KAWASAKI DISEASE – CLINICAL FEATURES

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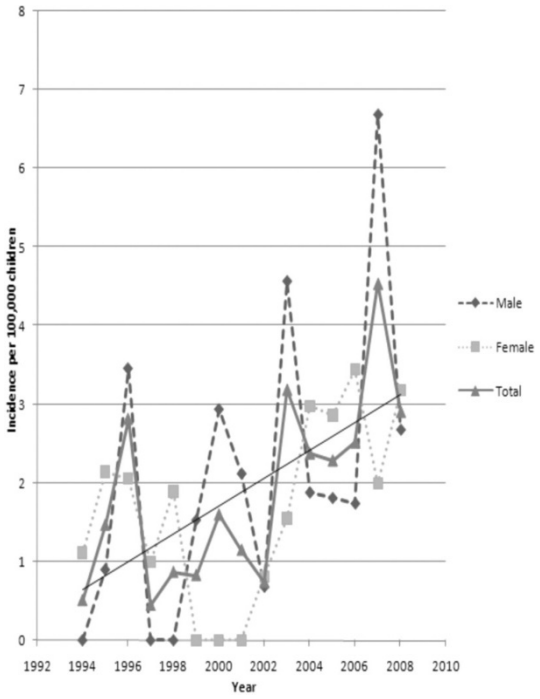
- Clinical Features
- Diagnosis
- Management
- Clinical Case scenarios
- Take home messages

Epidemiology of Kawasaki disease at Chandigarh, India

Between 1994 - 2008

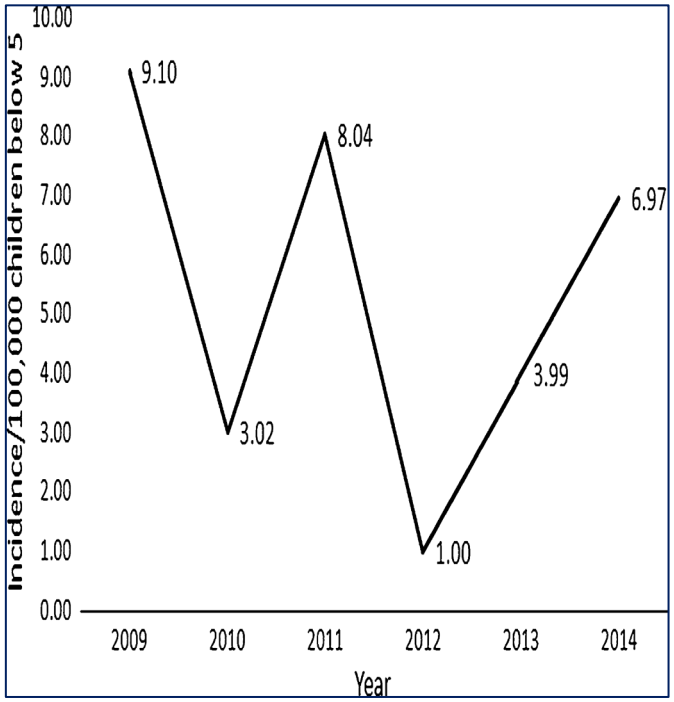


Incidence of KD in children <15 at Chandigarh (1994 – 2008)

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

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

Between 2009 - 2014

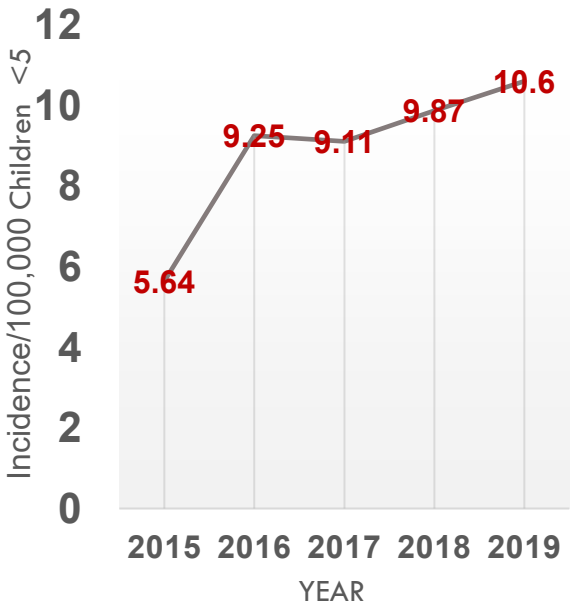


Incidence of KD in children <5 at Chandigarh (2009-2014)

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

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

Between 2015 - 2019



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

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

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."

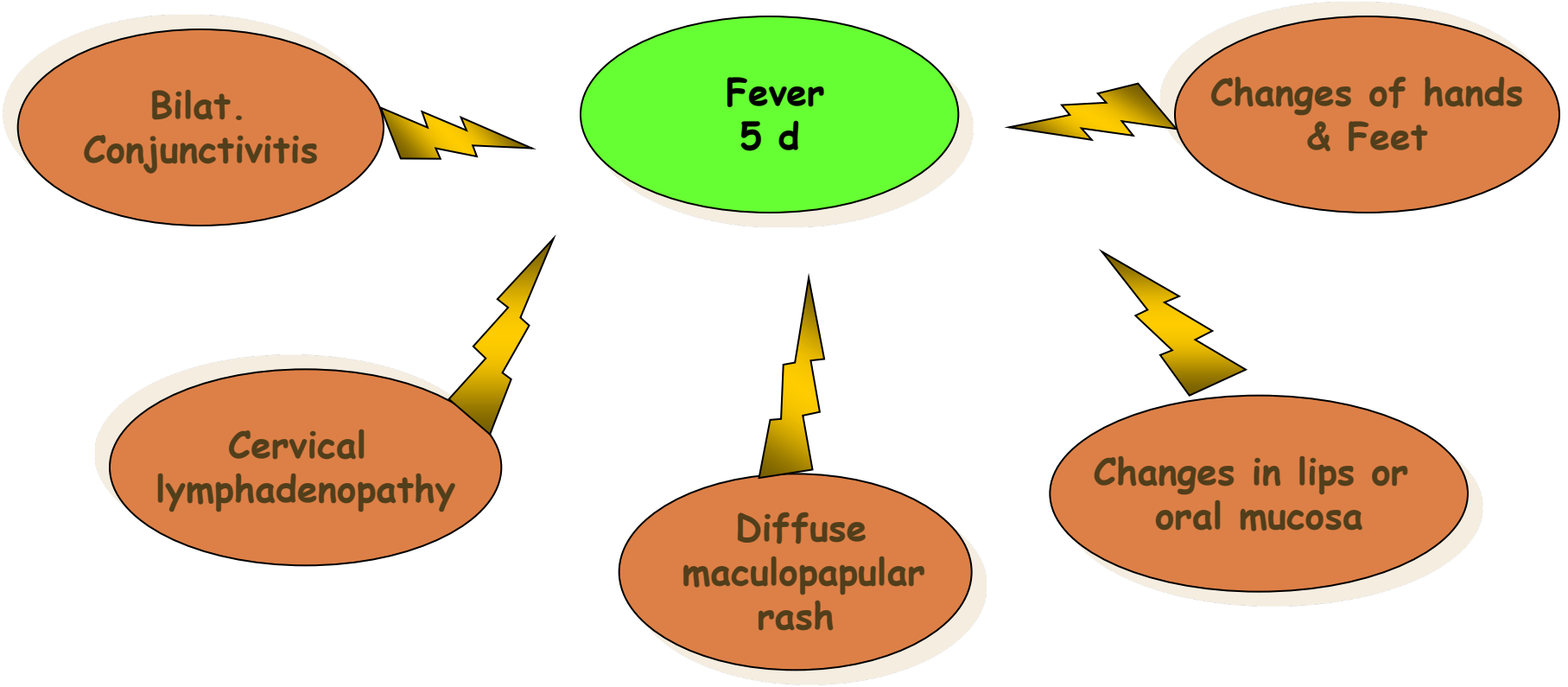
Jane Burns, MD*

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

- Classical Kawasaki
- Incomplete Kawasaki
- Atypical Kawasaki

Criteria for diagnosis

(Classic Kawasaki)



Other Clinical Findings/Non classical features

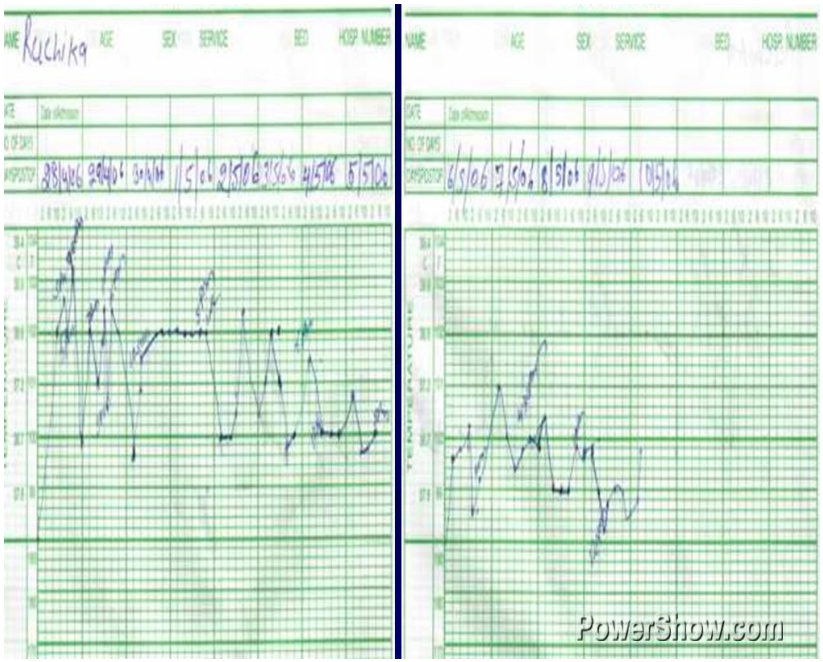
- Perianal or perineal desquamation is typically seen during the acute phase of KD, as early as day 6 of fever .
- Reactivation of BCG scar:
- Nervous system: Irritability is a common finding , marked in infants. It is usually out of proportion to the degree of fever and thought to be a manifestation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

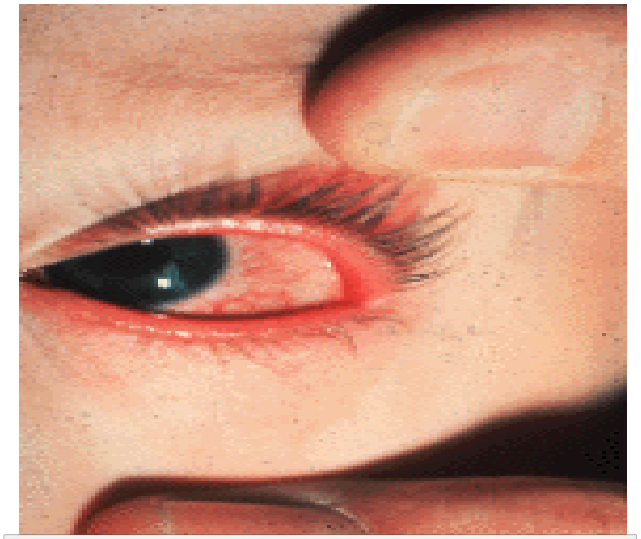
FEVER



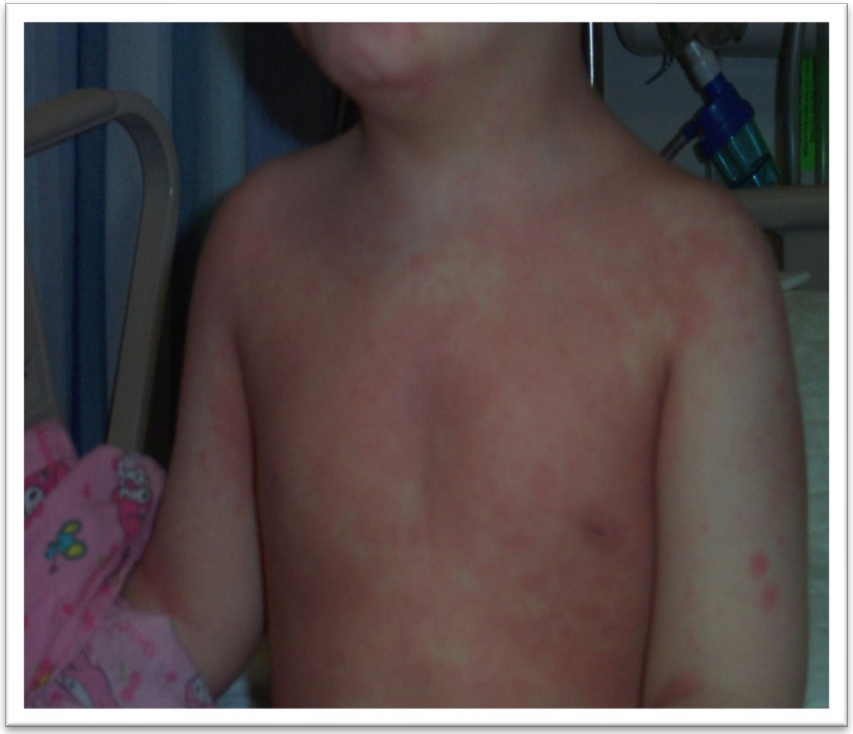
- Most common manifestation of KD
- High-spiking
- Peak temperatures>39°
- Without therapy, fever lasts a mean of 11 days but may last up to 4 weeks
- Usually resolves within 2 days of appropriate therapy

BULBAR CONJUNCTIVITIS

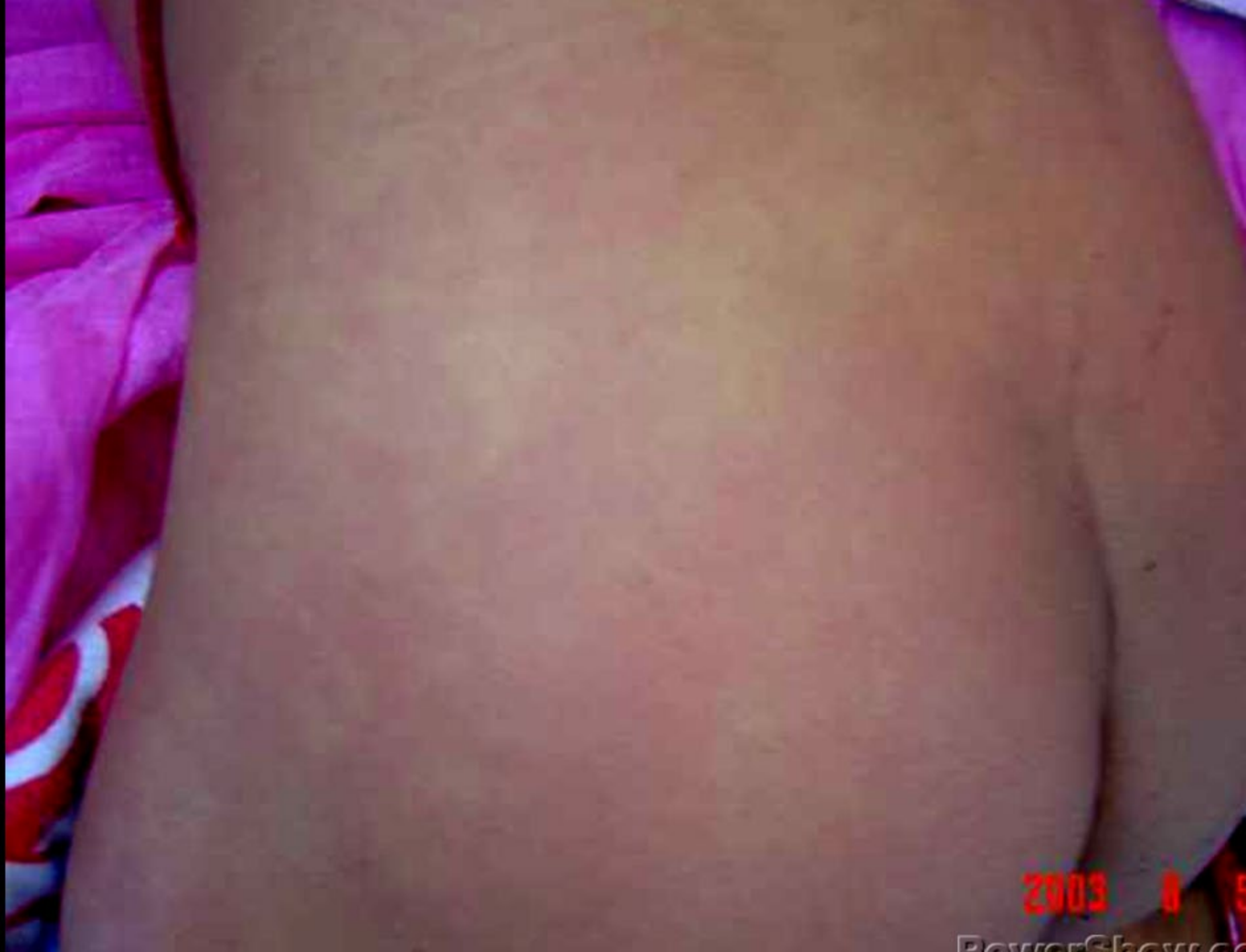
- Appears shortly after the onset of fever and is seen in 90% of patients
- Typically spares the limbus
- Painless and non-exudative
- Mild acute iridocyclitis or anterior uveitis may be seen on slit lamp exam



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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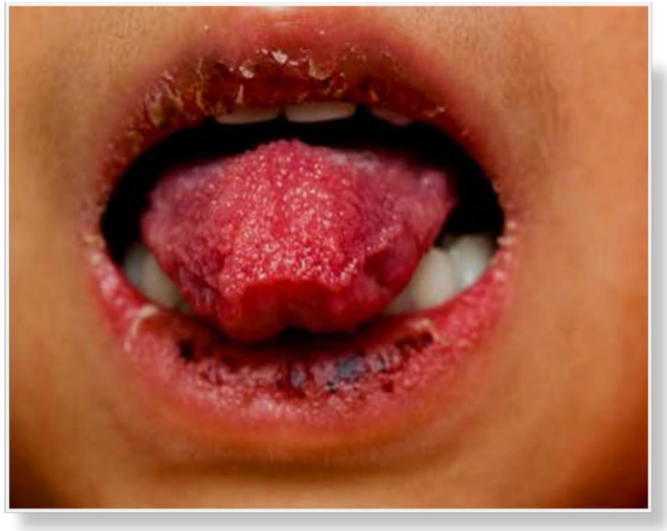
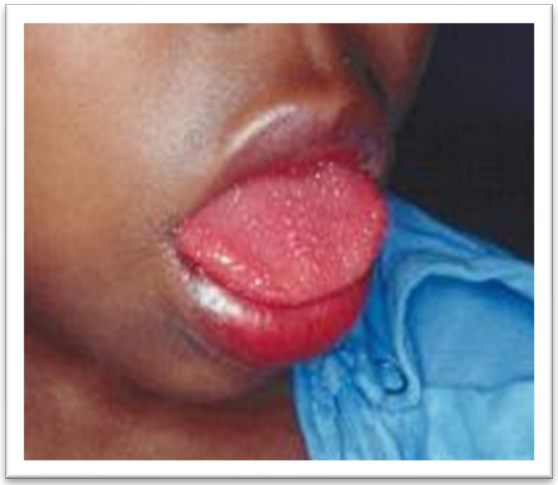
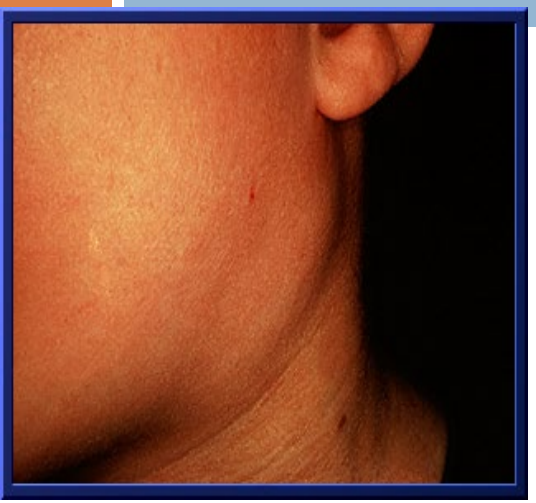
CHANGES IN THE LIPS AND ORAL CAVITY

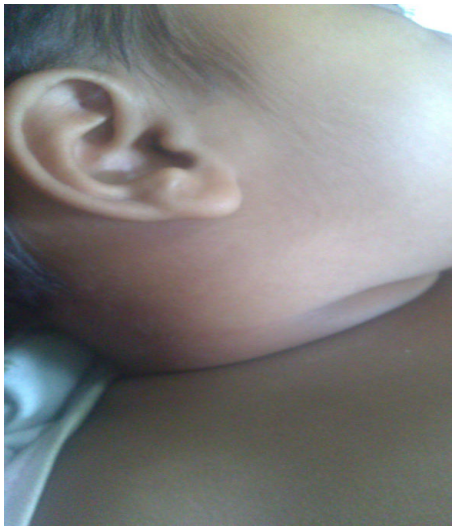




- Erythema, dryness, fissuring, peeling, cracking and bleeding of the lips
- “Strawberry tongue” with erythema and prominent papillae
- Diffuse erythema of the oral mucosa

CERVICAL LYMPHADENOPATHY



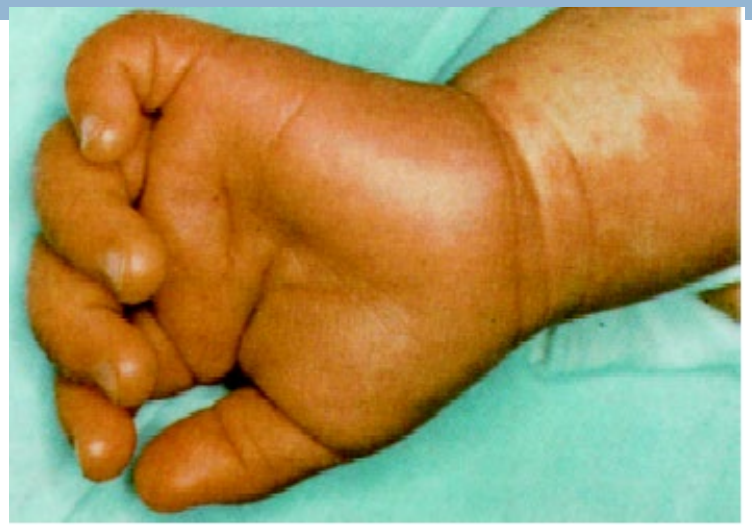


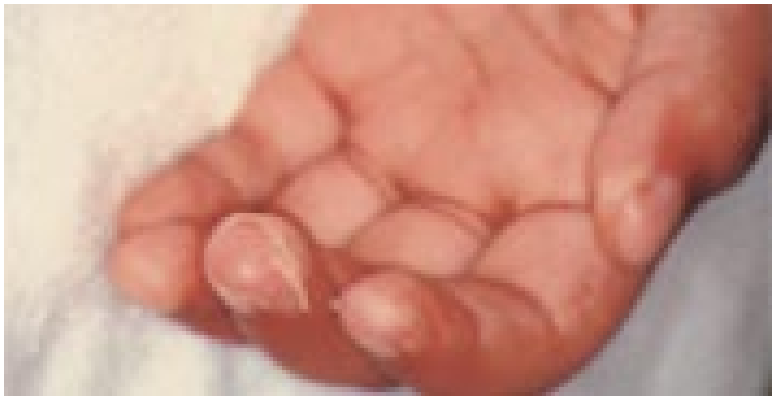
- Unilateral and confined to the anterior cervical triangle
- ≥ 1.5 cm in diameter

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

EXTREMITY CHANGES

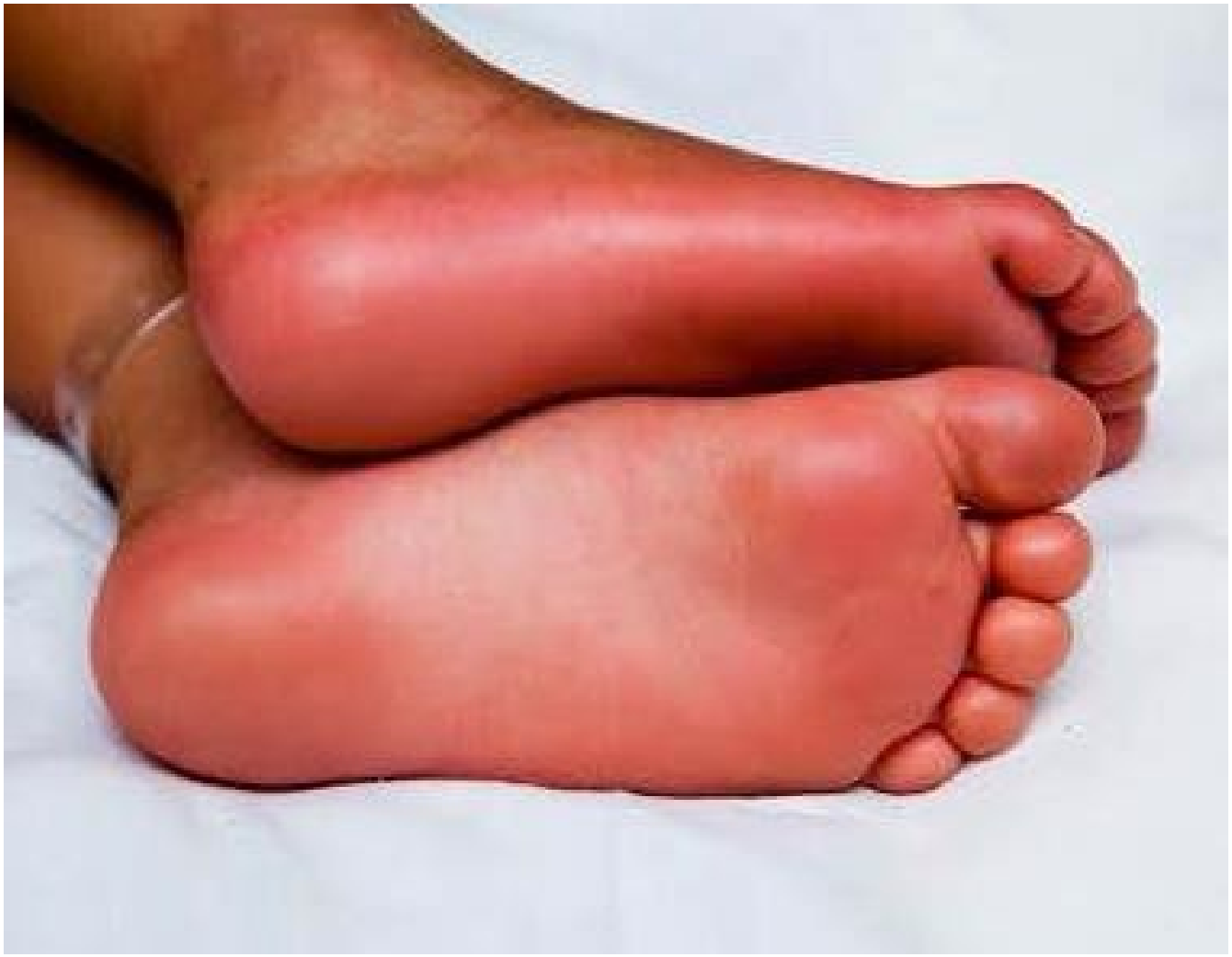
- Acute:
  - Erythema of the palms and soles and/or edema of the hands and feet
- Subacute (2-3 weeks):
  - Desquamation of the fingers and toes (70-98% of children)-



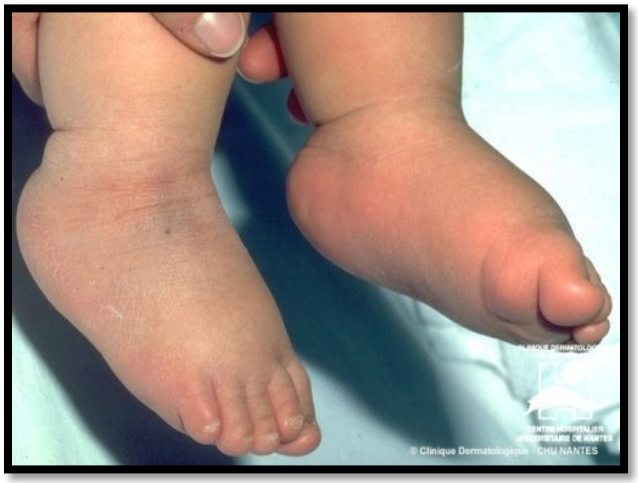


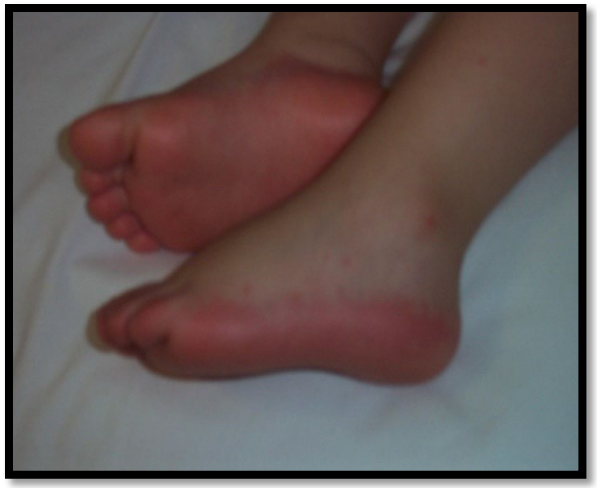
Typical Periungual Desquamation

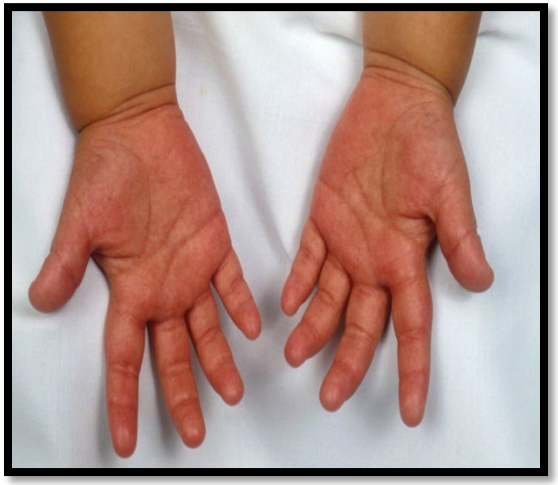
RED PALMS AND SOLES

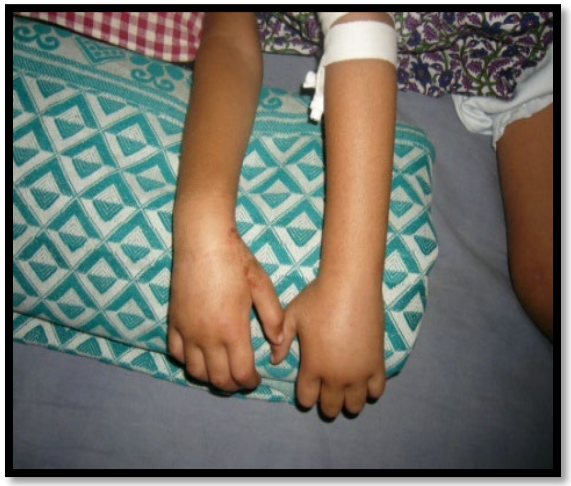


EDEMA AND ERYTHEMA OF HANDS & FEET

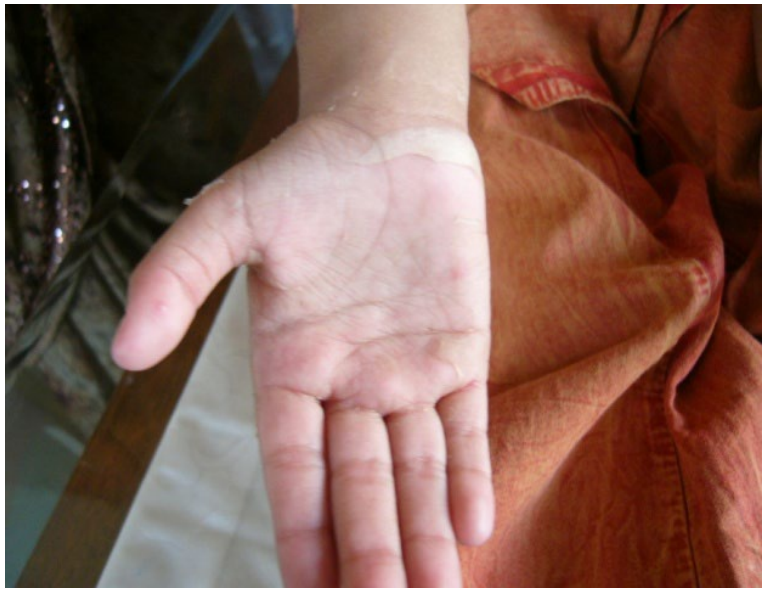


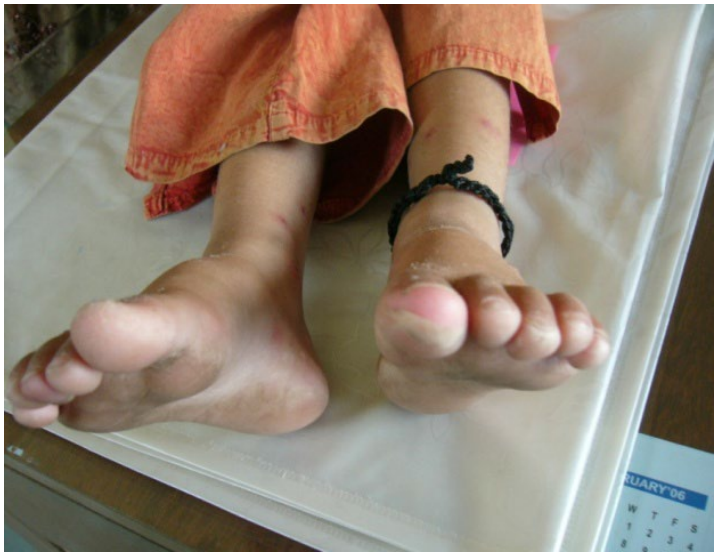


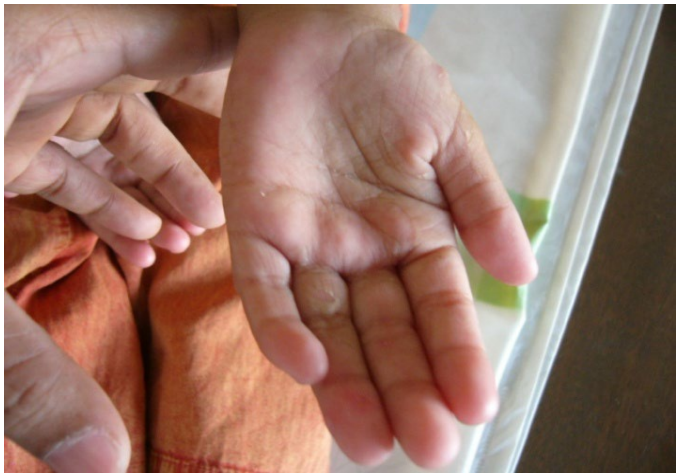




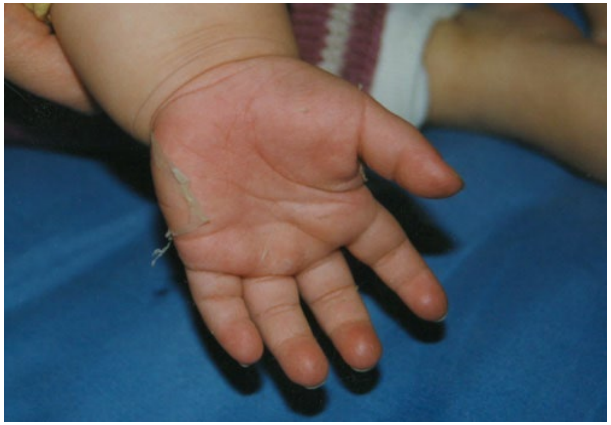
SKIN PEELING

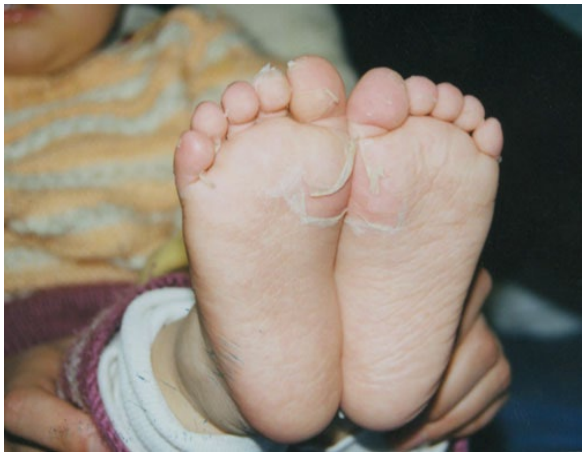


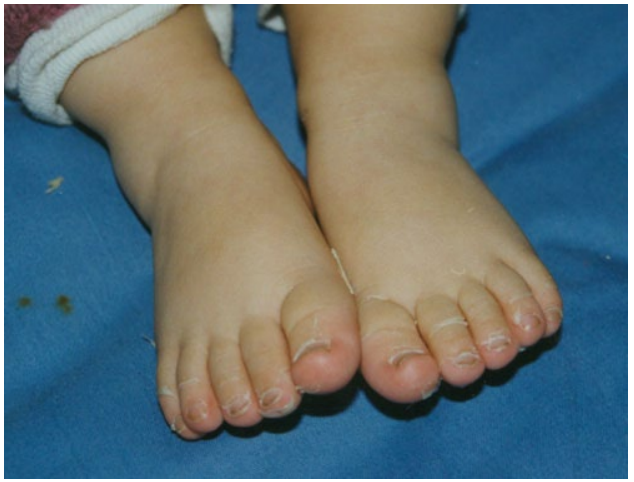




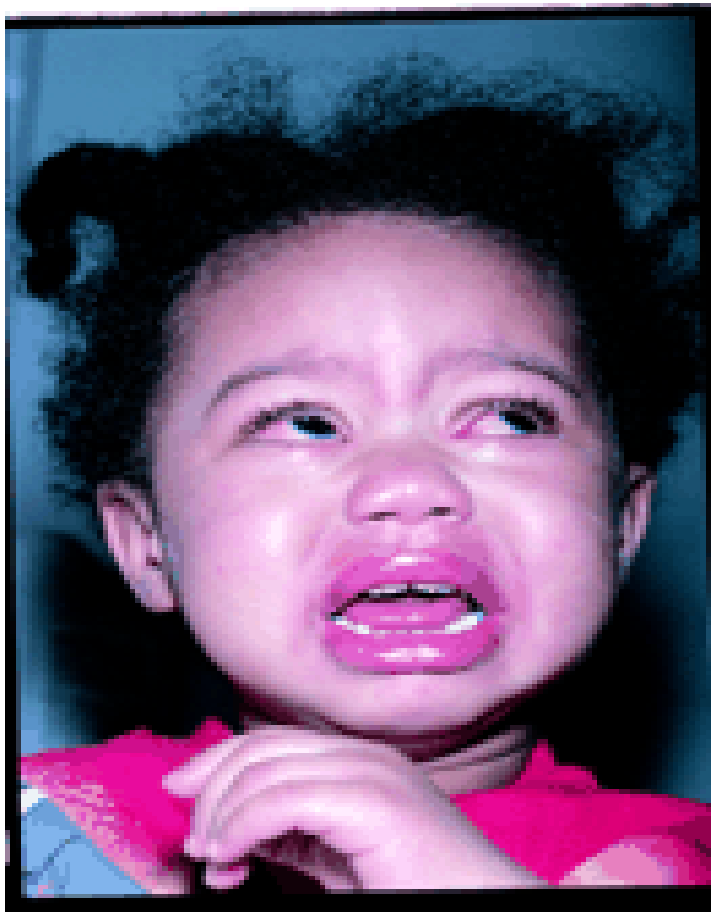
DESQUAMATION OF FINGERS AND TOES







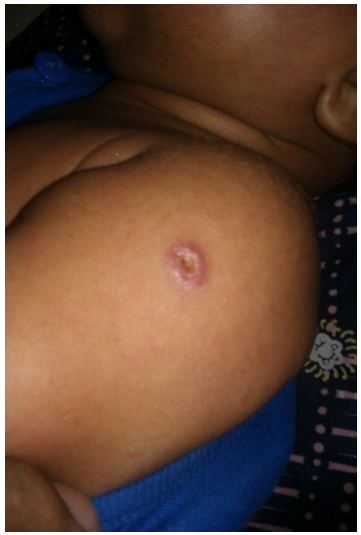
EXTREME IRRITABILITY

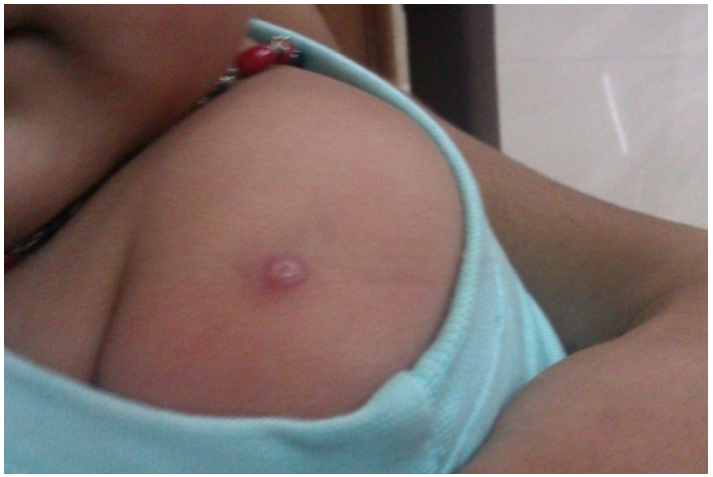


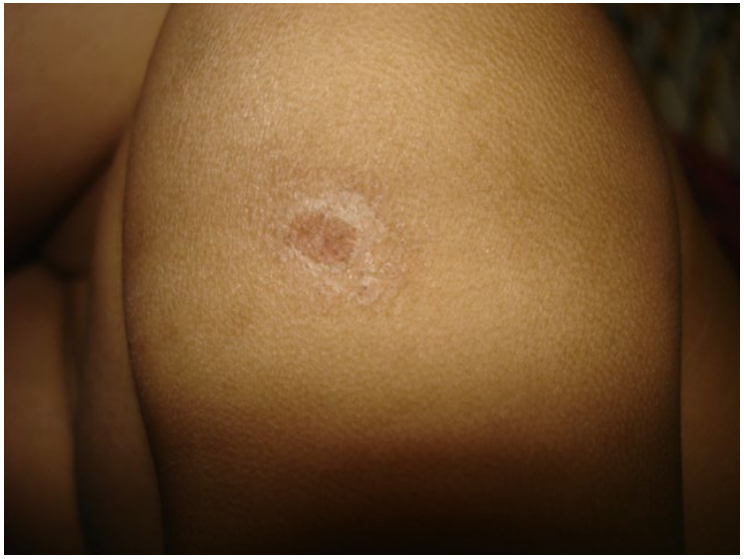
EXTREME IRRITABILITY AND RESPONSE TO TREATMENT WITH IVIG

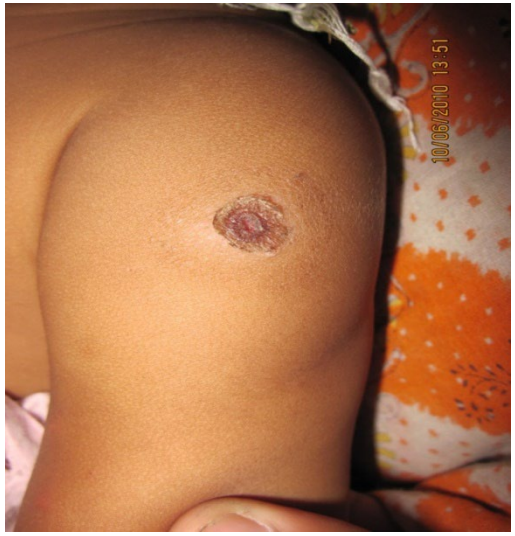
Reactivation of BCG Scar

- 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





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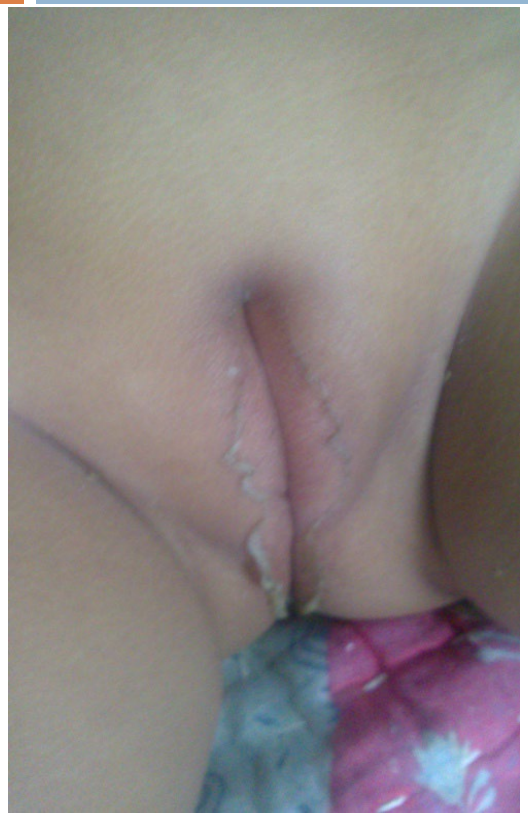
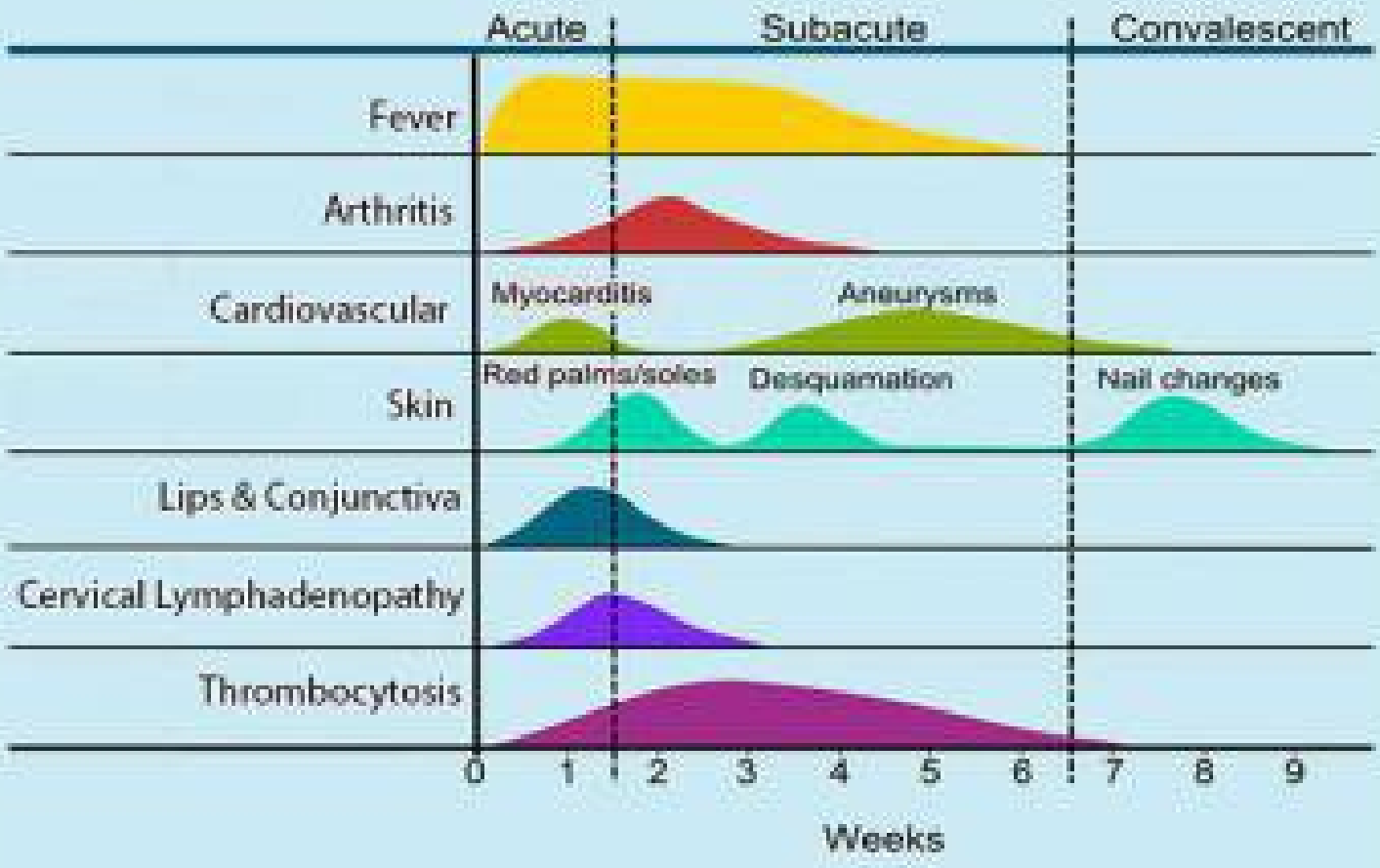
PERINEAL SKIN PEELING



Clinical manifestations of Kawasaki Disease



?

- 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

Circulation • Volume 150, Number 23 • https://doi.org/10.1161/CIR.0000000000001295

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

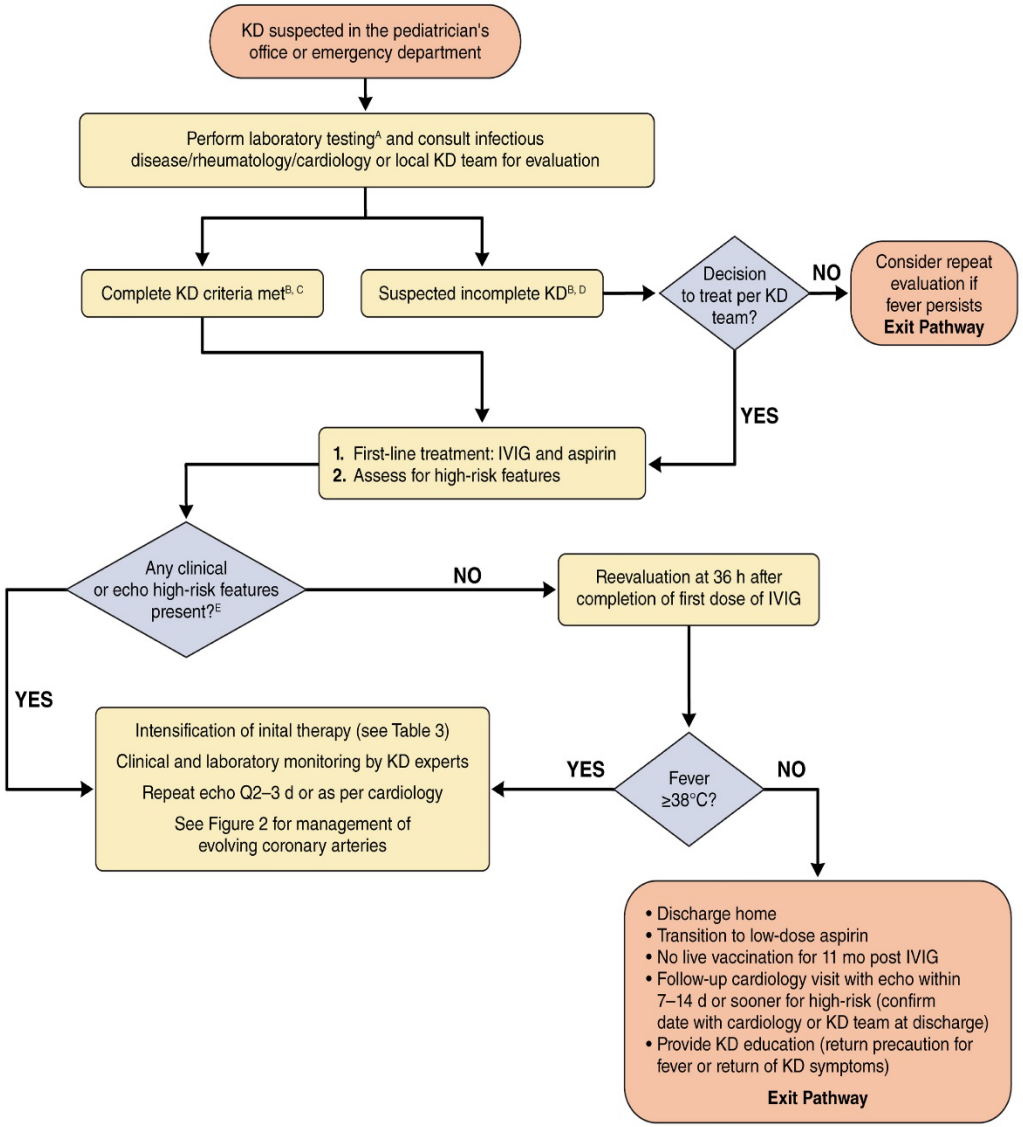
B CARDIAC EVALUATION
- ECG and Echo

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/mm^3
    - – 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

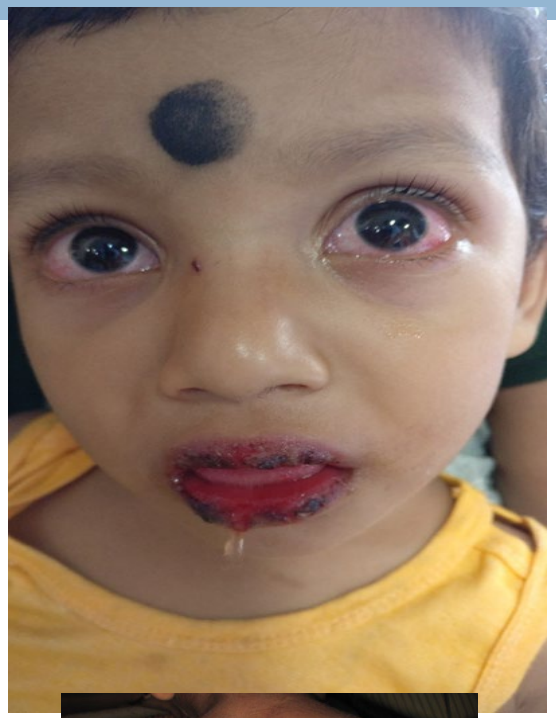


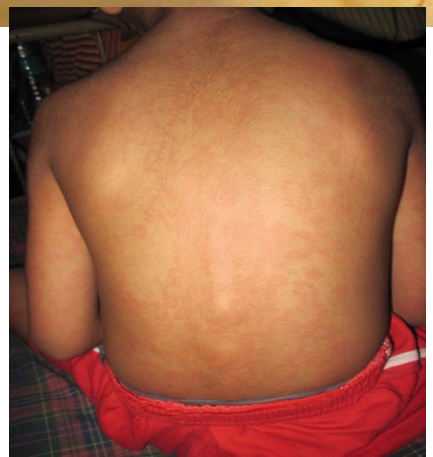
CASE 1

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.

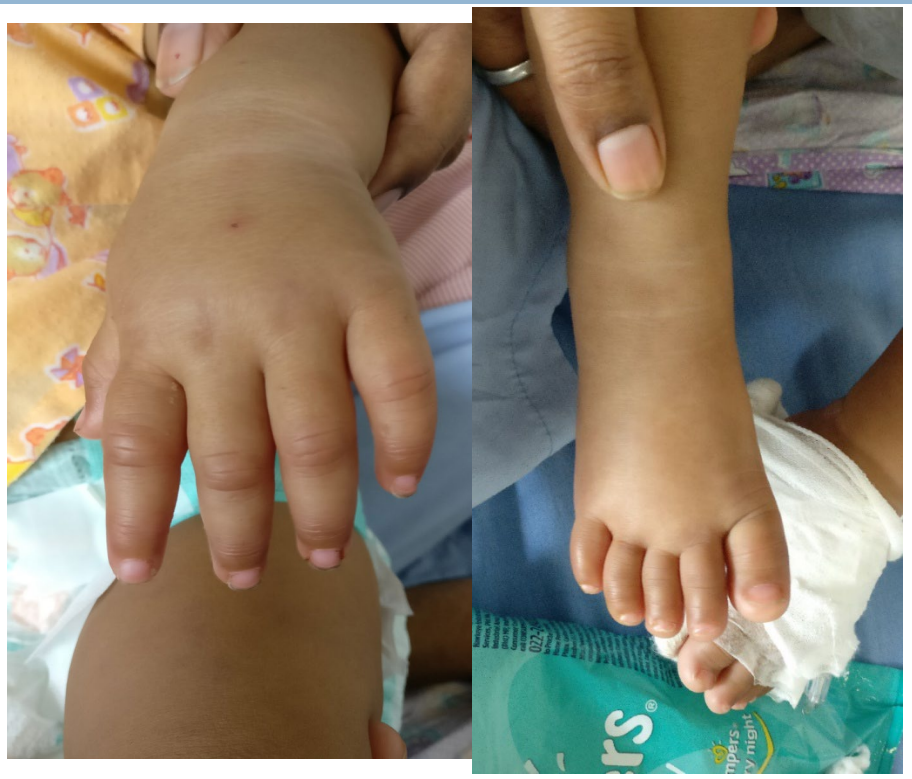
- More investigations:

  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

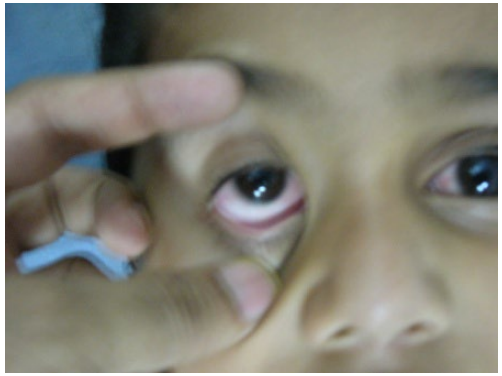
Sterile pyuria

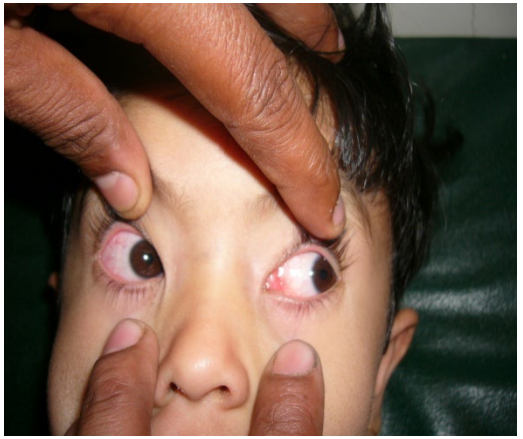
Consistent with the diagnosis of **Kawasaki disease**

- **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

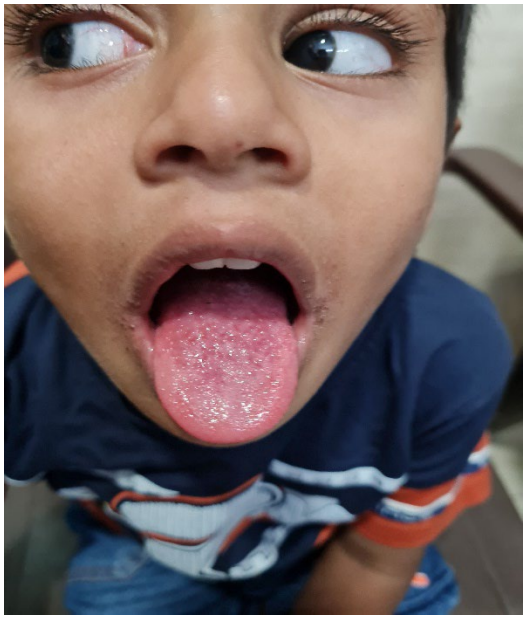
- Recurrence or persistence of fever, 36 hours beyond completion of IVIg infusion.
- Before proceeding further with second-line agents, it is prudent to review the diagnosis of KD.

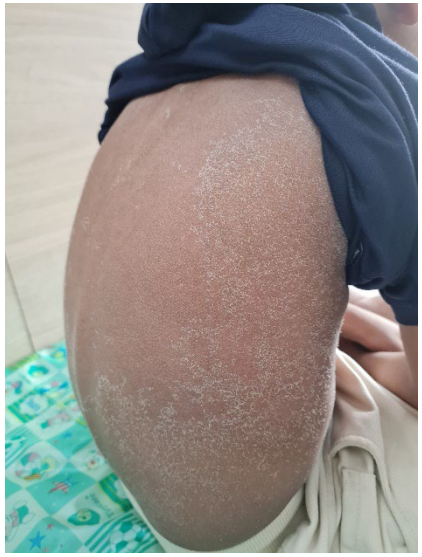
Case

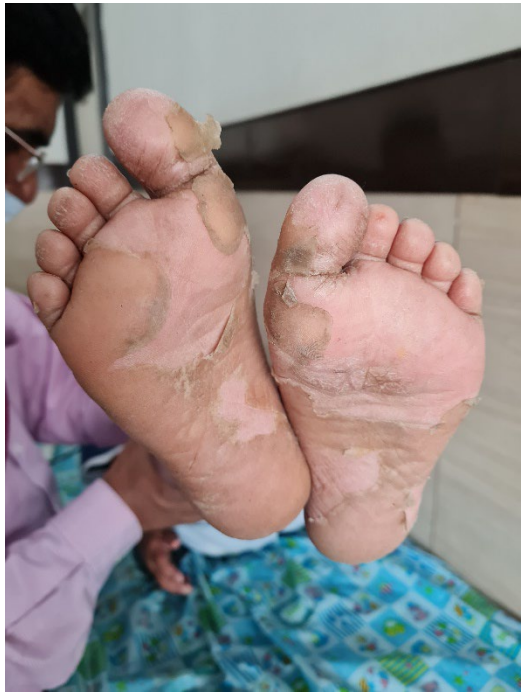
- 7yr old boy
  - High grade fever.
  - Difficulty in swallowing
  - Rashes on day 2 of illness - finely papular erythematous bright red intense in creases cheeks erythematous
  - Strawberry tongue & cracked lips.
  - Rashes faded on 4th day with desquamation.

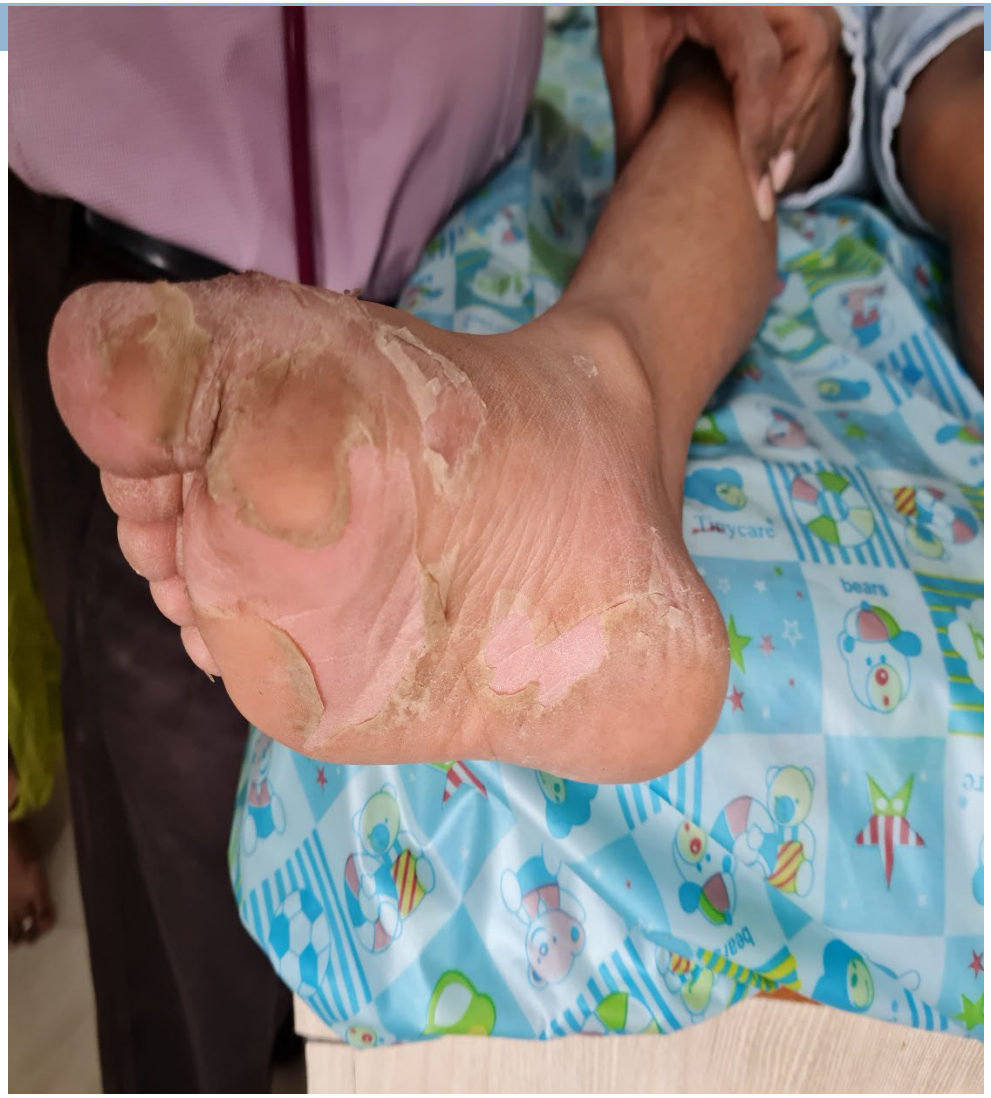
Scarlet fever

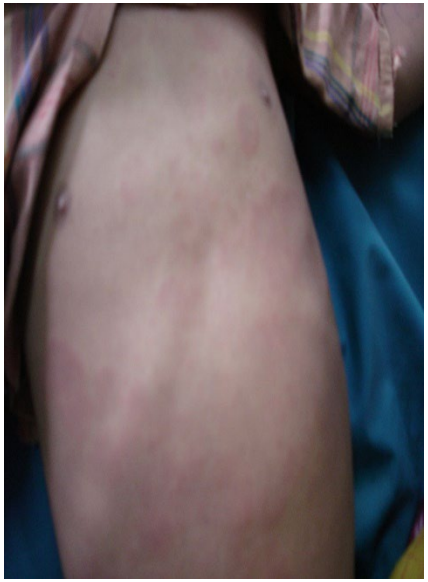
- Fever mod –high rash with neck trunk and extremities
- Diffuse finely papular erythematous bright red intense in creases cheeks erythematous
- Skin is goose pimple appearance and rough, sand paper appearance
- Pharyngitis with strawberry tongue
- Rashes fades by 3-4 days











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- 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