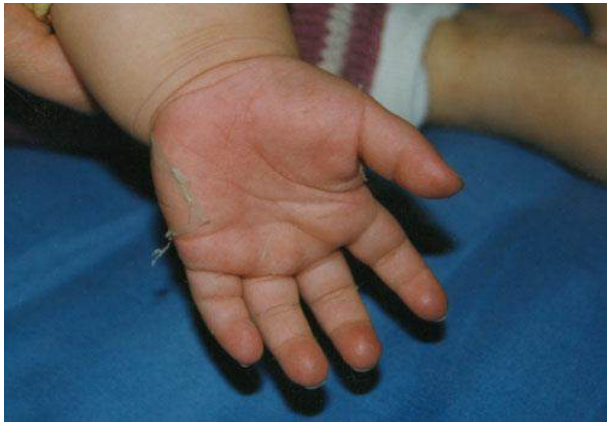
SKIN PEELING

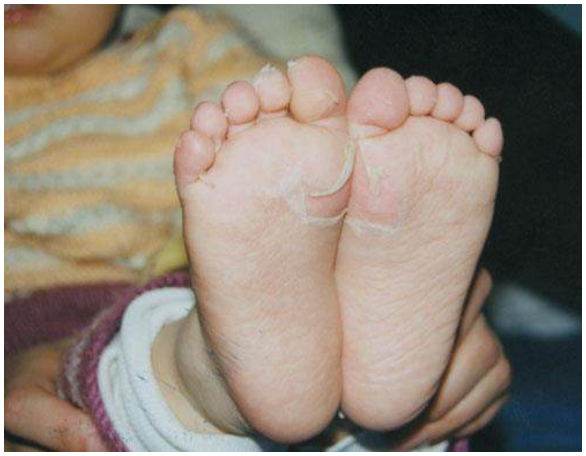


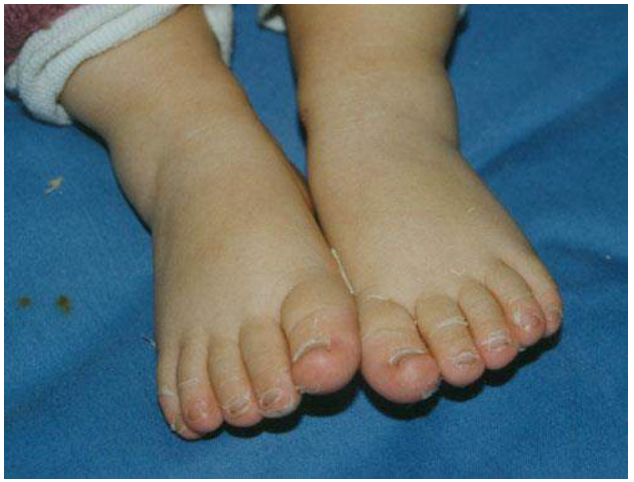




DESQUAMATION OF FINGERS AND TOES





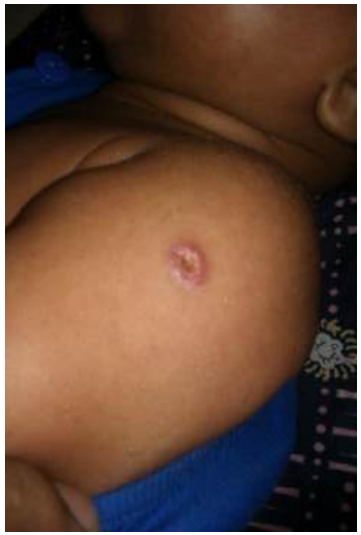


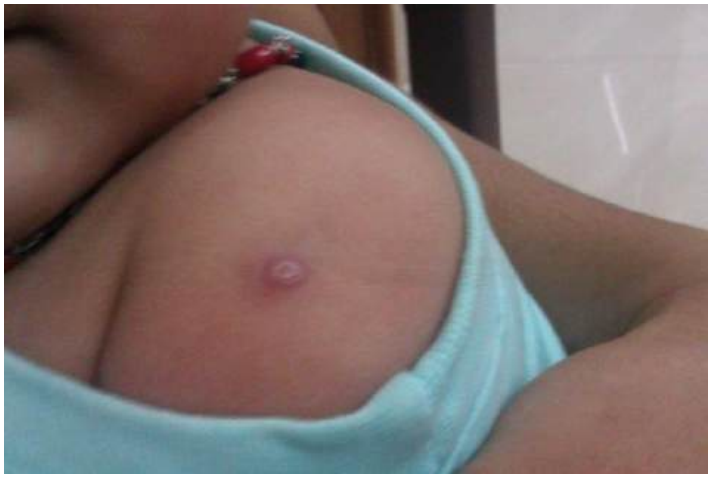
EXTREME IRRITABILITY

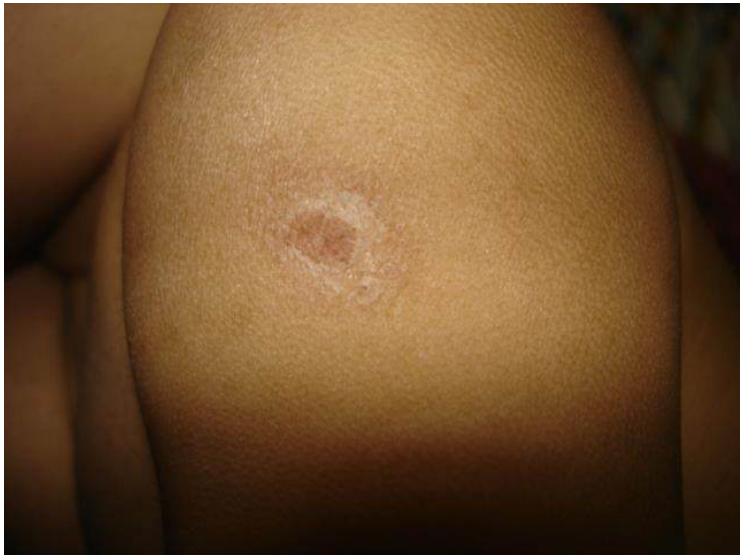
EXTREME IRRITABILITY AND RESPONSE TO TREATMENT WITH IVIG

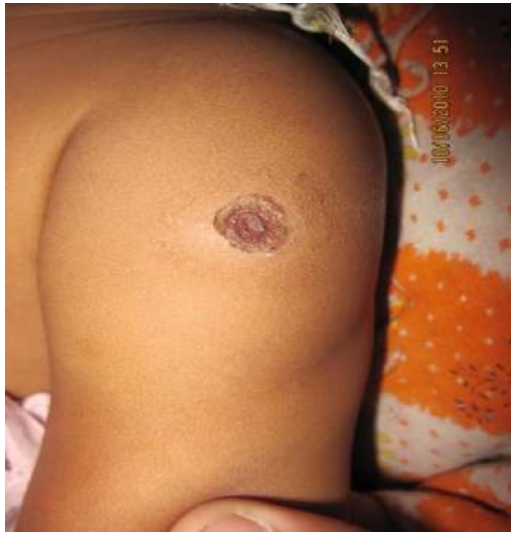
Reactivation of BCG Scar

- Erythema and Induration at the site of BCG
- Mechanism – Cross Reactivity of T cells in KD b/w specific epitopes of mycobacterial and human heat shock protein

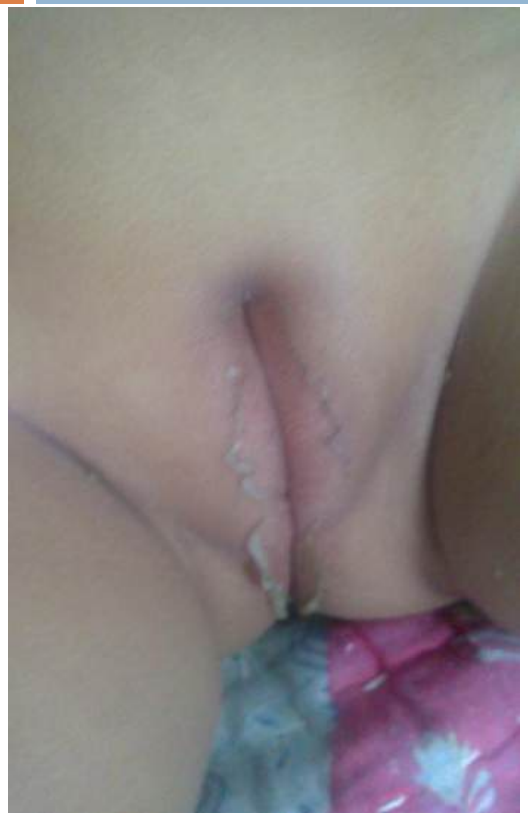


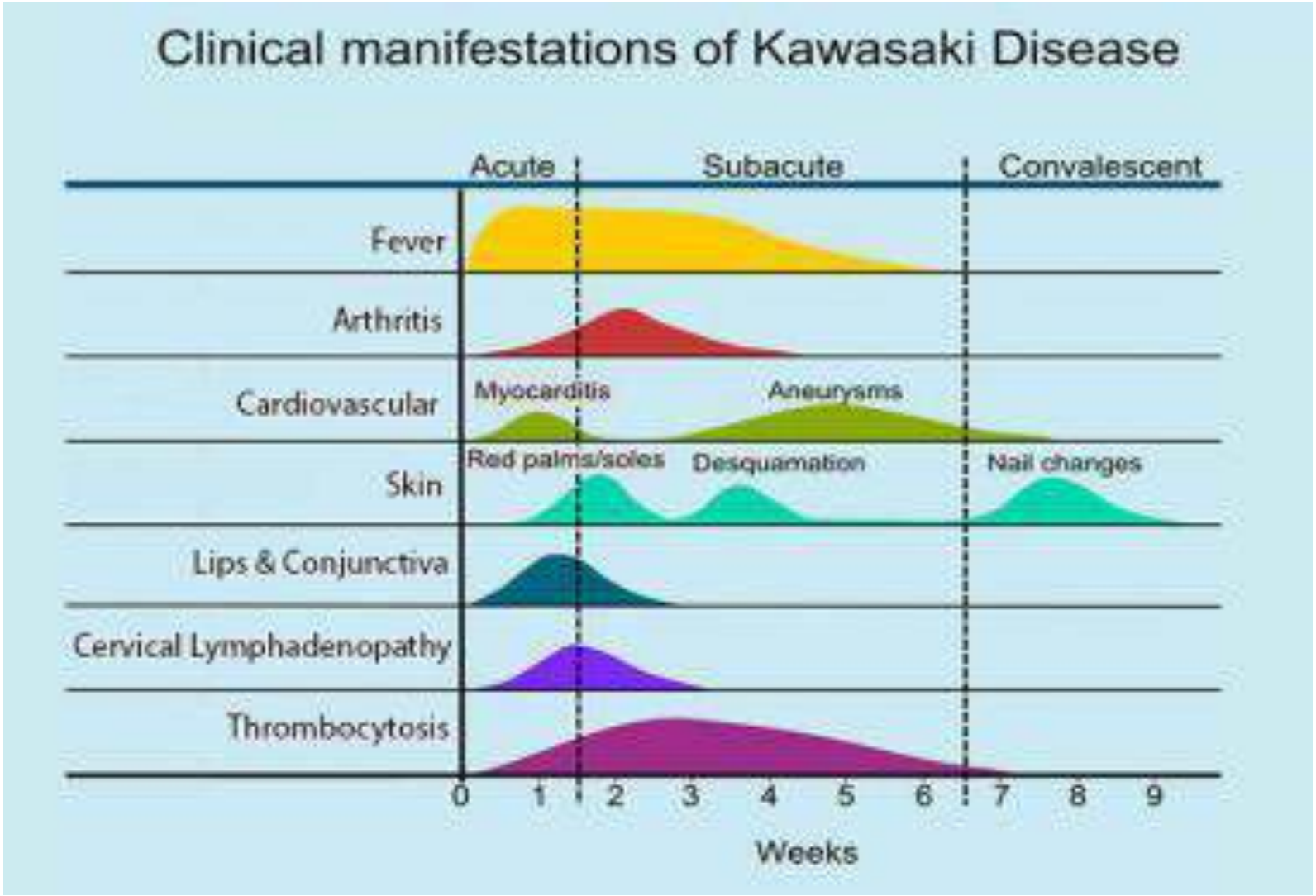






PERINEAL SKIN PEELING




Clinical manifestations of Kawasaki Disease
Acute
Subacute
Convalescent
Fever
Arthritis
Cardiovascular
Myocarditis
Aneurysms
Skin
Red palms/soles
Desquamation
Nail changes
Lips & Conjunctiva
Cervical Lymphadenopathy
Thrombocytosis
0 1 2 3 4 5 6 7 8 9
Weeks

?

- What are the clinical features where one should **NOT** think of KD?

Findings that suggest alternative diagnosis

- Pustular or vesicular rash
- Generalized lymphadenopathy, bilateral cervical nodes
- Hepatosplenomegaly
- Discrete oral lesions
- Tonsillar or pharyngeal exudates
- Exudative conjunctivitis
- Persistent coryza

Circulation 2004;110:2747–71

Common pitfalls in the diagnosis

- Fever and enlarged cervical lymph nodes – bacterial lymphadenitis
- Rash and mucosal changes
  - drug reaction
  - viral infection
- Sterile pyuria – UTI
- Fever, rashes, CSF pleocytosis – Viral meningitis
- Acute abdomen –surgical condition

Infection Triggered KD

- Diagnosis is often missed because the clinical features of KD overlap with common childhood infections.
- The etiology is still unknown, though multiple theories have been proposed based on available epidemiological data .
- Current consensus is that an infectious trigger initiates an abnormal and robust innate inflammatory response in genetically predisposed children .

Association of KD with viral infections

- Epstein–Barr virus,
- cytomegalovirus,
- adenovirus,
- parvovirus B19,
- herpes virus 6,
- parainfuenza type 3,
- measles,
- rotavirus,
- dengue virus,
- human immunodefciency virus,
- varicella,
- H1N1 2009 pandemic infuenza,
- coronaviruses, and
- coxsackie B3 virus .

Mahajan A, Yadav S, Maheshwari A, Mahto D, Divya K, Ackshaya R, Meena H, Shakya S, Kumar V. Profile of Children with Kawasaki Disease Associated with Tropical Infections. Indian J Pediatr. 2022 Aug;89(8):759-764. doi: 10.1007/s12098-021-03953-9. Epub 2021 Dec 22. PMID: 34935098; PMCID: PMC8691965.

Type of pathogen	Etiologic agent
Bacteria	*Staphylococcus aureus*
	Streptococcus pyogenes
	Mycoplasma pneumoniae and *Chlamydia pneumoniae*
Viruses	Epstein–Barr virus
	Adenovirus
	Parvovirus B19
	Herpesvirus 6
	Parainfluenza virus type 3
	Measles
	Rotavirus
	Dengue
	Human immunodeficiency virus
	Varicella
	2009 H1N1 pandemic influenza virus
	Coxsackie B3 virus
	Human coronavirus NL63
	Bocavirus

- **Principi N, Rigante D, Esposito S. The role of infection in Kawasaki syndrome. J Infect. 2013 Jul;67(1):1-10. doi: 10.1016/j.jinf.2013.04.004. Epub 2013 Apr 18. PMID: 23603251; PMCID: PMC7132405.**

Superantigen-mediated activation of T cells	*Staphylococcus aureus*, *Streptococcus pneumoniae*, *Yersinia pseudotuberculosis*, *Mycoplasma pneumoniae*, *Mycobacterium tuberculosis*

REVIEW ARTICLE | Originally Published 13 November 2024 |

Update on Diagnosis and Management of Kawasaki Disease: A Scientific Statement From the American Heart Association

Pei-Ni Jone, MD, FAHA, Chair, Adriana Tremoulet, MD, MAS, FAHA, Nadine Choueiter, MD, FAHA, Samuel R. Dominguez, MD, PhD, FAHA, Ashraf S. Harahsheh, MD, FAHA, Yoshihide Mitani, MD, PhD, FAHA, Meghan Zimmerman, MD, MPH, FAHA, Ming-Tai Lin, MD, PhD, and Kevin G. Friedman, MD, FAHA, Vice Chair on behalf of the American Heart Association Rheumatic Fever, Endocarditis, and Kawasaki Disease Committee of the Council on Lifelong Congenital Heart Disease and Heart Health in the Young; Council on Cardiovascular and Stroke Nursing; Council on Cardiovascular Radiology and Intervention; and Council on Clinical Cardiology | AUTHOR INFO & AFFILIATIONS

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A LABORATORY TESTING
- CBC with manual differential, ESR, CRP, basic metabolic panel, ALT, GGT, TBili; bagged or clean-catch UA + microscopy

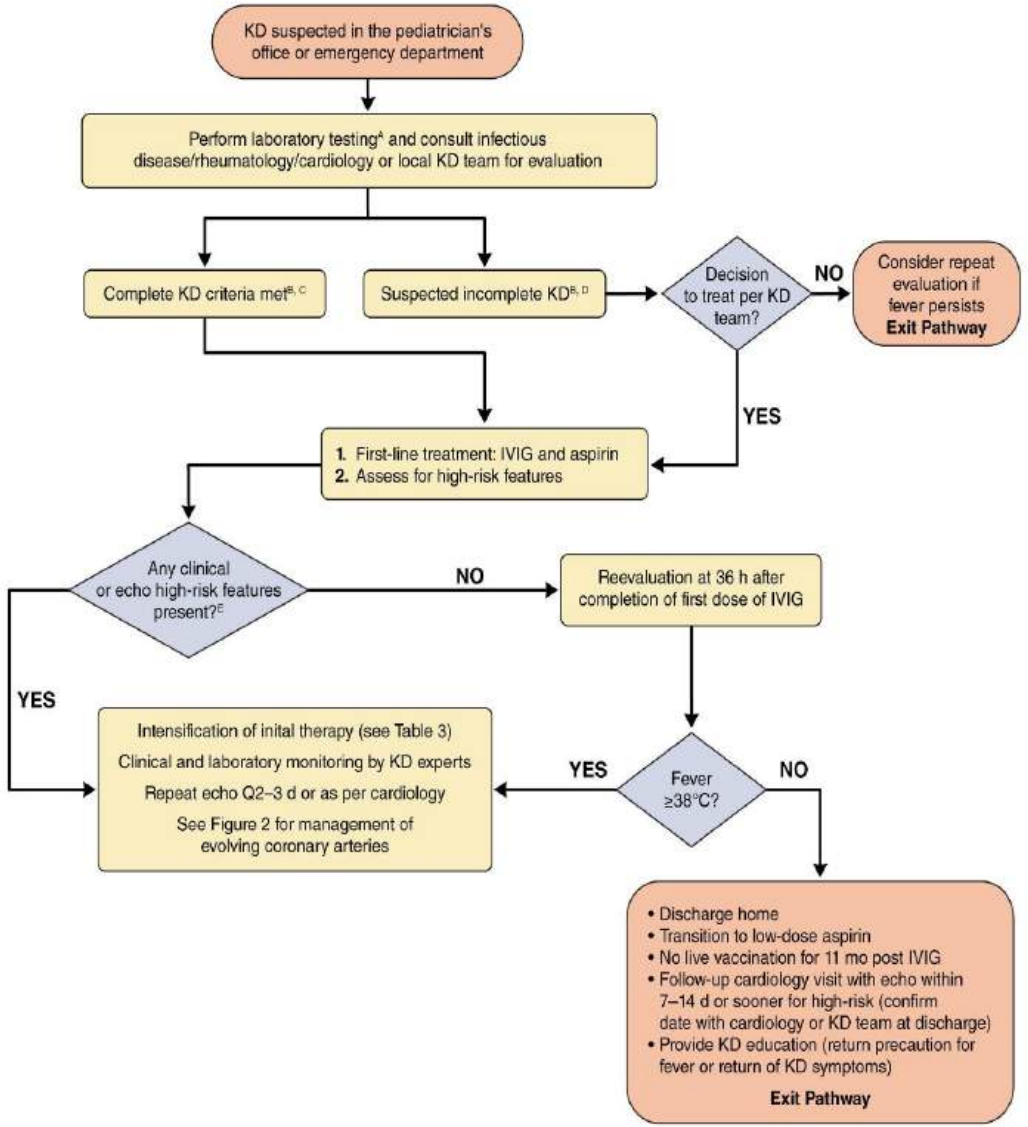
B CARDIAC EVALUATION
- ECG and Echo

C COMPLETE KD DIAGNOSTIC CRITERIA
- Fever for at least 4 d (the day of fever onset = day 1 of fever) + at least 4/5 principal clinical features at any point during the illness (does not need to be concurrent):
- Polymorphous rash
- Bulbar conjunctival injection without exudate; bilateral
- Oral changes: Erythema and cracking of lips, strawberry tongue, or erythema of oral and pharyngeal mucosa, or all of these
  - o Palmar and plantar erythema: usually accompanied by swelling; resolves with subsequent periungual desquamation in the subacute phase
- Cervical adenopathy: usually unilateral, cluster of nodes ≥1.5 cm in diameter
- Illness not explained by known alternative disease process

D SUSPECTED INCOMPLETE KD DIAGNOSTIC CRITERIA
- Prolonged unexplained fever and 2–3/5 clinical criteria OR infants with unexplained fevers 7 d (day 1 = day of the onset of fever) AND compatible laboratory or echocardiographic findings:
  - o CRP ≥3 mg/dL or ESR ≥40 mm/h, or both; +3 or more of the following:
    - – Anemia for age
    - – Platelets ≥450,000
    - – Albumin ≤3 g/dL
    - – Elevated ALT
    - – Elevated WBCs ≥15,000/mm³
    - – Urine WBCs ≥10/hpf
  - o Z score of LAD CA or RCA ≥2.5
  - o Or ≥3 other suggestive features exist, including decreased left ventricular function, mitral regurgitation, pericardial effusion or Z scores in LAD or RCA 2–2.5

E HIGH-RISK CRITERIA
- ≤6 mo of age
- LAD or RCA CA z-score ≥2.5 on baseline echo

Kawasaki Disease Evaluation and Management

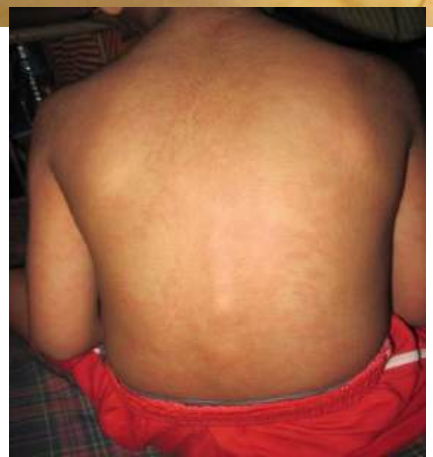


CASE 1

3 year old boy

Fever upto 103^0F

- Shown to a pediatrician on day 3
  - given oral amoxicillin-clavulanate
- Rash over trunk and eye redness on day 4



- Consulted a second pediatrician and dermatologist

  - ? **Drug rash**

- Antibiotics changed to oral cephalexin
- Day 6 – Continues to remain febrile

  Hb – 11, TLC – 12000 (N_{78}), PC 2.6 L

  ESR 70, CRP 50 mg/L

- Admitted and started on Inj ceftriaxone and amikacin

- Day 9 – Fever ++

  Swelling of feet and hands.

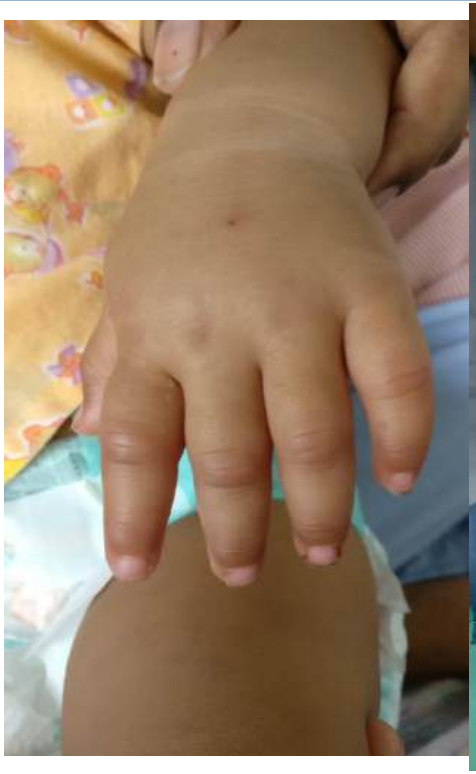
- More investigations:

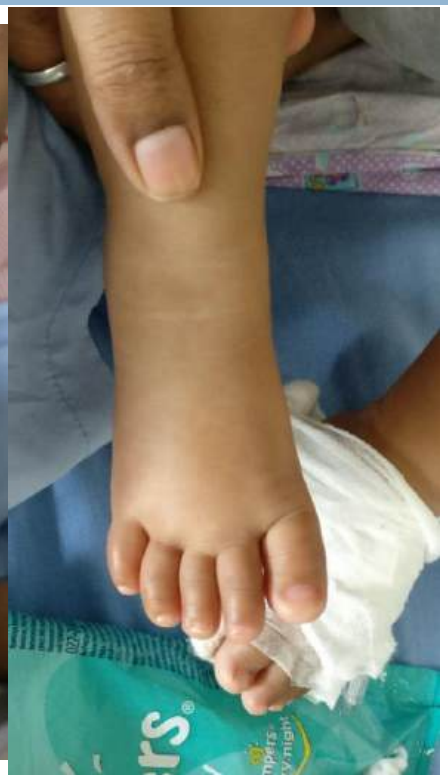
  Rickettsia/dengue/widal negative

  Urine examination – 15 pus cells/hpf, culture sterile.

- **Diagnosis - ? Sepsis/ ? UTI**

- Changed to vancomycin and meropenem.





Summing up:

3 year old boy

Fever, rash (confused with drug rash), red eyes (no discharge), red lips and peripheral edema

High ESR and CRP

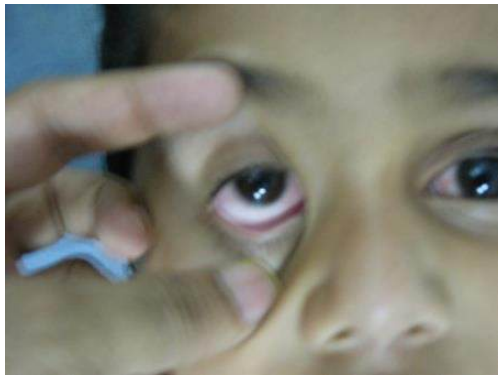
Sterile pyuria

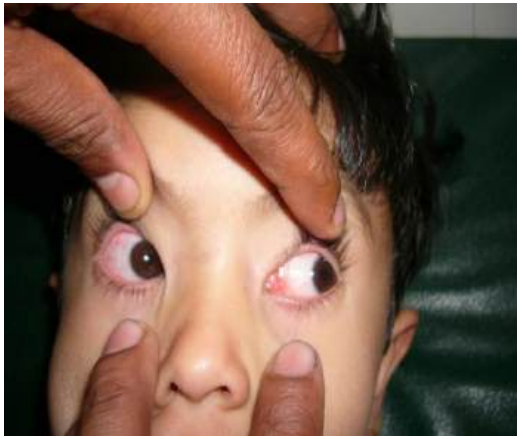
Consistent with the diagnosis of **Kawasaki disease**

- **Clinical manifestations in KD (rash, red eyes etc.) are transient**.
- These do not appear at the same time. Hence, at the point of examination, one may not find these manifestations.
- A good clinical history and supportive laboratory parameters (elevated ESR and CRP) would guide the diagnosis.
- Treated with IVIG & aspirin - improved

CASE 2

- 4 year child
- Fever 7 days
- Red eyes, non purulent
- Red lips and mouth
- Edema of feet





- TC 15000 per cmm
- ESR 110 per mm
- CRP 52 mg per dl
- Platelet count 5.5 L per cmm
- SGOT / SGPT 88/96
- 2-D echo - CAA

- Presence of CAA confirms KD diagnosis, but absence DOESNOT rule out diagnosis. Initial echoes are often normal by D7 of illness.

- **Complete KD is a clinical diagnosis** supported by laboratory parameters. Echo findings are important for diagnosing Incomplete/ Atypical KD.

CASE 3

- 2 years female, fever 6 days
- Rashes 2 days - Extreme irritability
- Red lips and tongue
- TC – 25600
- D6 – echo - normal

  – IVIG given + aspirin, Fever persisted

What will you do?

fever persisted, 2nd dose of IVIG given

- D12 – methylpred given

  - perineal peeling seen

- D19 –Repeat 2D Echo - mild dilatation of prox coronary artery

- D21 - Fever continued , infliximab given

- Improved

IVIG Resistant KD responding to Infliximab

CASE NO.

- 3 months male , fever 5 day
- Red lips
- Swelling right axilla
- CRP 96 mg/l
- U/S axilla – sub clavian artery aneurysm – 4*3 cms
- Echo done D8
- Result - CAA (LMCA, LAD, RCA)

KD in infants is an aggressive disease

- Treated with IVIG + aspirin
- Fever persisted - IVIG 2nd dose given
- Again fever persisted – methyl pred given
- Fever persisted – infliximab
- Clopidogrel (1mg/kg/day) + injection Clexane
- Repeat U/S , Increasing aneurysm
- Child developed apnea resuscitated, but died

Treatment of IVIG- resistant KD

There are multiple options for treatment of IVIg-resistant KD.

- **2nd dose of IVIG**
- **Inj Infliximab (10 mg/kg) single dose**
- **IV Methyl Prednisolone 30 mg/kg / day** (1-3 pulses) followed by oral steroids (taper over 2-4 weeks)

Currently, various centres that regularly treat KD use these therapies based on their individual experience and confidence.

There are not enough studies to suggest which of these treatments is superior.

IVIg-resistant KD

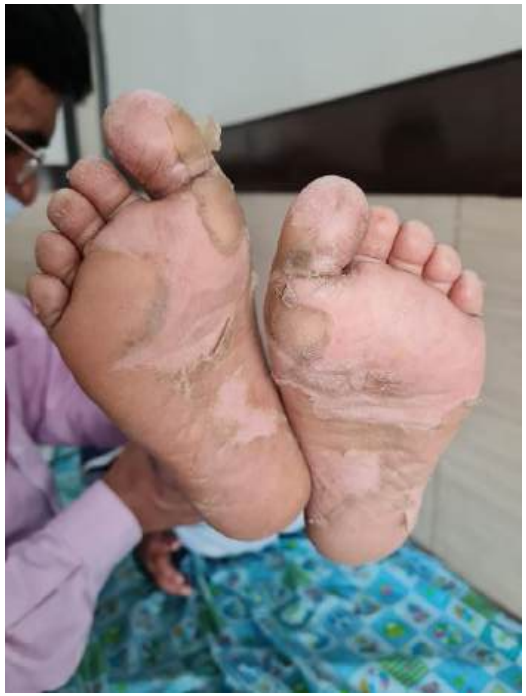
- Recurrence or persistence of fever, 36 hours beyond completion of IVIg infusion.
- Before proceeding further with second-line agents, it is prudent to review the diagnosis of KD.

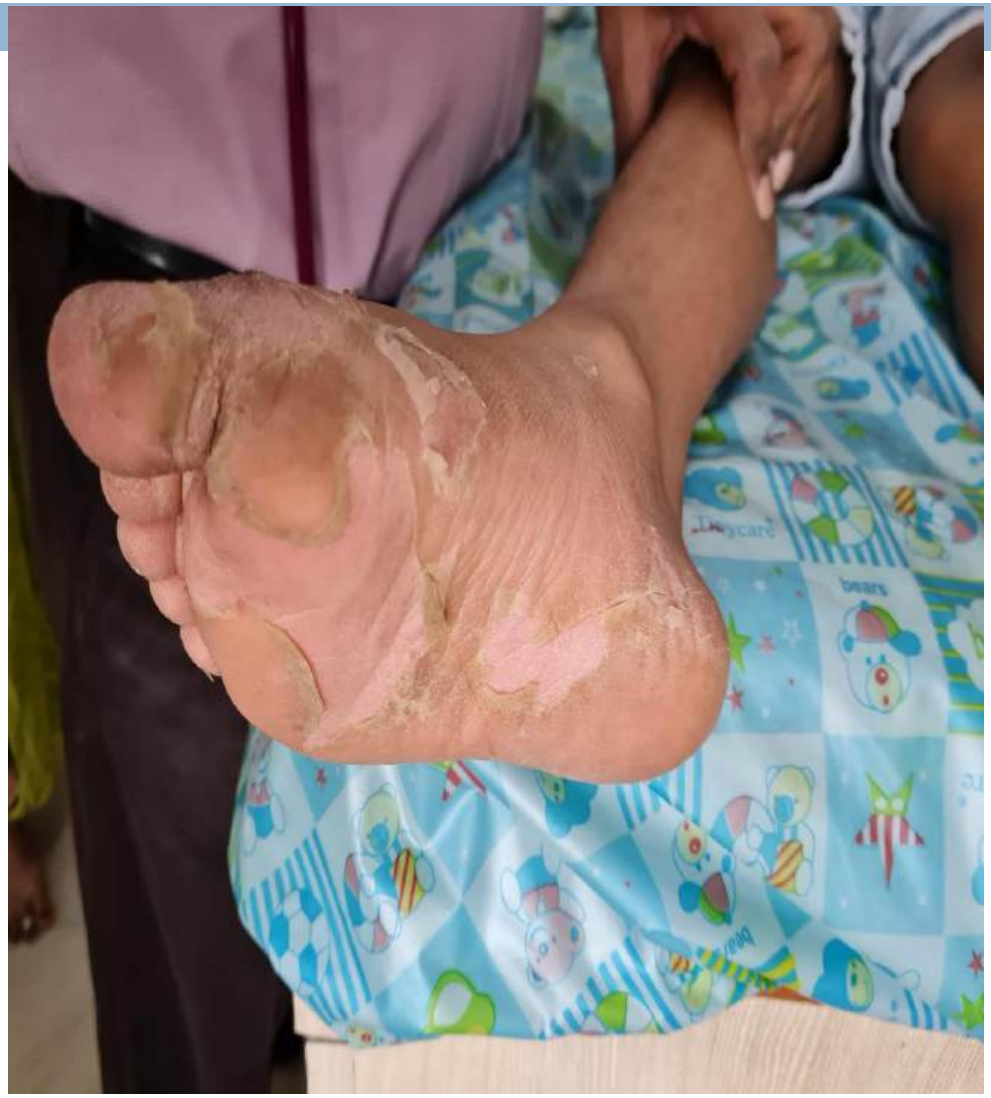
Case

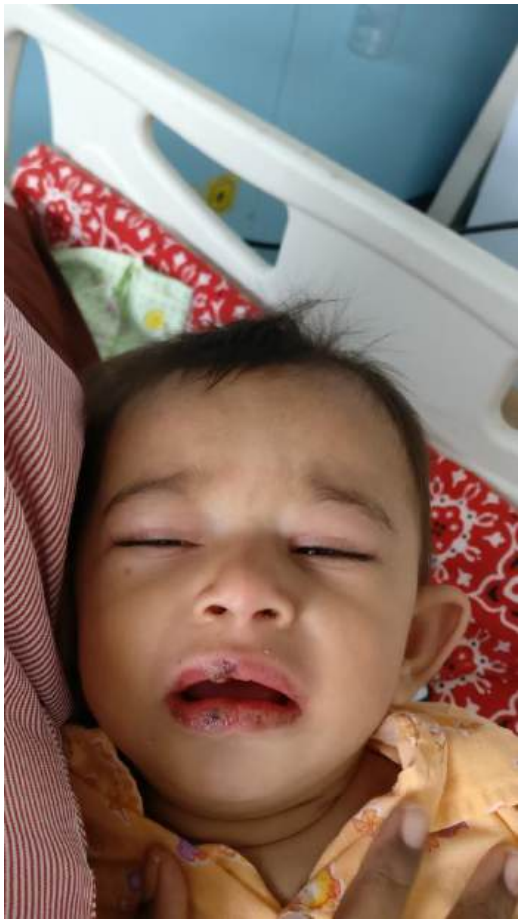
- 7yr old boy
  - High grade fever.
  - Difficulty in swallowing
  - Rashes on day 2 of illness - finely papular erythematous bright red intense in creases cheeks erythematous
  - Strawberry tongue & cracked lips.
  - Rashes faded on 4th day with desquamation.

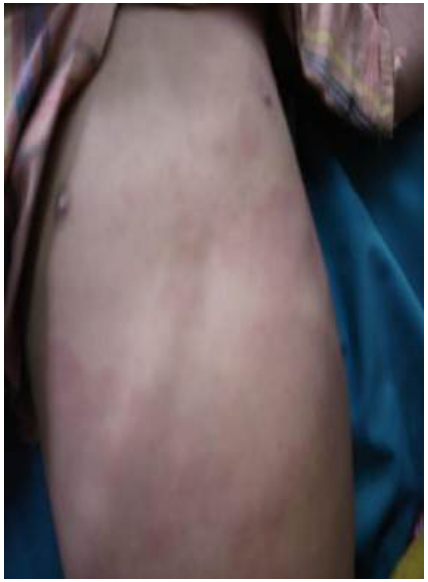
Scarlet fever

- Fever mod –high rash with neck trunk and extremities
- Diffuse finely papular erythematous bright red intense in creases cheeks erythematous
- Skin is goose pimple appearance and rough, sand paper appearance
- Pharyngitis with strawberry tongue
- Rashes fades by 3-4 days









?

- How do you differentiate scarlet fever/streptococcal lymphadenitis and Kawasaki disease?

	KD	SCARLET FEVER
Strawberry tongue	Present	Present
Red eyes	Present (non- Exudative)	Absent
Red lips	**Present**	Absent
Response to antibiotics	Does not respond	Brisk response in 48 hours
Peeling	Perineal and periungual	Generalised, sand paper appearance
Follicular tonsillitis	Usually absent	May be present
Edema of extremities	Present	Absent
H/O Throat ache	Absent	Present
Leukocyte counts	Elevated	May be Elevated
ESR and CRP	Elevated	May be normal

?

What are the other diseases that are close mimics for KD?

How do you differentiate them from KD?

Illnesses that mimic KD

Illness	Features common with KD	Features of KD not seen with illness	Features of illness not seen with KD
Measles	Fever, rash, eye redness	Conjunctival injection, perianal peeling/ BCG reactivation, lip changes, periungual peeling, hydrops of GB	Koplik spots, persistent coryza and cough
Scarlet fever	Fever, rash, peeling, strawberry tongue	Conjunctival injection, lip changes, periungual peeling, hydrops of GB	Tonsillar exudates, generalized peeling (sand-paper consistency), pastia's lines, fever settles within 24 hour of antibiotic initiation

Illnesses that mimic KD

Illness	Features common with KD	Features of KD not seen with illness	Features of illness not seen with KD
Toxic shock syndrome	Fever, rash, eye redness, shock	Conjunctival injection, BCG reactivation, lip/ tongue changes, periungual peeling, hydrops of GB	Purulent conjunctivitis, pustular rash
Stevens Johnson syndrome	Fever, oro-mucosal changes, rash	Prominence of fever, conjunctival injection, BCG reactivation, periungual peeling, hydrops of GB	Targetoid lesions with temporal association to drug, mucosal ulcerations
Dengue/ Scrub typhus	Fever, rash, peripheral edema, eye changes	BCG reactivation, perianal/ periungual peeling, hydrops of GB	Generalized capillary leak, systemic dysfunction in afebrile phase (dengue), HSM

How are infants with KD different from the usual KD?

KD in infants – AHA 2017 guidelines

- Infants <6 M with prolonged fever & irritability
- Infants with prolonged fever & unexplained aseptic meningitis
- Infants with prolonged fever & culture negative shock
- Infants with prolonged fever & cervical lymphadenitis unresponsive to antibiotics
- Infants with prolonged fever & retro/parapharyngeal phlegmon, unresponsive to antibiotics

KD in infants

- Often don't fulfill standard diagnostic criteria
- Incomplete KD in majority
- Morbidity and mortality highest in this age group
- Fever and excessive irritability may be the only manifestation in below 6 months child
- Risk of CAA highest
- Fever and pyuria mistaken for UTI

Differential diagnosis

- Staphylococcal infection (such as scalded skin syndrome, toxic shock syndrome)
- Streptococcal infection (such as scarlet fever, toxic shock-like syndrome)
- Measles and other viral exanthems
- Leptospirosis
- Rickettsial disease
- Stevens-Johnson syndrome
- Drug reaction
- Juvenile rheumatoid arthritis

Why the diagnosis of KD is often missed?

- Diagnosis based on typical temporal sequence of constellation of clinical features
- No feature is individually of diagnostic significance
- Clinical features evolve over a period of time
- Mimics other common febrile illnesses
- Poor awareness among health professionals
- Non – availability of trained paed. Cardiologists
- Under reporting of cases
- No lab test is confirmatory

WHY SHOULD WE NOT MISS K.D?

- CAA develops in 15-25% of untreated children
- Serious cardiac sequele – MI, IHD, sudden death
- Risk factor for cardiac disease in young adult
- Can be prevented with early recognition and treatment

DECISION MAKING

- When encountered with an atypical case, therapeutic decision making may be extremely difficult
- When confronted with such a case, ask 1 question – **What else could it be?**
- If the answer is nothing, it is likely that the diagnosis is correct (even if criteria are not completely fulfilled)

Ref- Cassidy's Textbook of Pediatric Rheumatology

Diagnosis of KD can be made before the 4th day of fever in the hands of experienced clinicians

- The ‘‘5 days of fever’’ rule to establish the diagnosis of KD was part of the epidemiologic case definition AHA guidelines.
- The study has been widely misinterpreted to mean that somehow giving IVIG before the 5th day of fever was less effective and that IVIG treatment should be withheld until five days of fever had elapsed.
- patients diagnosed before the 5 day of Illness were sickest patients dramatic signs of inflammation-likely to be IVIG resistant.
- **Treatment should be administered as soon in the course of the KD as possible**.

TAKE HOME MESSAGES

1. KD should be on DD in any child with unexplained fever more than 5 days
2. Symptoms are sequential, than simultaneous; Clinical manifestations overlap with many infections & vasculitis
3. Young infants present with fever & few principle clinical features with elevated inflammatory markers – consider echo
4. Echo should be done by a pediatric cardiologist & insist on Z scores.
5. Patients with incomplete KD are at greater risk for CAA – high index of suspicion warranted
6. Early treatment within 10 days of onset with I.V.I.G. markedly reduces coronary complications.
7. Because of serious cardiac sequelae, all pediatricians need to be aware of this illness

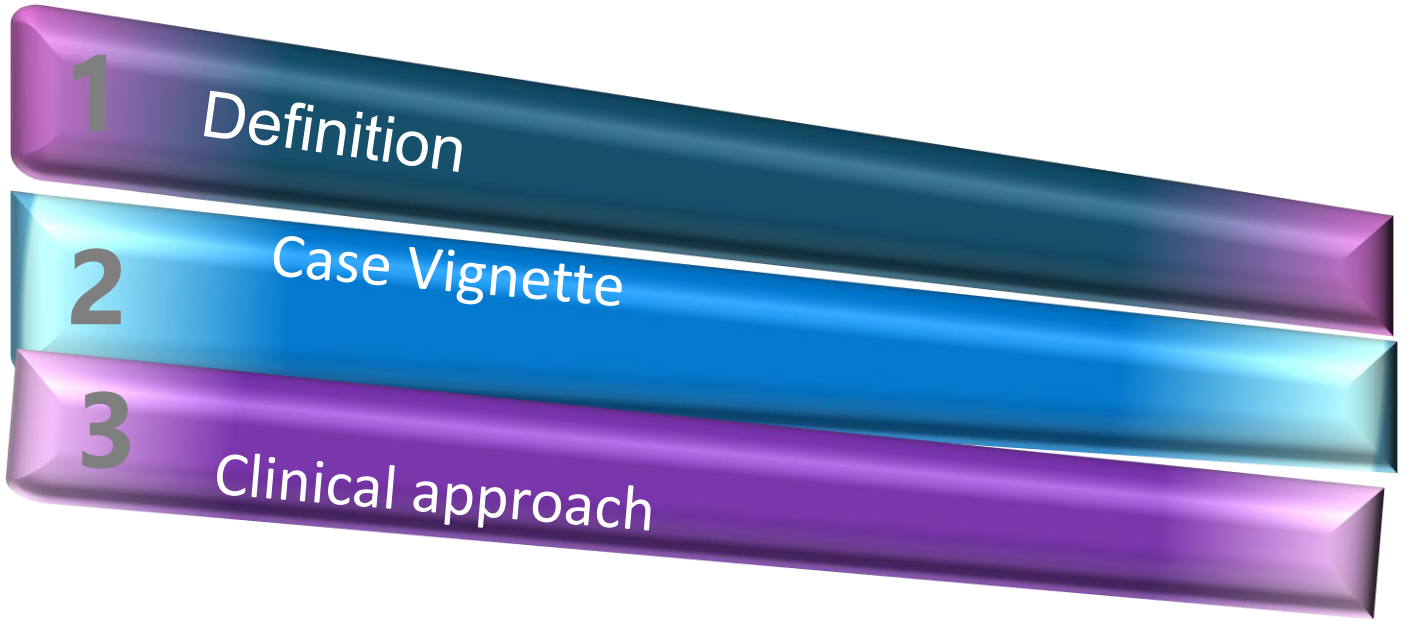
THINK KD

‘Call a Friend’ if in doubt

Incomplete or Atypical KD

Dr. Pratap Kumar Patra

Incomplete or Atypical Kawasaki Disease



Definition

Incomplete KD

- Fever lasting for more than 5 days with 2 or 3 of classical features
- The real incidence is difficult to define

Atypical KD

- Renal impairment
- Facial nerve palsy
- Testicular nodule
- Pleural effusion
- Diarrhea, abdominal pain
- Acute abdomen

Atypical KD/ Incomplete KD in children

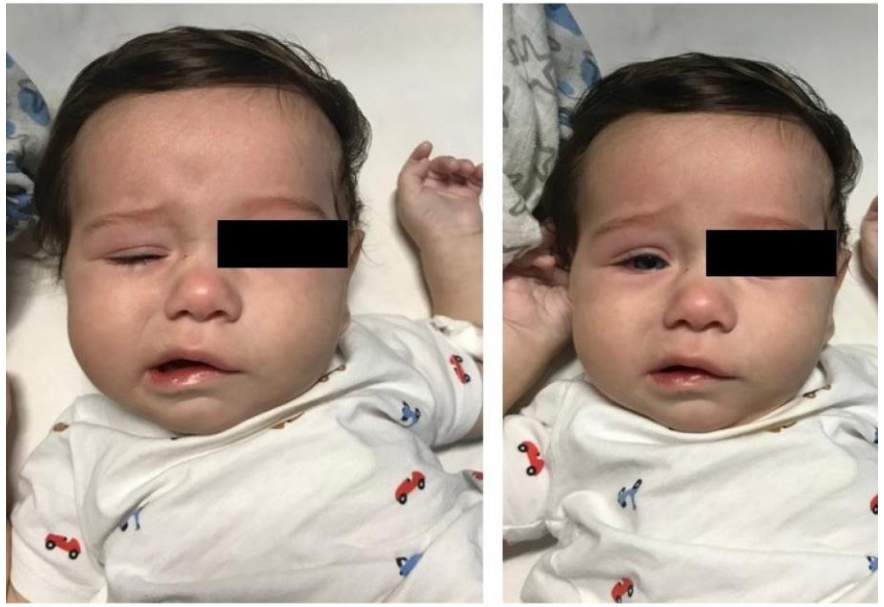
1. More common in young infants
2. Consider in any child fever > 5 days
3. Fewer than 4 classical criteria
4. High risk of Coronary arteries abnormalities
5. Compatible laboratory parameters
6. Coronary artery imaging
7. High index of suspicion is needed

Case vignette 1

- 7-month-old girl developmentally normal, was admitted to hospital with 18 days of fever
- She had a history of bilateral conjunctival injections
- Since 4-days developed drooping of the left side of her mouth

Differential diagnosis to be considered…

- Acute otitis media
- Chronic otitis media
- Meningitis



Would you consider the diagnosis of Kawasaki disease?

Physical examination revealed fever (38.5°C), lethargy, desquamation of the skin at fingertips, and LMN facial nerve palsy

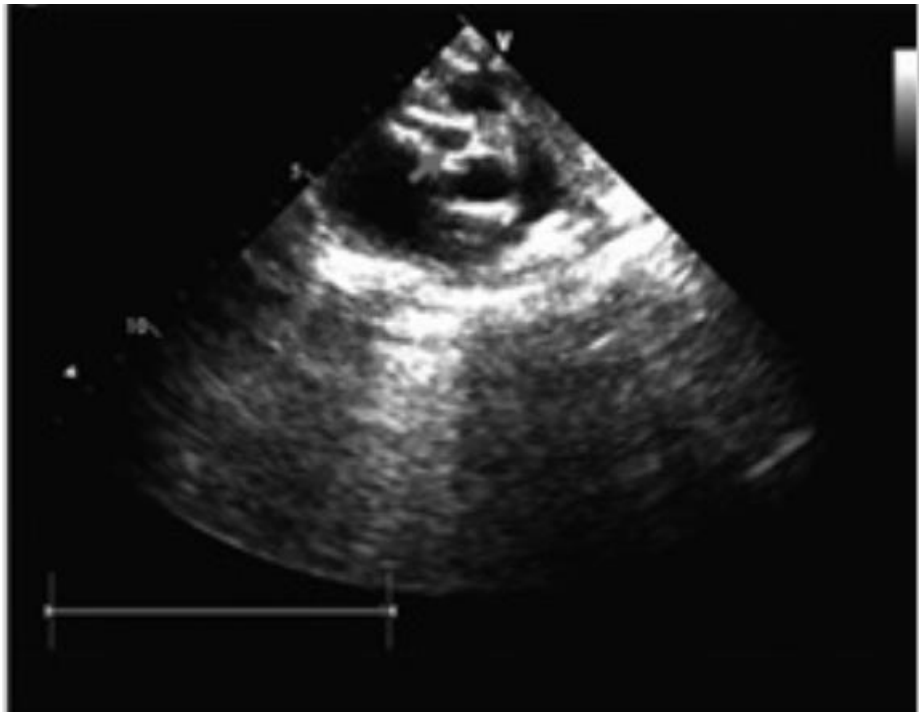
Investigations

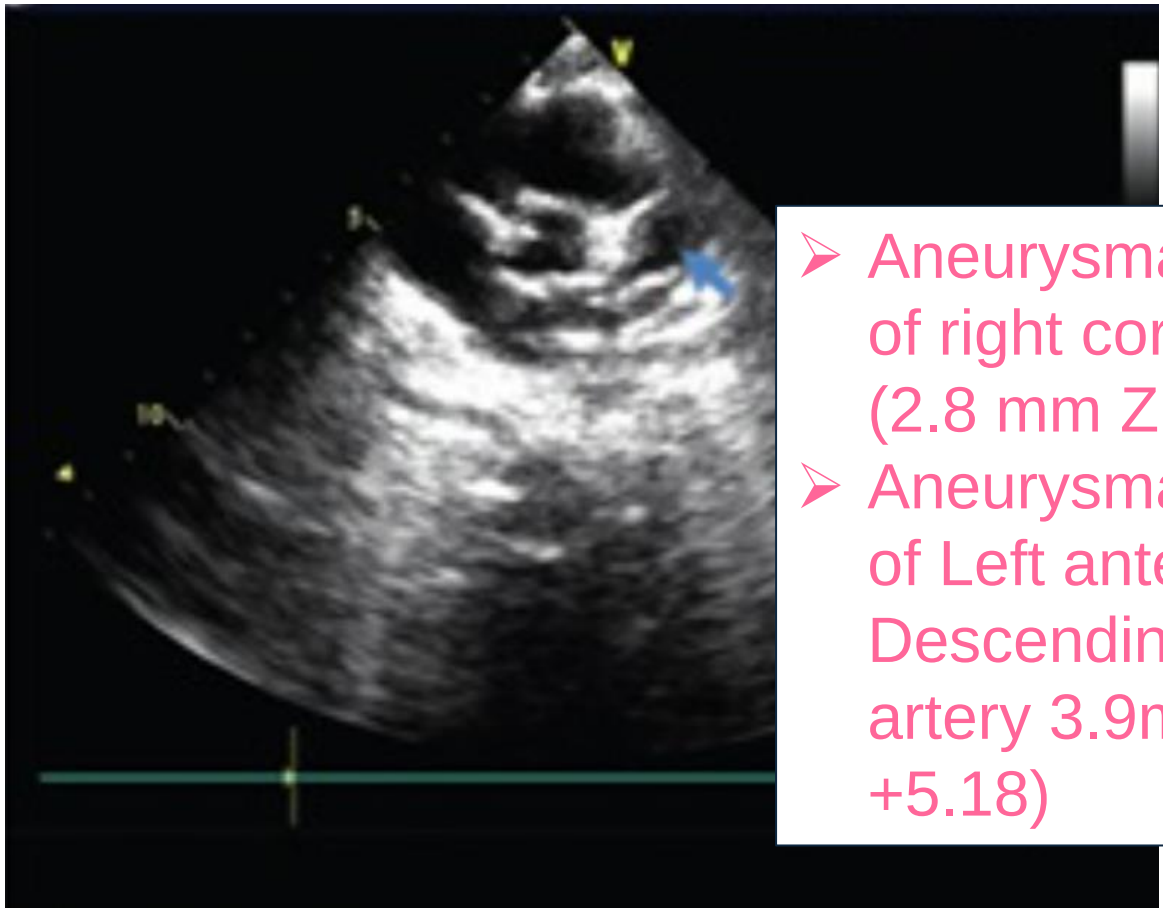
Laboratory parameters	
Hb	9.9g/dL
Total leucocyte count	18.11x10^9 /L
Platelet count	828 × 10^9 /L
ESR	120mm/h
CRP	70mg/L
CSF	36 cells
CSF Glucose & protein	Normal

- Anemia
- Leucocytosis
- Thrombocytosis
- Increased inflammatory parameters
- Aseptic meningitis

What will you do next?

2D-Echocardiography





- Aneurysmal dilatation of right coronary artery (2.8 mm Z Score +3.5)
- Aneurysmal dilatation of Left anterior Descending coronary artery 3.9mm (Z score +5.18)

Treated with IVIG 2/gm/kg and aspirin 30mg/kg/ in 4 divided doses

Key massage…

Facial palsy at times the manifestation of KD

Fever more than 5 days in any child KD should be a differential diagnosis

Increased inflammatory parameters are adjunct to the diagnosis of KD

2D Echocardiography crucial to identify coronary artery abnormalities

Case 2

- ✓ 4-year-old boy
- ✓ High grade fever x 7 days
- ✓ Unilateral neck swelling x5 days

On examination:

- ➢ Febrile with Temperature 104^0 F
- ➢ Extremely irritable
- ➢ Tender cervical lymphadenopathy over the left cervical region

What are the differential diagnosis ?

Case continued…

- There was no evidence of BCG site's reaction or perianal peeling
- Oropharyngeal examination – Normal

Differential diagnosis of bacterial lymphadenitis was considered

Received I.V. Antimicrobials x 5 days
However there was no improvement

What will you do next?

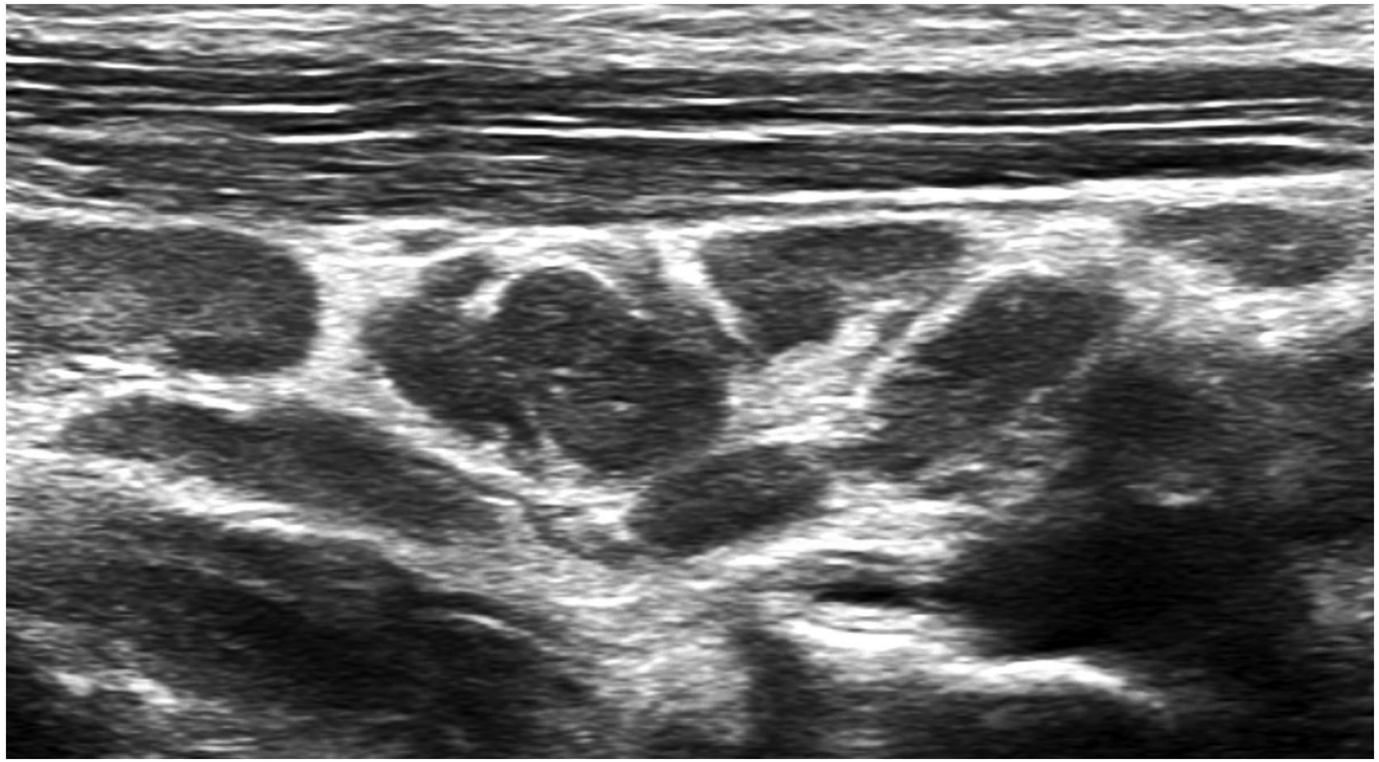
Investigations

- Haemoglobin - 8.5g/dL
- Total leucocyte count- $21.76x10^{9}/L$
- ESR- 56mm/1^{st} hour
- CRP –110mg/L

Case continued…

Neck Ultrasonography

Multiple enlarged uniformly hypoechoic well circumscribed lymph nodes without necrosis



"A cluster of grapes appearance"

Unique feature of KD lymphadenitis

2D Echo: Normal coronary arteries

Case continued…

- Final diagnosis- Kawasaki disease
- Received IVIg 2gm/Kg over 24 hours
- Aspirin 50 mg/kg till afebrile
- Lymph node swelling gradually subsides after 5 days admission

Key Message…

- Unilateral tender Lymph node enlargement at times the presenting features of KD
- Often termed as “Node First”
- Mistaken as infectious lymphadenitis
- Ultrasonography is an important tool demystifying the diagnosis bed side
- Lymph nodes are uniformly enlarged and hypoechoic without necrosis
- Well circumscribed margin and well visualised echogenic hilum

Case 3

18 months old boy

- Admitted with a 4-days of fever
- Associated with nasal congestions
- Cough and vomiting

- ✓ Had significant past history
- ✓ Urinary tract infection at 4 months of age
- ✓ Complex febrile seizure at 9 months

On examination:

Nasal congestion

Vitals- normal

Investigations:

- ✓ Total leucocyte counts: $14x10^9/L$
- ✓ ESR- 52mm 1^{st} hour
- ✓ CRP- 294mg/L
- ✓ Urine RE – 12 pus cells per HPF

Case continued…

What would be the next step?

He was started on Inj. Ceftriaxone as there was pyuria after sending urine culture

Urine culture: *Escherichia coli* (pan sensitive)

Continue to have fever despite antibiotics therapy

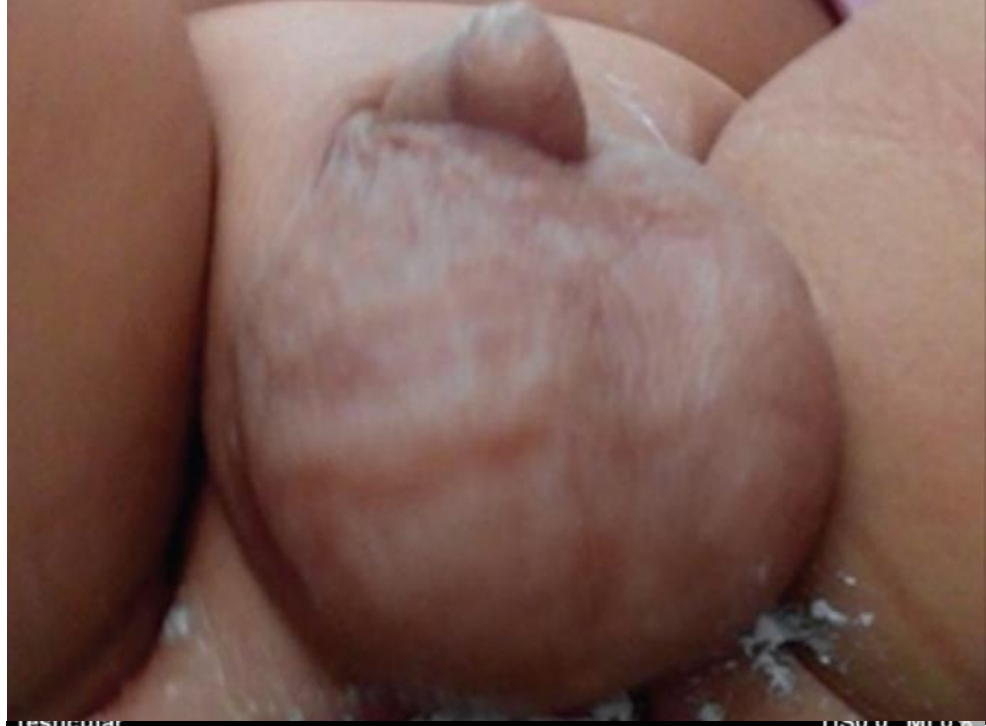
What should one do now?

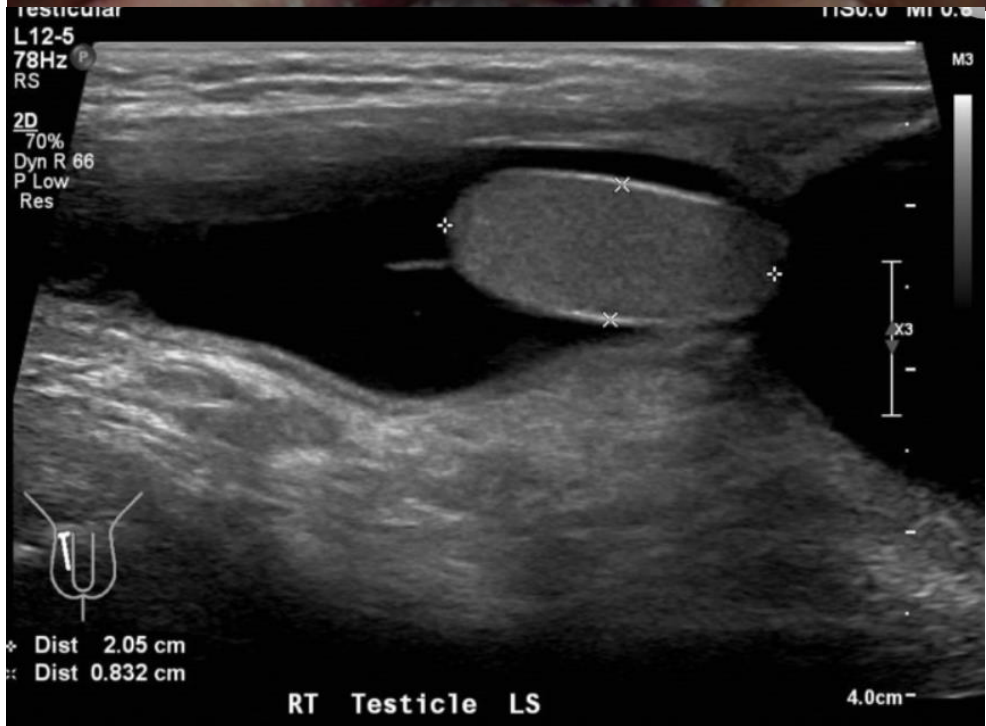
Ultrasonography of Abdomen: Left focal pyelonephritis without hydronephrosis

Case continued…

- Noted to have sudden onset scrotal swelling on day 8 of fever
- USG scrotum – Hydrocele
- Small right testis appendix
- Right hydrocele extended into the inguinal region, with patent processus vaginalis
- Also developed rash over the trunk on day 8 of fever

What should one do next?





Case continued…

Repeat investigations:

Haemoglobin: 10.5g/Dl

Total Leucocyte counts: 16.24×10^9/L

Erythrocyte sedimentation rate: 118mm

C- reactive protein - 220mg/L

Serum Na+ - 130meq/L

Serum albumin- 2.6mg/dL

SGOT – 20 IU/L

SGPT- 32 IU/L

Atypical Kawasaki Disease

Two of the classical features

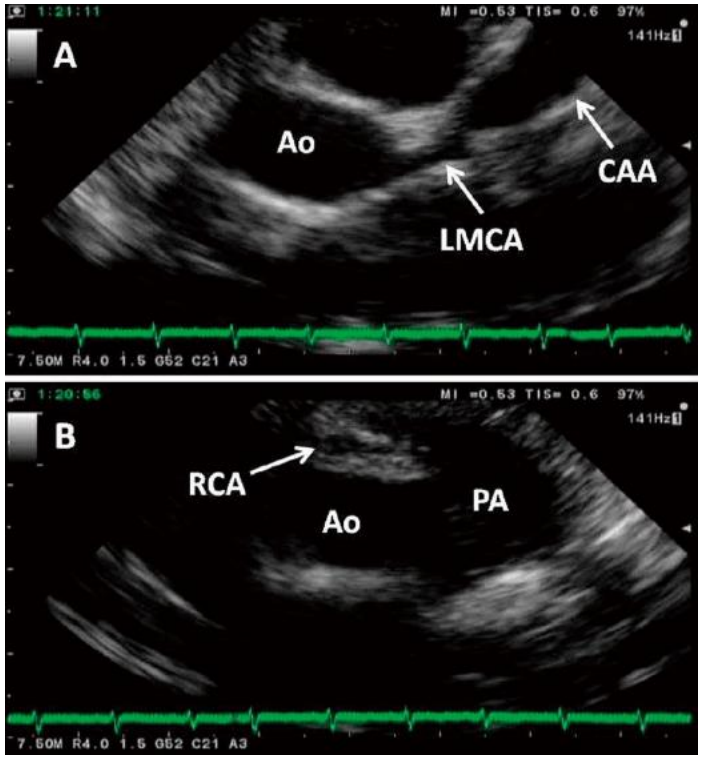
- Prolonged fever
- Rash
- Increased ESR, CRP
- Hypoalbuminemia
- Hyponatremia

Started on IVIg 2gm/Kg + aspirin 50mg/Kg and became afebrile

What would you do next?

Case continued…

- 2 D Echocardiography
- Aneurysmal dilatation of LMCA, RCA and left anterior descending artery



Key message…

- ❖ Hydrocele and scrotal swelling may be seen in Kawasaki disease
- ❖ Likely related to underlying inflammatory state leading to fluid extravasation
- ❖ Clinicians dealing with diagnostic dilemmas involving inflammatory processes should always consider Kawasaki Disease as a potential differential diagnosis

Case 4

- A 3-year-old boy
- Fever, Rash, icterus, and swollen and painful joints x5 days
- On examination lethargic
- Afebrile

What is first differential diagnosis?

Acute hepatitis?

On examination

- His conjunctivas were bilaterally hyperemic and icteric
- Distal and proximal interphalangeal joints in the lower and upper limbs and both knees were painful
- Developed fever after admission to hospital
- What will you do next?

Investigations

Hemoglobin 11.4g/dL

Platelet: 360000/ul

CRP: 105 mg/L

Bilirubin 5.4mg/dL

AST 149 U/L

ALT 150 U/L

Alkaline phosphatase 425 U/L

Albumin 3.1

Hospital course

- Ultrasound abdomen showed a normal gallbladder
- No intrahepatic or extrahepatic biliary ductal dilatation to suggest biliary obstruction
- Platelets 6.7 lacs ESR 113 mm/hr
- CRP 135mg/L
- Antistreptolysin O
- Hepatitis B surface antigen
- Hepatitis B core antibody
- Hepatitis immunoglobulin (Ig) M hepatitis C antibody,
- Cytolomegalo virus IgG/IgM,Toxoplasmosis IgG/IgM,
- Monospot, blood cultures, and leptospirosis testing were negative

Negative

Hospital course

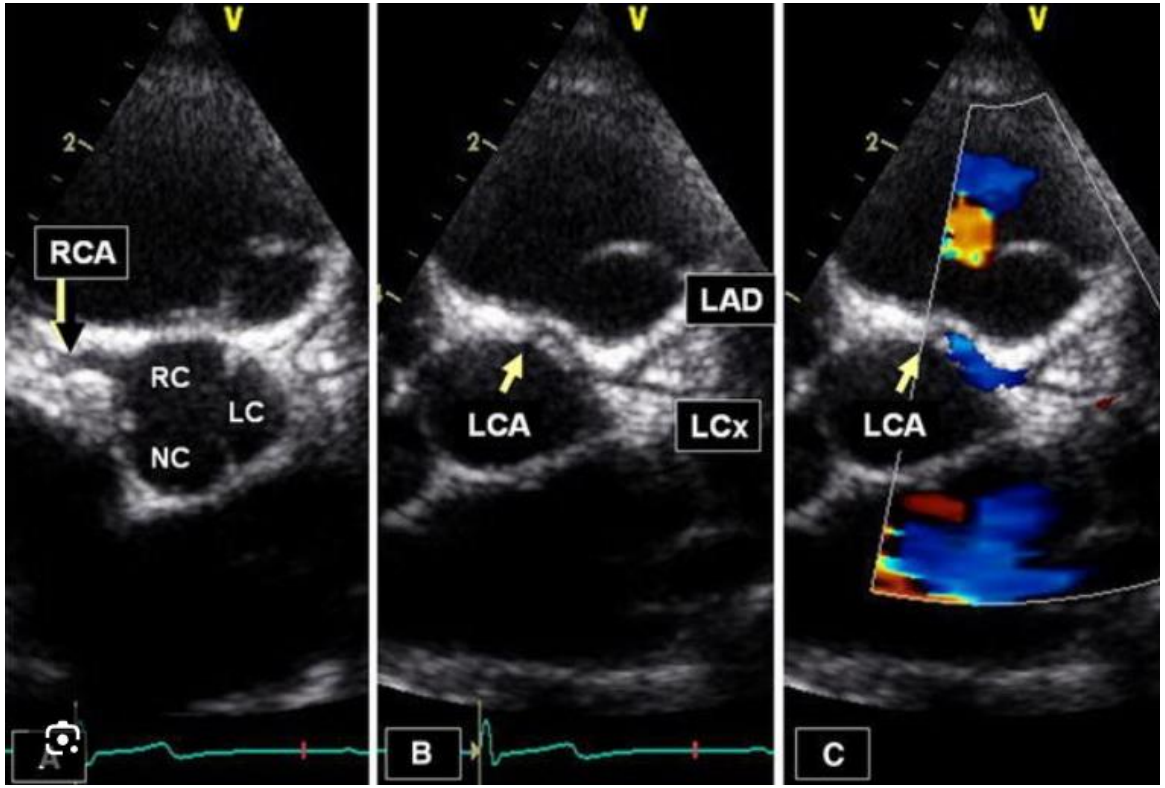
- On day seven of illness- B/L cervical lymphadenopathy
- He continued to spike fevers
- Poor response to antipyretics
- What would be next step?
- Repeat investigations

Elevated ALT, low albumin, thrombocytosis, and elevated WBC

What will you do next?

Diagnosed as atypical Kawasaki disease

Echocardiography



Normal

- IVIg infusion 2 gm/Kg
- Aspirin 50mg/Kg in divided doses
- Afebrile after 36 hours
- Continued on low doses aspirin
- Repeat 2D Echo normal

Key message

- Diagnosis incomplete KD was particularly challenging in absence of fever before hospitalization
- Unexplained jaundice with associated features should prompt physicians to consider KD
- High level of suspicion for KD when a child presents with febrile or afebrile obstructive jaundice

Case 5

- 11-year-old boy
- 4-day history of high fever
- Headache, generalized arthralgia, and rash, with nausea, vomiting, and diarrhea
- At the admission, he was febrile (40.4^{o}C)
- BP: 70/55 mmHg
- CFT – 5 Sec
- Clinical examination : bilateral non-purulent conjunctivitis, erythematous rash over the trunk and extremities

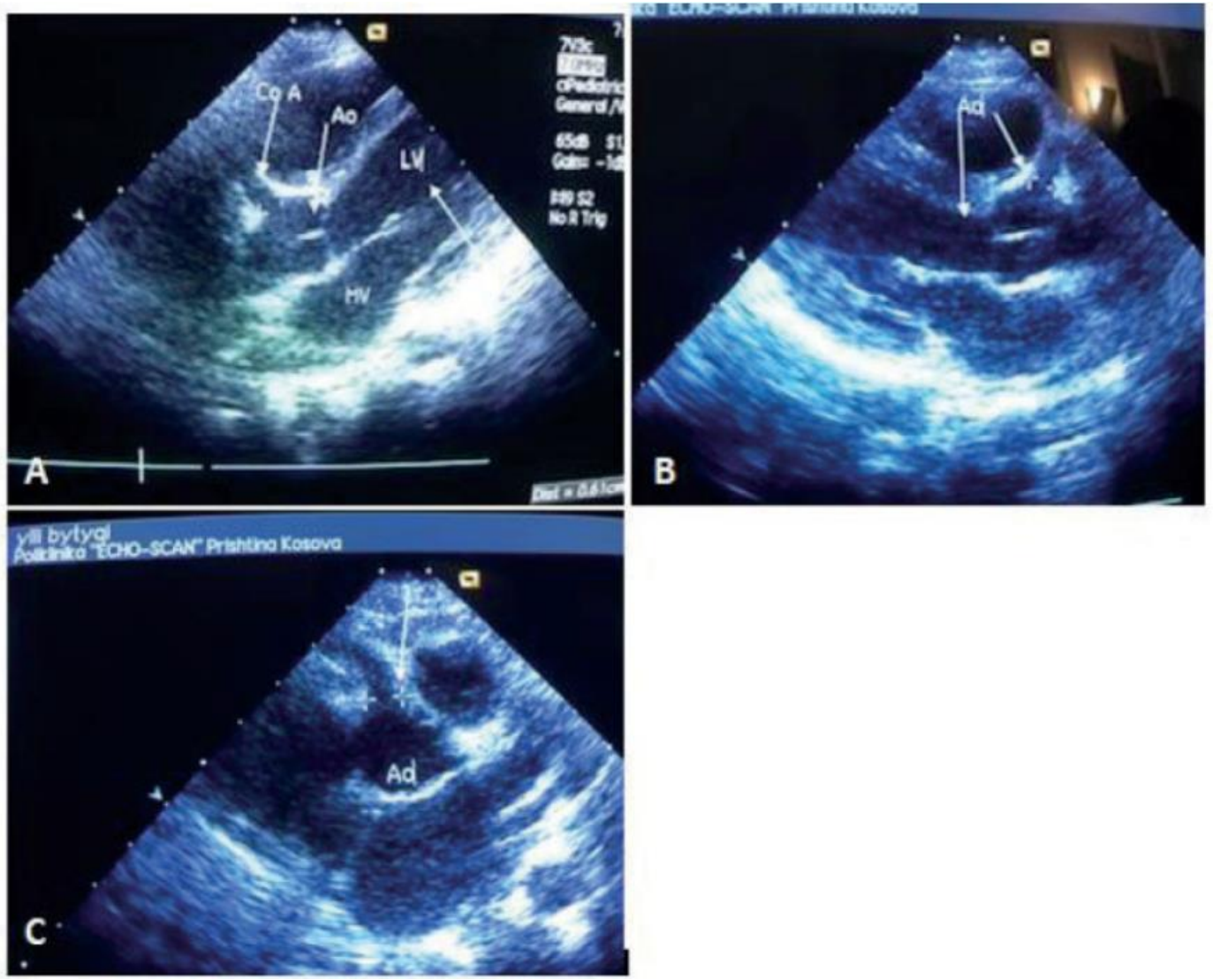
Laboratory investigations

- Hb – 10.g/dl
- TLC – 14,09X 10^9/L
- DC- N 72 L26 E 02 M 02
- Platelet count – 92,000
- Erythrocyte sedimentation rate of 122 mm/h
- CRP - 288 mg/L

- Na - 129 Meq/L
- K^+ - 3.6 Meq/L
- SGOT – 66 IU/L
- SGPT – 79 IU/L
- Serum Urea- 122 mg/dl
- Serum creatinine – 1.2mg/dl
- B-natriuretic peptide was 5560 ng/l (normal range < 100 ng/l)
- Blood culture - sterile

Hospital course

- His hypotension persisted despite adequate fluid resuscitation
- Inotropic support : Adrenalin maximum 0.4µg/kg/min
- ECG was normal
- 2 D Echocardiography
- Severe biventricular dysfunction
- Dilatation of right coronary artery



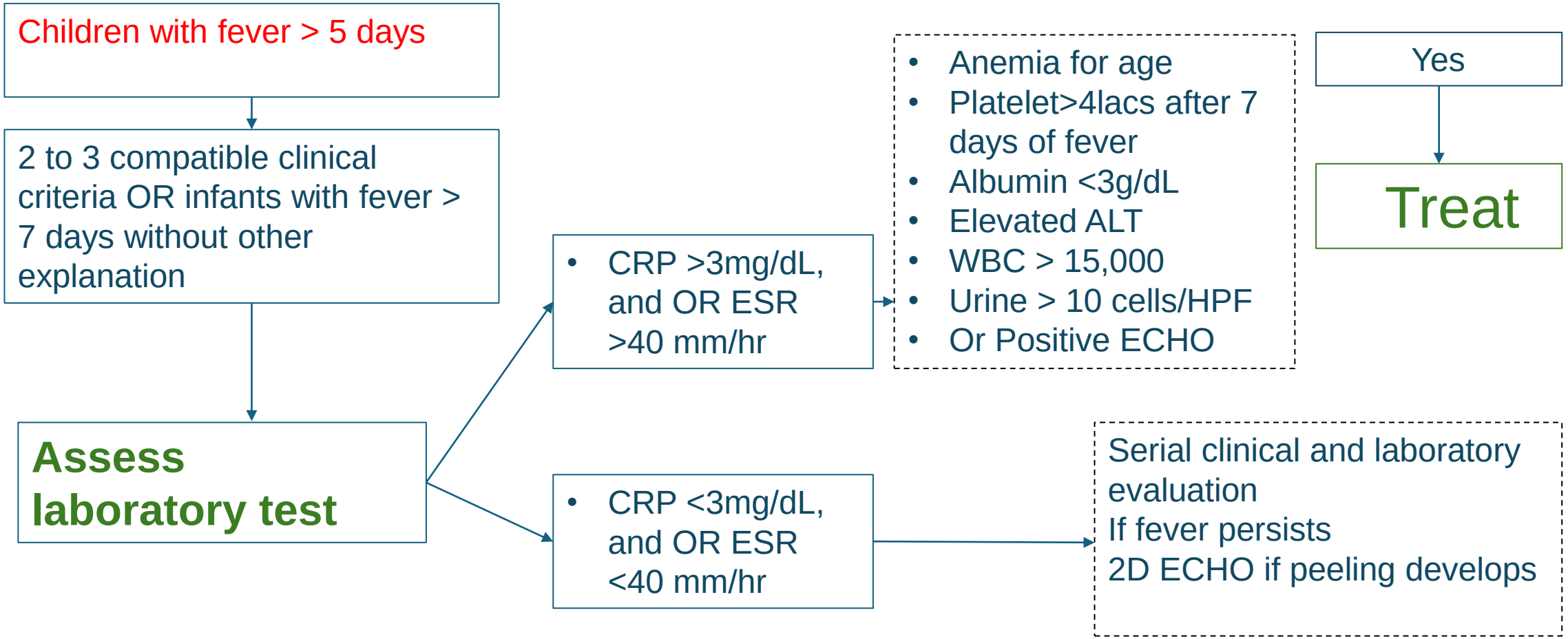
Treatment

- Treated with 2 g/kg IVIG
- Aspirin -50 mg/kg/d in four divided doses
- His general condition improved during the next 36 hours and subsequently became afebrile.
- After 2 weeks of admission a repeat transthoracic echocardiogram showed normal biventricular function
- Persistent RCA dilatation
- Discharged on low dose of aspirin

Key message

- Shock syndrome at times the manifestation of KD
- KDSS should be considered in all children with Hemodynamic instability , hypotension and myocardial dysfunction.
- Echocardiography should be performed frequently to look for coronary artery involvement and aggressive treatment is warranted

Atypical / Incomplete KD: Clinical Approach



RED FLAGS …

- Infants <6 months old with prolonged fever and irritability
- Infants with prolonged fever and unexplained aseptic meningitis
- Infants or children with prolonged fever and unexplained or culture-negative shock
- Infants or children with prolonged fever and cervical lymphadenitis unresponsive to antibiotic therapy
- Infants or children with prolonged fever and retropharyngeal or parapharyngeal phlegmon unresponsive to antibiotic therapy

Common Pitfalls in Diagnosis

- Infant <6 months of age, prolonged fever and irritability may be the only clinical manifestations of KD
- Delayed diagnosis is common in older children and adolescents with KD,

they appear to have a high prevalence of coronary artery abnormalities

- Presence of fever and pyuria in an infant or young child can be mistakenly attributed to a urinary tract infection
- Patients with cervical lymphadenitis as the primary clinical manifestation can be misdiagnosed as having bacterial adenitis
- KD shock may be misdiagnosed as having bacterial sepsis or staphylococcal or streptococcal toxic shock

A high index of suspicion required for the diagnosis

Role of laboratory investigations and imaging in Kawasaki disease

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Background

- Role of various laboratory investigations in the diagnosis of KD
- Role of 2-D echocardiography in diagnosis of KD
- Limitations of 2-D echocardiography
- Role of coronary CT angiography and magnetic resonance imaging

Facts about Kawasaki disease

- **Diagnosis of KD is clinical**
- **Laboratory investigations only support a diagnosis of KD**
- **2-D echocardiography should NEVER be used to diagnose KD but only to assess the coronary artery abnormalities**

Laboratory findings commonly seen in KD

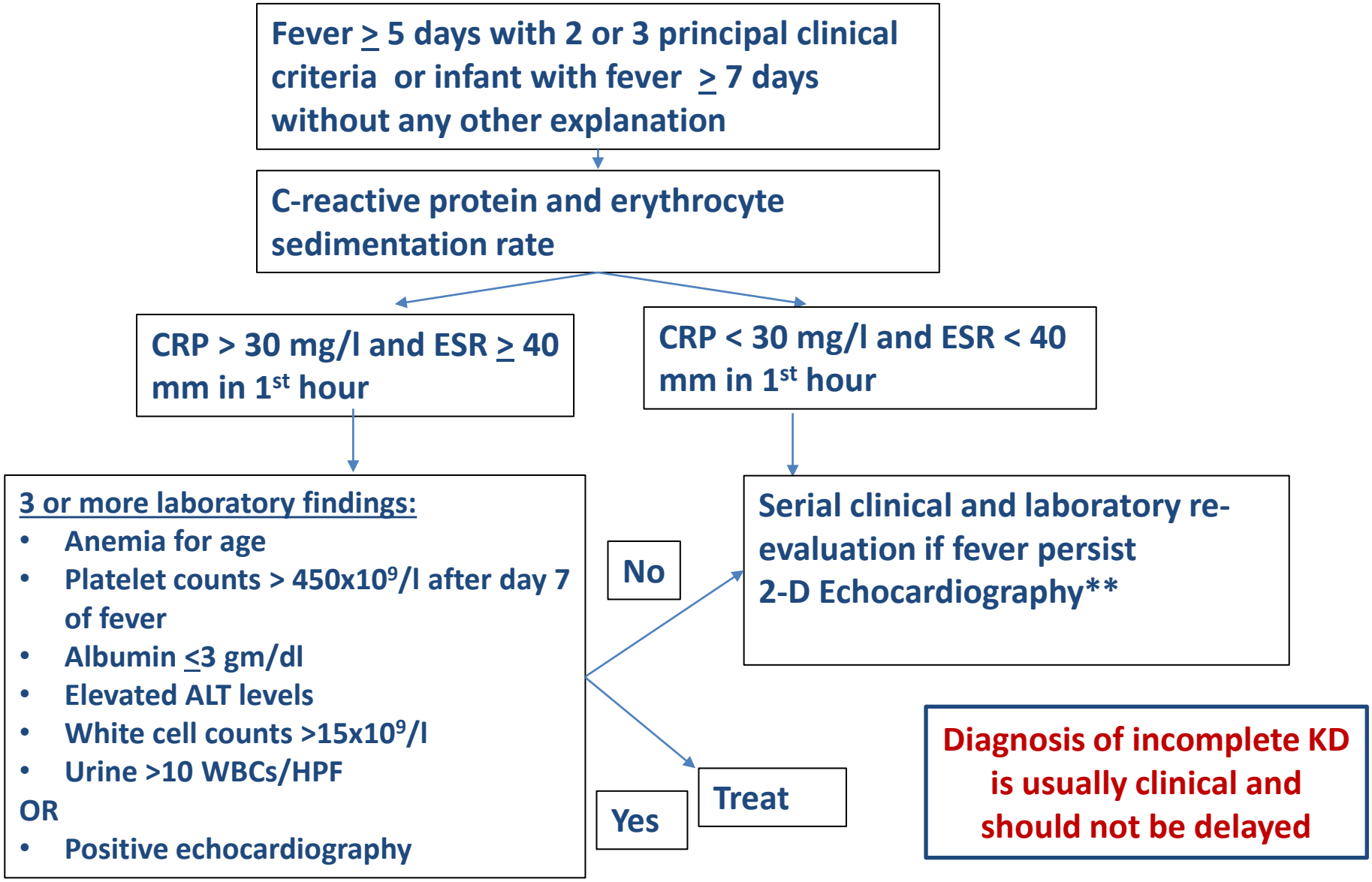
Often non-specific

1. Neutrophilic leukocytosis
2. Elevated ESR and CRP
3. Anemia
4. Thrombocytosis (thrombocytopenia may be seen in the acute phase)
5. Sterile pyuria (may be confused with UTI)
6. Elevated transaminases
7. CSF pleocytosis (may be confused with meningitis)
8. Elevated N-terminal pro-BNP (useful marker)

Reddy M, Singh S, Rawat A, et al. Pro-brain natriuretic peptide (ProBNP) levels in North Indian children with Kawasaki disease. Rheumatol Int. 2016 Apr;36(4):551-9

Iwashima S, Ishikawa T. B-type natriuretic peptide and N-terminal pro-BNP in the acute phase of Kawasaki disease. World J Pediatr. 2013 Aug;9(3):239-44.

Evaluation of suspected incomplete KD



Age appropriate upper limit for ProBNP

Patient age	NT-proBNP, Cut-off value (pg/mL)	Median (pg/mL)
1–11 months	1000	140
1 year	900	130
2 years	800	110
3 years	700	90
4 and 5 years	600	80
6 and 7 years	500	60
8 and 9 years	400	50
10–15 years	300	30

Hirai S, Nakamura T, Misawa M. Predictive potential of age- group cut- off values of N- terminal pro- brain natriuretic peptide in Kawasaki disease. Pediatr Int. 2022;64:e15371

Imaging modalities in Kawasaki disease

- 2 D echocardiography: remains the standard imaging modality for assessment of coronary artery abnormalities

- Other imaging modalities include
  - CT coronary angiography
  - Magnetic resonance coronary angiography
  - Catheter angiography

2-D echocardiography

- Echocardiography remains the standard imaging modality for patients with KD in the acute phase
- The initial echocardiogram should be performed as soon as the diagnosis is suspected, but initiation of treatment should not be delayed by the timing of the study
- An initial echocardiogram in the first week of illness is typically normal and does not rule out the diagnosis

2-D echocardiography

- Aneurysms are classified as saccular if axial and lateral diameters are nearly equal or as fusiform if symmetrical dilation with gradual proximal and distal tapering is seen
- Sometimes aneurysms occur in series with interposing narrow segments
- When a coronary artery is dilated without a segmental aneurysm, the vessel is considered ectatic

Views in 2-D echocardiography

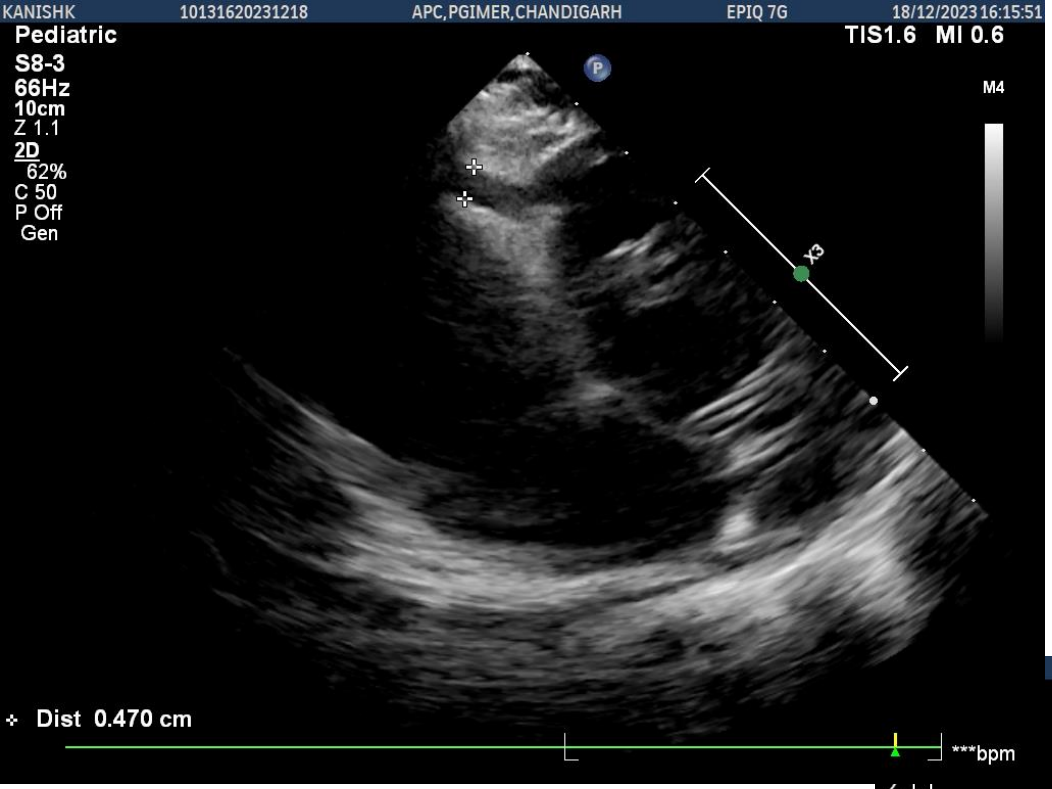
- **Parasternal short axis view**
- **Parasternal long axis view**
- **Apical 5 chamber view**

Definition of aneurysms

- The Japanese guidelines classify coronary arteries by absolute or relative internal lumen diameter
- **Dilation or small aneurysms:** Localized dilation of the internal lumen diameter but <4 mm, or if the child is ≥5 years of age, dilation but with an internal diameter of a segment measuring ≤1.5 times that of an adjacent segment
- **Medium aneurysms:** Internal lumen diameter >4 mm but ≤8 mm, or if the child is ≥5 years of age, an internal diameter of a segment measuring 1.5 to 4 times that of an adjacent segment
- **Large or giant aneurysms:** Internal lumen diameter >8 mm, or if the child is >5 years of age, an internal diameter of a segment measuring >4 times that of an adjacent segment.

Z-Score Classification of aneurysms

- **No involvement:** Always <2
- **Dilation only:** 2 to <2.5; or if initially <2, a decrease in Z score during follow-up ≥1
- **Small aneurysm:** ≥2.5 to <5
- **Medium aneurysm:** ≥5 to <10, and absolute dimension <8 mm
- **Large or giant aneurysm:** ≥10, or absolute dimension ≥8 mm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66Hz
10cm
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C 50
P Off
Gen
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M4
X3
Dist 0.470 cm
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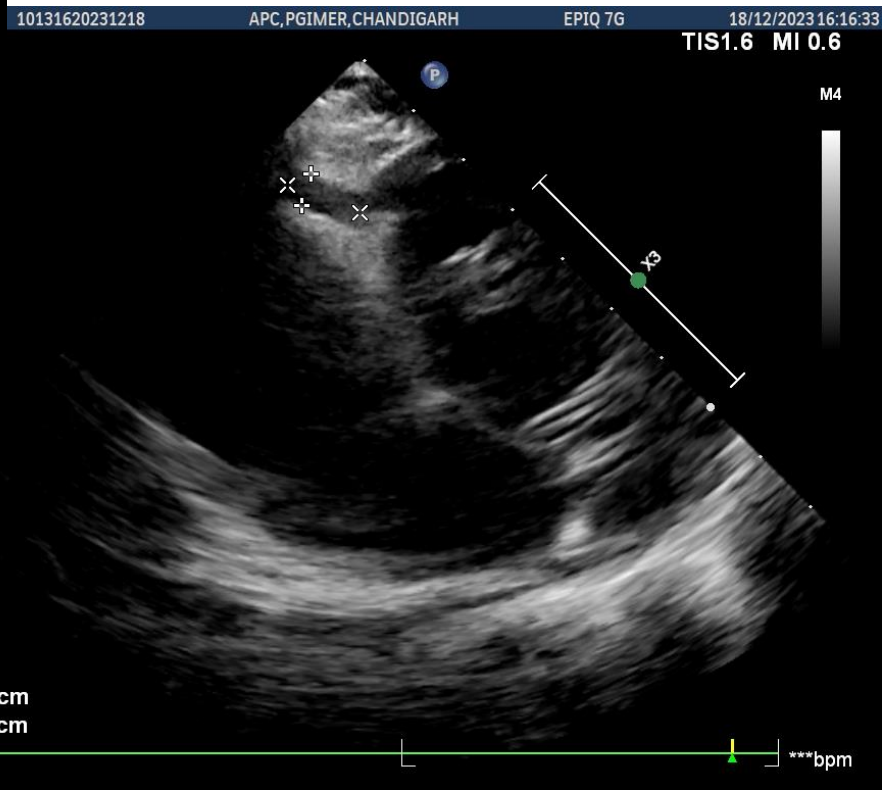
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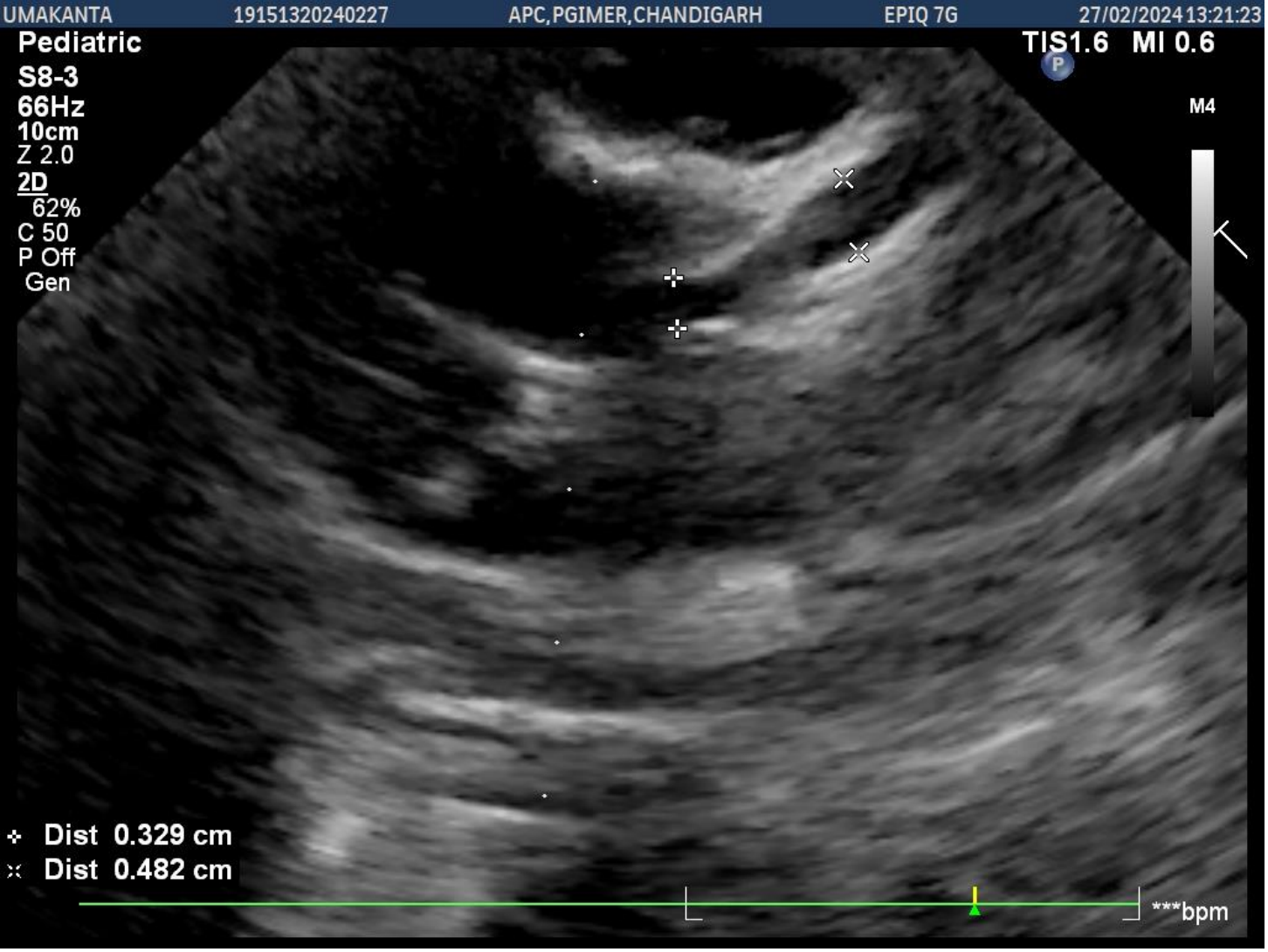
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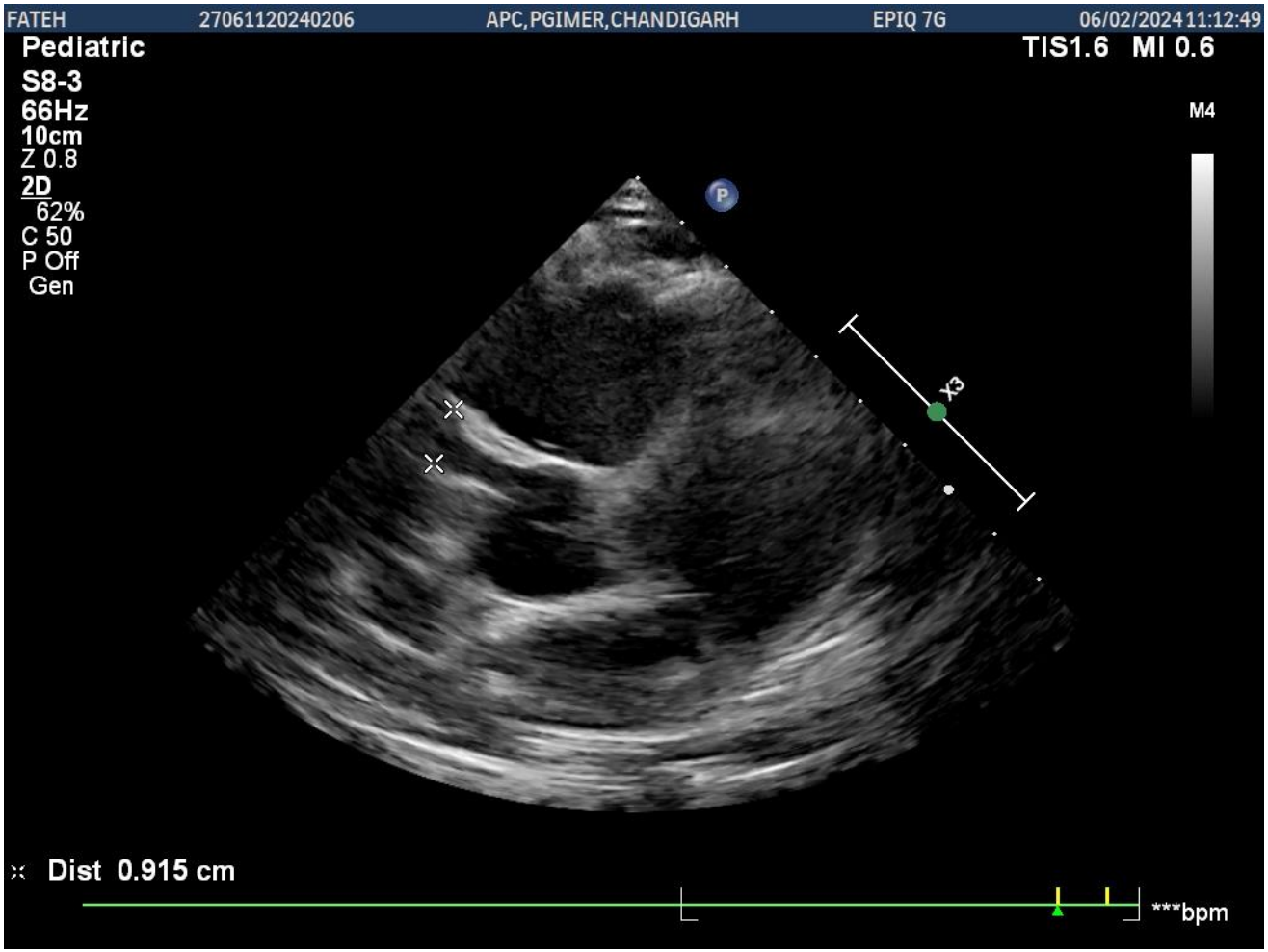
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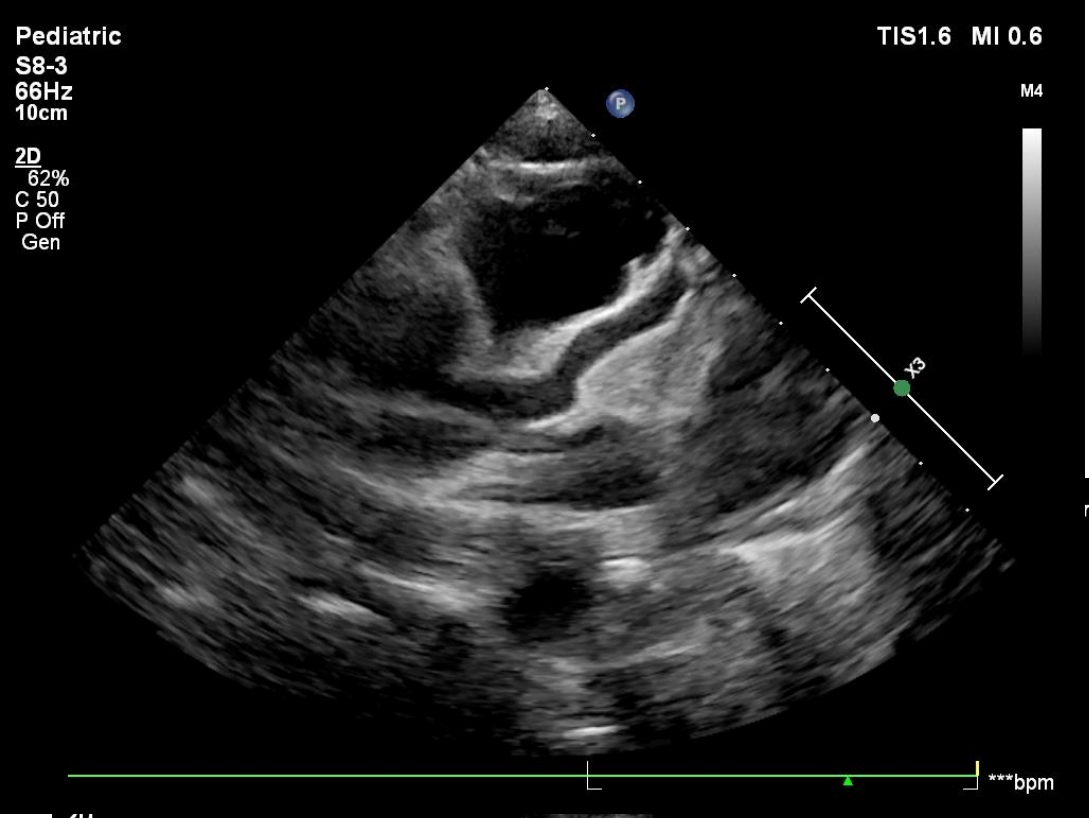
Pediatric
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C 50
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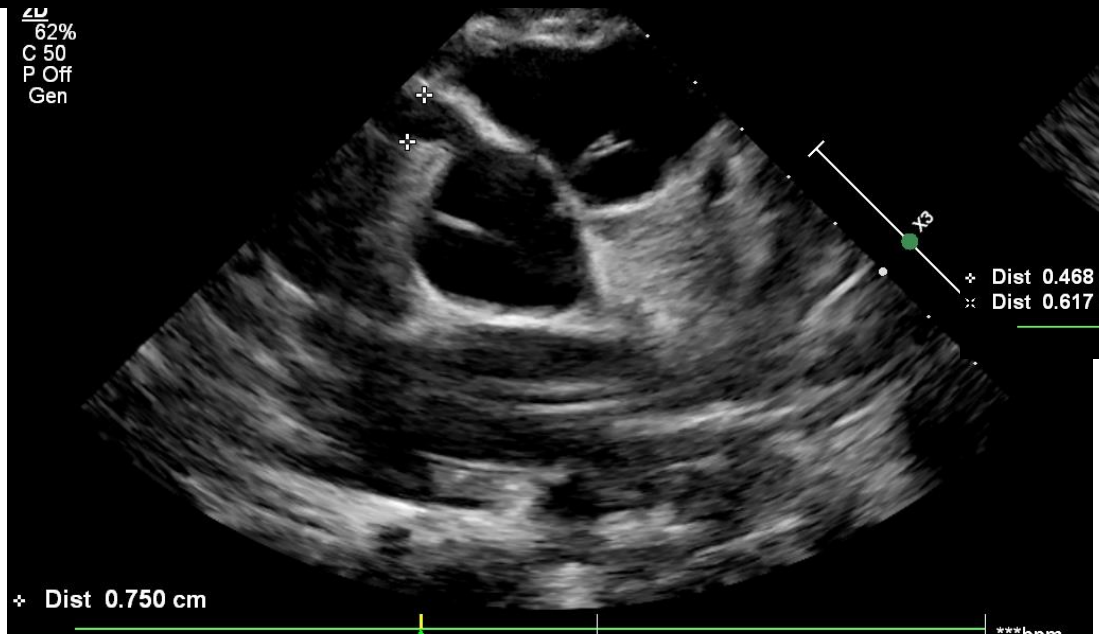
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62%
C 50
P Off
Gen
X3
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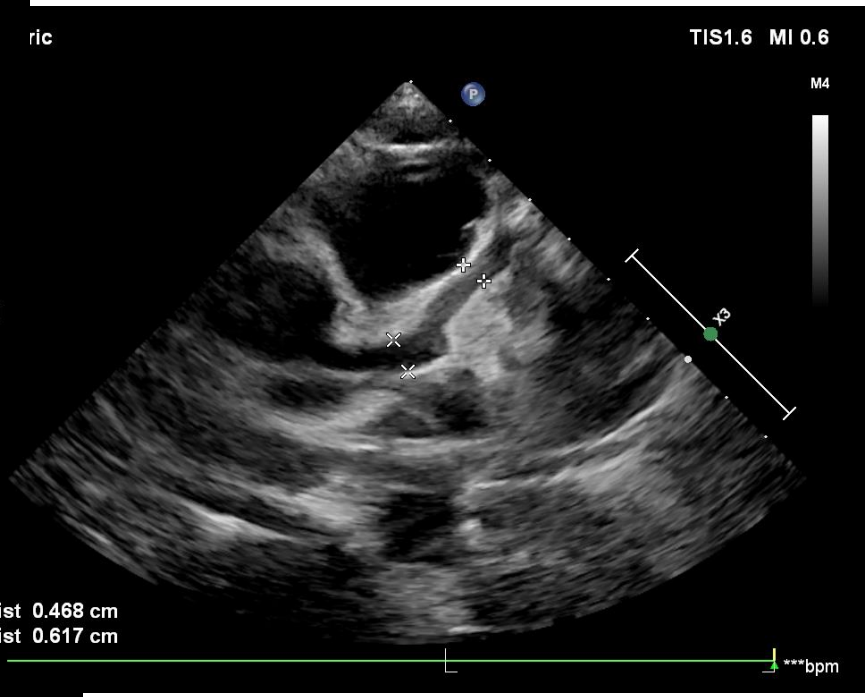

TIS1.6 MI 0.6
M4
X3
Dist 0.468 cm
Dist 0.617 cm
***bpm

Limitations of 2-D echocardiography for assessment of coronary artery abnormalities in KD

- Difficulty to visualize left circumflex coronary artery and distal segments of coronary arteries
- Observer dependent
- Difficult to interpret in older children because of thick chest wall
- Problems with 'Z' score calculations

Jrad M, Ben Salem F, Barhoumi C,et al. The Role of Computed Tomography Coronary Angiography in Kawasaki Disease: Comparison with Transthoracic Echocardiography in a 25-Case Retrospective Study. Pediatr Cardiol. 2019 Feb;40(2):265-275.
Chu WC, Mok GC, Lam WW, Yam MC, Sung RY. Assessment of coronary artery aneurysms in paediatric patients with Kawasaki disease by multidetector row CT angiography: feasibility and comparison with 2D echocardiography. Pediatr Radiol. 2006 Nov;36(11):1148-53.
Singhal M, Singh S, Gupta P, Sharma A, Khandelwal N, Burns JC. Computed Tomography Coronary Angiography for Evaluation of Children With Kawasaki Disease. Curr Probl Diagn Radiol. 2018 Jul-Aug;47(4):238-244.

A. Should Z scores be used for assessment of CAAs in patients with KD?

- **Yes, definitely**

B. Which Z scores to be used?

	De Zorzi et al[138]	Kurotobi et al[142]	Tan et al[143*]	McCrindle et al[139]	Olivieri et al[144]	Kobayashi et al[145]	Dallaire et al[146]
Year of publication	1998	2002	2003	2007	2009	2009	2011
Number of subjects	89	71	390	221	432	5344	1036
Country	USA	Japan	Singapore	USA	USA	Japan	Canada
Regression method for model fitting of BSA	Linear	Linear	Linear	Exponential	Logarithmic	LMS	Square root
BSA calculation method	NS	NS	NS	Haycock	Dubois	Haycock	Haycock
Values for left circumflex	No	No	No	No	No	Yes	Yes

Review › Circulation. 2017 Apr 25;135(17):e927-e999. doi: 10.1161/CIR.0000000000000484. Epub 2017 Mar 29.

Diagnosis, Treatment, and Long-Term Management of Kawasaki Disease: A Scientific Statement for Health Professionals From the American Heart Association

Brian W McCrindle, Anne H Rowley, Jane W Newburger, Jane C Burns, Anne F Bolger, Michael Gewitz, Annette L Baker, Mary Anne Jackson, Masato Takahashi, Pinak B Shah, Tohru Kobayashi, Mei-Hwan Wu, Tsutomu T Saji, Elfriede Pahl;
American Heart Association Rheumatic Fever, Endocarditis, and Kawasaki Disease Committee of the Council on Cardiovascular Disease in the Young; Council on Cardiovascular and Stroke Nursing; Council on Cardiovascular Surgery and Anesthesia; and Council on Epidemiology and Prevention

parameter
by Rady Children's Hospital

Go to Rady Children's Hospital (

120 cm
Height

25 kg
Weight

6 years
Age

Female
Sex, Birth Assigned

17.36
BMI

0.91
BSA
Haycock

Echocardiography

Coronary Artery Z Scores (Dallaire & Dahdah, JASE 2011)

New equations and a critical appraisal of coronary artery Z scores in healthy children.
Dallaire F, Dahdah N.
J Am Soc Echocardiogr. 2011 Jan;24(1):60-74.; 2011

AGE	BSA
0.16 - 18 years old	0.08 - 2.72 m2

Find a specific area of interest

Left Main Coronary Artery	3.6	mm	2.34 1.77 - 3.46
Left Anterior Descending Coronary Artery	2.5	mm	1.24 1.24 - 2.80
Circumflex Coronary Artery	2.4	mm	0.97 1.09 - 2.85
Proximal Right Coronary Artery	2.6	mm	0.62 1.45 - 3.20
Mid Right Coronary Artery	2.2	mm	0.46 1.11 - 2.88
Distal Right Coronary Artery	2.5	mm	1.42 1.08 - 2.74

120 cm
Height

25 kg
Weight

6 years
Age

Female
Sex, Birth Assigned

17.36
BMI

0.91
BSA
Haycock

Echocardiography

Coronary Artery Z-Scores using LMS Method (Kobayashi et al., JASE 2016)

Find a specific area of interest

Left Main Coronary Artery	3.6	mm	2.73 1.78 - 3.27
Left Anterior Descending Coronary Artery	2.5	mm	1.28 1.43 - 2.80
Circumflex Coronary Artery	2.4	mm	1.48 1.18 - 2.63
Proximal Right Coronary Artery	2.6	mm	1.19 1.47 - 2.92

Summary

120 cm
Height

25 kg
Weight

6 years
Age

Female
Sex, Birth Assigned

17.36
BMI

0.91
BSA
Haycock

Echocardiography

PHN Echocardiographic Z Scores (Lopez et al., Circ CV Img 2017)

Relationship of Echocardiographic Z Scores Adjusted for Body Surface Area to Age, Sex, Race, and Ethnicity: The Pediatric Heart Network Normal Echocardiogram Database.
Lopez L, Colan S, Stylianou M, Granger S, Trachtenberg F, Frommelt P, Pearson G, Camarda J, Cnota J, Cohen M, Dragulescu A, Frommelt M, Garuba O, Johnson T, Lai W, Mahgerefteh J, Pignatelli R, Prakash A, Sachdeva R, Soriano B, Soslow J, Spurney C, Srivastava S, Taylor C, Thankavel P, van der Velde M, Minich L
Circ Cardiovasc Imaging. 2017 Nov;10(11).; 2017

AGE

Find a specific area of interest

Aortic Isthmus	0 mm		
Left Main Coronary Artery	3.6 mm	1.40 1.74 - 3.93	
Left Anterior Descending Coronary Artery	2.5 mm	2.07 1.17 - 2.48	
Proximal Right Coronary Artery	2.6 mm	0.70 1.17 - 3.28	
Pulmonary Valve Annulus	0 mm		
Pulmonary Valve Annulus, PLAX	0 mm		
Main Pulmonary Artery	0 mm		

C. Are there specific Z scores for Indian population?

- **No published data**
- **Small cohort data from Chandigarh, India (reliability and reproducibility??)**

- ***Urgent need to develop Body surface area appropriate, gender appropriate and race appropriate CAA 'Z' scores for Indian children***

- ***Till then, we may use the 'Z' score criteria proposed by Dallaire et al***

A few important tips

- ***It is important to use the same 'Z' score criteria every time***
- ***A small error in measurement of the CA dimension can translate into a significant difference in Z scores, changing the CA classification, particularly in young patients***
- ***Accurate weight and height measurements (at each visit) are necessary for accurate body surface area calculation to avoid errors in measurements that may lead to over- or underestimation of CA Z scores***

Role of coronary CT angiography and magnetic resonance imaging

- ***Availability and expertise needed to analyze the imaging is a limitation***
- ***CT coronary angiography is a better imaging modality for left circumflex coronary artery and to assess distal coronary arteries. It can also assess the calcification, thrombosis and stenosis.***
- ***Role of cardiac magnetic resonance imaging is under investigation***

Distal Coronary Artery Abnormalities in Kawasaki disease: experience on CT Coronary Angiography in 176 children. Singhal M, Pilania R, Jindal AK et al. Rheumatology, 2022.

- **176 patients underwent CTCA** (128-Slice Dual Source scanner)
- **CTCA identified 60 aneurysms:** 37 proximal (36 fusiform; 1 saccular) and **23 distal (17 fusiform; 6 saccular)**
- **9 patients showed non-contiguous aneurysms in both proximal and distal segments**

- **Four patients showed distal segment aneurysms in absence of proximal involvement of same coronary artery**
- **On 2-D echocardiography, only 40 aneurysms could be identified**
- **CTCA also identified complications (thrombosis, mural calcification and stenosis) that were missed on 2-D echocardiography**

KAWASAKI DISEASE-TREATMENT

DR. PRIYANKAR PAL

MD, MNAMS,FIAP, FRCPCH

Prof. and Head of Pediatrics
Unit Head Pediatric Rheumatology
Institute of Child Health, Kolkata,India
Past President, Pediatric Rheumatology Society of India
President, Indian Society for Kawasaki Disease

To the uninitiated, the diagnosis of KD may seem like an enigma. There seems to be more of “art” than “science” in arriving at a diagnosis. **KD remains purely a clinical diagnosis** and is a delight for the hardcore clinician.

It cannot be overemphasized that the diagnosis rests on the recognition of a typical temporal sequence of a constellation of clinical features, with none of the features taken individually being of any diagnostic significance whatsoever.

Kawasaki Disease – An Indian Perspective

SURJIT SINGH AND TOMISAKU KAWASAKI

INDIAN PEDIATRICS

Why identify KD?

Untreated 20% to 25 % incidence of coronary artery aneurysms.

Commonest cause of MI in children

Incidence of MI-1.9%(39% in those with persistent aneurysms).

Majority of MI within 1 year of onset,mortality 20%

Goals of Therapy

Control of the acute inflammation

+ **prevent long-term sequelae** and, **most importantly, coronary artery abnormalities**.

How to treat?

Intravenous immunoglobulin (IVIG) **+** high-dose aspirin have traditionally been the cornerstones of Kawasaki disease management, *although the role of high dose aspirin has been called into question.*

IVIg treatment of KD is one of the most cost effective medical therapies available,leading to short and long term savings.

IVIg

IVIG prevents the development of coronary aneurysms in a dose-dependent fashion.

A single dose of 2 g per kg is administered over 12 hours.

Start with a slow infusion rate, increase rate after the first few hours.

Available brands: Immunorel (Reliance), Intas, Plasmagen, Gamma Safe(Halsted)

Potential Mechanisms of Intravenous Immunoglobulin

- Provides antibodies against infectious agent
- Provides antibodies against circulating toxin
- Provides anti-idiotypic antibodies
- Blockades Fc receptors
- Accelerates clearance of activated complement fragments

- IVIg reduces the incidence of CAA to 1-5%
- IVIG also improves myocardial function in KD patients having myocarditis
- Usually very prompt defervescence, but irritability may persist for days.

S/E:

- Infusion reactions -fever, rash, nausea, and hypotension—

managed by slowing the rate of infusion and treating with an antiallergic.

Headache up to 72 hours after the infusion is common

Anemia

Timing of IVIG therapy

Therapy should be instituted **within the first 10 days** of illness and, if possible, within 7 days of illness.

.

However, this 10 days watershed zone was arbitarily fixed and so .....

if a patient presents late with persistent fever, aneurysms, or inflammation , DONOT HESITATE to administer IVIG.

Late diagnosis are often complicated by aneurysms at diagnosis and requires augmentation of therapy (Infliximab/ Steroids)

ASPIRIN

Anti-inflammatory regimens using medium dose (30 mg/kg/day) have been recommended during the acute phase of the illness.

However some centres would favour initiation with 3-5 mg/kg/day.

- In cases of aspirin sensitivity, another antiplatelet agent, such as dipyridamole, should be considered.

- Risks : transaminitis , transient hearing loss, and, rarely, Reye syndrome.

NOT to be used for associated arthritis

No defervescence by 48 hours of completion of IVIG or disease recrudescence within 2 weeks: IVIG nonresponders

- 10- 15 % fails to respond to 1st dose IVIg
- Increased risk of developing coronary artery aneurysms

0PTIONS??

- 2 nd dose IVIg 2gm/kg
- Pulse methyl-prednisolone 30 mg/kg/dose for 1-3days
- **Infliximab**

IVIg nonresponders

Others---

Cyclophosphamide

Cyclosporin

Doxycycline

Ulinastatin

Anakinra

Cases with persistent active disease unresponsive to conventional therapy

2ND Dose IV Ig

Failure rate — 30%

INFLIXIMAB – preferred treatment mode in most centers

Single infusion of 10 mg/kg

After the infliximab infusion, majority of patients had a **rapid decrease in their temperature within 24 hours** and had rapid improvement in their inflammatory markers .

Screening tests for tuberculosis (chest x-ray, Tuberculin test, QuantiFERON-TB Gold test) not necessary prior to IFX.

Plasmapheresis

A **dramatic response** to plasmapheresis has been reported.

Best to **reserve when ALL available medical interventions fail**, including multiple doses of IVIG, intravenous methylprednisolone, and TNF inhibition

When to use IVIG+ STEROIDS ??

1. Suspected IVIG resistance according to risk scores.
2. Coronary aneurysms at diagnosis
3. Complicated by macrophage activation syndrome
4. Pre emptively for therapy intensification in infantile KD

KD in Infants

- Diagnose (The Trickiest part) : 50-70% can have incomplete/ atypical presentations.
- Consequently late diagnosis and higher incidence of aneurysms at diagnosis.

- Hence, primary therapy needs to be intensified in majority with steroids or Infliximab

Efficacy of immunoglobulin plus prednisolone for prevention of coronary artery abnormalities in severe Kawasaki disease (RAISE study). LANCET 2012

Patients with severe Kawasaki disease were randomly assigned by a minimisation method to receive either intravenous immunoglobulin (2 g/kg for 24 h and aspirin 30 mg/kg per day) or intravenous immunoglobulin plus prednisolone (the same intravenous immunoglobulin regimen as the intravenous immunoglobulin group plus **prednisolone 2 mg/kg per day given over 15 days after concentrations of C-reactive protein normalised.**

Interpretation

Addition of prednisolone to the standard regimen of intravenous immunoglobulin improves coronary artery outcomes in patients with severe Kawasaki disease in Japan.

Kobayashi Risk Score(2006) -

identifies patients with Kawasaki syndrome at high risk of being resistant to intravenous immunoglobulin

Sodium <133 mmol/L
Days of illness at initial treatment < 4
Aspartate aminotransferase > 100 IU/L
Percentage of neutrophils > 80%
C-reactive protein >10 mg/dL
Age < 12 months
Platelet count < 300000

Although there is no conclusive body of evidence defining the best second and third-line therapies for Kawasaki patients, Infliximab and steroids are currently the two agents that have been most studied.

Anticoagulation in KD

1. Giant aneurysm, multiple or complex aneurysms, presence of thrombus
2. Associated stenosis
3. Peripheral gangrene

Initiate with LMW heparin followed by oral warfarin to maintain INR of 2-2.5

For arterial thrombosis/ peripheral gangrene- **thrombolytics** have been tried in addition to anticoagulation

ROLE OF THE PEDIATRIC CARDIOLOGIST

- Catheter intervention with angioplasty, rotoablation, and stenting and surgical intervention with internal mammary artery bypass grafts and cardiac transplantation reserved for patients with severe coronary artery damage and ischemia.

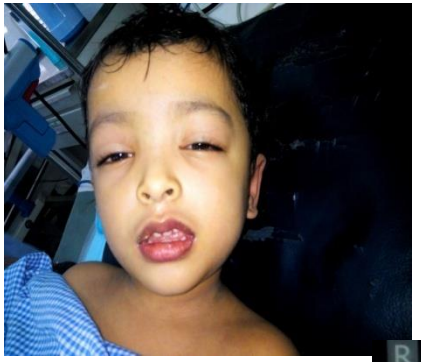
TREATING ASSOCIATED COMPLICATIONS

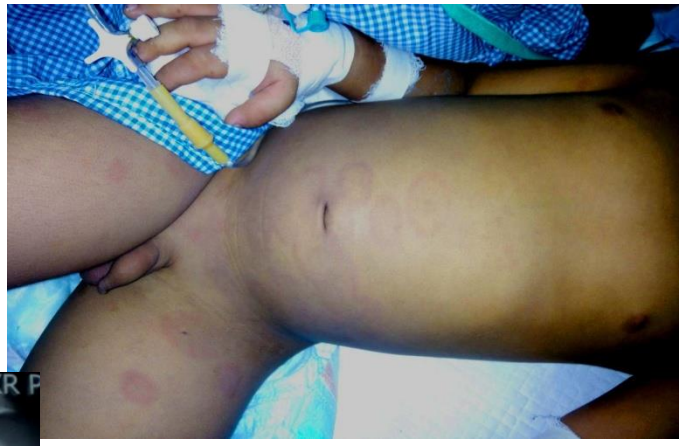
Arthritis- 5-10% develop a reactive arthritis.

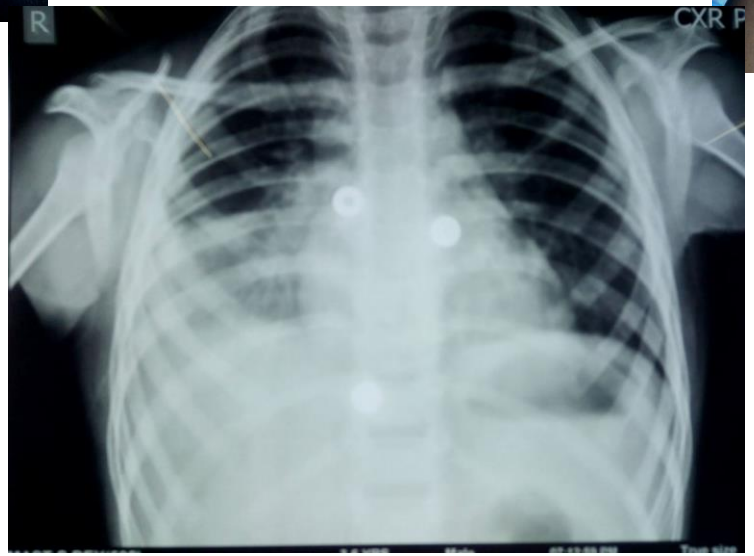
Tm- NSAID/ steroids

FAILURE TO RESPOND????

An associated Infection / Infectious Mimic







FAILURE TO RESPOND????

- **Incomplete, atypical kawasaki disease or evolving systemic juvenile idiopathic arthritis.** Cases Journal 2009
- **Failure to distinguish systemic-onset juvenile idiopathic arthritis from incomplete Kawasaki disease in an infant.** J Paediatr Child Health. 2007
- **Incomplete Kawasaki syndrome followed by systemic onset-juvenile idiopathic arthritis mimicking Kawasaki syndrome.** Rheumatology International 2010

FAILURE TO RESPOND????

Macrophage Activation Syndrome in Kawasaki Disease

MAS may rarely complicate the course of KD; prompt treatment with **pulse methylprednisolone** result in favourable outcome .

KD with coronary artery aneurysm at presentation

PEDIATRICS®

Article

Treatment Intensification in Patients With Kawasaki Disease and Coronary Aneurysm at Diagnosis

Audrey Dionne, Jane C. Burns, Nagib Dahdah, Adriana H. Tremoulet, Kimberlee Gauvreau, Sarah D. de Ferranti, Annette L. Baker, Mary Beth Son, Patrick Gould, Anne Fournier, Jane W. Newburger and Kevin G. Friedman

Pediatrics June 2019, 143 (6) e20183341; DOI: https://doi.org/10.1542/peds.2018-3341

CONCLUSIONS: Among a high-risk group of patients with Kawasaki disease with CAA on baseline echocardiography, those treated with corticosteroids or infliximab in addition to IVIg had less progression in CAA size compared with those treated with IVIg alone.

Repeat echocardiography at 2 and 6 weeks

If aneurysm +/- thrombus at presentation, more frequent (every 1 to 2 days for 10 to 14 days)

Fate of Aneurysms

50-70% will regress over a period of 1-2 years

Unresolved ones persist and develop stenosis and / thrombosis

Risk Stratification

Allows for INDIVIDUALISATION of patients—

- sorts out those who are at greatest risk of Myocardial Infarction

RISK STRATIFICATION

Risk Level	Pharmacological Therapy	Physical Activity	Follow-up and Diagnostic Testing	Invasive Testing
I (no coronary artery changes at any stage of illness)	None beyond initial 6–8 weeks	No restrictions beyond initial 6–8 weeks	Cardiovascular risk assessment and counseling at 5-year intervals	None recommended
II (transient coronary artery ectasia that disappears within initial 6–8 weeks)	None beyond initial 6–8 weeks	No restrictions beyond initial 6–8 weeks	Cardiovascular risk assessment and counseling at 3- to 5-year intervals	None recommended
III (small to medium solitary coronary artery aneurysm)	Low-dose aspirin (3–5 mg/kg aspirin per day), at least until aneurysm regression is documented.	For patients in first decade of life, no restriction beyond initial 6–8 weeks. For second decade, physical activity guided by stress testing every other year. Contact or high-impact sports discouraged for patients on anti-platelet agents.	Annual cardiology follow-up with echocardiogram and ECG, combined with cardiovascular risk assessment and counseling. Stress testing with radioisotope perfusion scan or stress echocardiogram every other year.	Angiography, if non-invasive test suggests ischemia
IVa (one or more large or giant coronary artery aneurysms), or IVb (multiple or complex aneurysms, without obstruction)	Long-term anti-platelet therapy and warfarin (target: INR 2.0–2.5) or LMW heparin (target: antifactor Xa level 0.5–1.0 unit/mL) should be combined in giant aneurysms.	Contact or high-impact sports, isometrics, and weight training should be avoided because of the risk of bleeding. Other physical activity recommendations guided by outcome of stress testing or myocardial perfusion scan.	Biannual follow-up with echocardiogram + ECG. Annual pharmacological or exercise stress testing.	Initial angiography at 6–12 months. Repeated angiography if non-invasive test, clinical or laboratory findings suggest ischemia. Elective repeated angiography under some circumstances (see text)
V (coronary artery obstruction)	Long-term low-dose aspirin. Warfarin or LMW heparin if giant aneurysm persists. Use of β-blockers should be considered to reduce myocardial oxygen consumption	Contact or high-impact sports, isometrics, and weight training should be avoided because of the risk of bleeding. Other physical activity recommendations guided by outcome of stress testing or myocardial perfusion scan.	Biannual follow-up with echocardiogram and ECG. Annual pharmacological or exercise stress testing.	Angiography is recommended to address therapeutic options.

IF IN DOUBT- TREAT

The consequences of failure to treat a child appropriately with KD are so important that, error on the side of premature or unnecessary therapy is preferable to delayed or missed therapy for a child for whom the diagnosis is uncertain.

Textbook of Pediatric Rheumatology: Cassidy, Petty

- Vessels show histological and functional abnormalities at the sites of healed aneurysms, and vascular reactivity to endogenous vasodilators is abnormal in children who have had KD, regardless of whether they have detectable coronary artery abnormalities.
- **LIFELONG FOLLOW UP is required.**