

Indian Academy of Pediatrics Position Paper on Kawasaki Disease

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ABSTRACT

Objective: To formulate practice guidelines on diagnosis and management of Kawasaki disease (KD) for Indian children. **Justification:** KD is a systemic vasculitis that predominantly affects infants and children less than 5 years of age. Coronary artery abnormalities (CAA) develop in around 15-25% of untreated children with KD. Coronary artery involvement can lead to long-term cardiovascular implications such as development of premature coronary artery disease. Diagnosis of KD is essentially clinical based on recognition of a constellation of characteristic symptoms and signs. Timely diagnosis and initiation of intravenous immunoglobulin (IVIg) therapy is known to produce five-fold reduction in the incidence of CAA. As there is no confirmatory laboratory test for KD, the diagnosis may be missed if one is not familiar with the nuances of clinical diagnosis. **Process:** A committee was formed under the auspices of Indian Academy of Pediatrics in early 2018 for preparing guidelines on KD in Indian children. A meeting of the consultative committee was held in Mumbai, and a draft protocol was devised. All members scrutinized the recent publications on the subject and an attempt was made to arrive at a broad consensus. Published guidelines on the subject were also reviewed. **Recommendations:** The diagnosis is clinical and is aided by laboratory and 2D echocardiography. First line of therapy is IVIg, and should be started expeditiously once the diagnosis is made.

Keywords: *Coronary artery abnormalities, Diagnosis, Intravenous Immunoglobulin, Infliximab, Management.*

Kawasaki Disease (KD) is an acute febrile illness that commonly affects children below 5 years of age. Classified under predominantly medium vasculitides, it has a predilection to involve coronary arteries. Ever since the first report by Dr Tomisaku Kawasaki from Japan in 1967 [1], the disease has been increasingly reported worldwide. KD has become one of the leading causes of acquired heart disease among children in many developed countries.

Incidence of KD has been increasing significantly over the last decade possibly due to a combination of an actual increase in incidence and also due to heightened awareness amongst the Pediatricians [2]. A high index of suspicion supported with relevant laboratory tests and imaging (2D echocardiogram) is often needed in establishing the diagnosis. Though various consensus guidelines are available for diagnosis and management of KD, a nation-wide consensus for a resource constrained setting like ours is the need of the hour.

DIAGNOSIS

We have two established criteria that could be used as a guide for diagnosis of KD- The American Heart Association (AHA) criteria [1] and the Japanese criteria [7]. AHA criteria have been discussed in this document and are detailed in **Box I**.

Clinical Features

Thorough history and assessment of clinical findings play a major role in the diagnosis, as there are no specific tests.

Principal Clinical Findings

Diagnosis of KD is usually made on the basis of fever for ≥ 5 days along with the history/presence of ≥ 4 out of the 5 key clinical features. Diagnosis is made as per features given in **Box I** but the presence of classic clinical presentation or coronary artery abnormality, the diagnosis of KD can be made in less than 5 days.

Fever: The most common manifestation is fever, which is often high grade and remittent type. If untreated, fever continues for 1-3 weeks and resolves spontaneously by 3 to 4 weeks, mean duration of fever being 11 days.

Conjunctival injection: Bilateral, painless and non-exudative conjunctival injection with peri-limbal sparing usually begins in first few days after fever onset, seen in 80-90% cases. Slit lamp examination might reveal anterior uveitis during the first week of fever. Purulent conjunctivitis should suggest an alternate diagnosis.

Oral changes: Bleeding, crusting, dryness, erythema and fissuring of lips are common mucosal changes noted in KD patients. Oral mucosal and pharyngeal erythema can also be seen. Erythema of tongue along with the presence of prominent papillae results in a strawberry tongue appearance.

Cervical lymphadenopathy: Cervical adenopathy is usually non-specific and the least common clinical finding. Unilateral enlargement of a cervical node ≥ 1.5 cm diameter in the anterior triangle of neck may be noted. Occasionally the lymph node mimics suppurative lymphadenitis and may be associated with retropharyngeal / parapharyngeal edema (phlegmon) mimicking a retropharyngeal abscess on MRI. But presence of associated clinical features of KD helps in clinching the diagnosis.

Rash: A maculopapular erythematous rash that begins in trunk, later extending to extremities and face, is usually seen by 5 days of onset of the illness. Sometimes it resembles a scarlatiniform, erythroderma, erythema multiforme, or urticaria like rash. Bullous, vesicular or petechial rashes are usually not seen and suggests an alternate diagnosis.

Extremity changes: During the acute phase, erythema of palms and soles along with edema and induration of hands and feet may be seen. Desquamation of fingers and toes usually occurs 10-20 days after the onset of fever and typically starts in the periungual region. It may extend to involve the entire palm and sole.

Other Clinical Findings

Perianal or perineal desquamation is typically seen during the acute phase of KD, as early as day 6 of fever and is a useful clinical pointer.

Reactivation of BCG scar: Erythema and induration can occur at the site of BCG scar. Though noted in a small proportion of children with KD, it is virtually pathognomonic when other findings are missing [1].

Nervous system: Irritability is a common finding especially 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 can be present.

Genitourinary system: Urethritis/meatitis is a common feature in the acute phase presenting as sterile pyuria. Less common features are hydrocele and phimosis.

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 are the cardiovascular manifestations of KD.

About 5% of children may present with cardiovascular collapse and shock that may be difficult to differentiate from toxic shock [8,9]. High index of suspicion and presence of accessory clinical features helps in clinching the diagnosis. 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.

Definitions used in KD diagnosis are provided in **Box II**, and approach to a child with suspected incomplete KD is shown in **Fig. 1**.

Laboratory Tests

Diagnosis of KD is about pattern recognition with impetus being on a good history and detailed physical examination. Laboratory tests are non-specific and are only supportive and laboratory findings vary with the course of illness.

Hemoglobin: Mild to moderate normocytic, normochromic anemia is common.

Leucocyte count: Leukocytosis is usually seen in acute phase of illness with neutrophilic predominance.

Platelet count: Thrombocytosis is one of the significant lab findings in KD. Platelet count starts rising after first week, reaching a peak in the third week and normalizing by 4-6 weeks. Thrombocytopenia

is uncommon but can occur in first week. Thrombocytopenia is a risk factor for development of CAA and may be a marker of incipient macrophage activation syndrome [10,11].

Acute phase reactants like Erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) are almost always elevated in KD. IVIG therapy by itself can cause an elevation in ESR leading to doubts in the mind of the treating physician. Hence, CRP is more useful to assess response to treatment with IVIG. Macrophage activation syndrome which can rarely complicate KD should be suspected in patients with severe clinical disease associated with minimally elevated ESR and markedly elevated CRP. It might be prudent to look for an elevated serum ferritin to confirm this suspicion.

Serum transaminases: Mild to moderate elevation is seen in around 50% of patients.

Serum albumin: Hypoalbuminemia is often noted in the acute phase suggesting severe inflammatory process.

Sterile pyuria (>10 cells/high power field with sterile cultures): This is due to urethritis and sometimes be mistaken for urinary tract infection in infants.

Procalcitonin levels are usually normal, but elevated levels are associated with increased risk of IVIG resistance and CAA [12]. Serum Pro-BNP (Pro-brain natriuretic peptide) and N terminal Pro BNP (NT-ProBNP) levels are elevated in KD and can serve as useful biomarkers in distinguishing incomplete KD and closely mimicking febrile illnesses. Serum levels of NT-Pro-BNP > 225 pg/ml can assist in the diagnosis of KD (suggesting myocardial dysfunction) (86.5% sensitivity and 94.8% specificity) [13]. ECG may reveal evidence of myocarditis and conduction disturbances. An ultrasound of the abdomen may show hepatomegaly, hepatosplenomegaly, acalculous cholecystitis (gall bladder hydrops).

Echocardiography

Echocardiography is the imaging modality of choice for diagnosis, risk stratification, treatment planning, prognostication and follow up of any suspected or confirmed KD. KD is a clinical diagnosis and role of echocardiography is to only confirm/exclude cardiac involvement especially coronary arteritis. Thus, treatment of KD should not be withheld for local non-availability of pediatric cardiologist. Simultaneously, the pediatrician should refer to the pediatric cardiologist if pyrexia of unknown origin lasts longer than 7 days.

Objectives of echocardiography in KD are:

- To confirm the diagnosis in case of suspected incomplete KD, though a normal echocardiogram does not exclude the diagnosis.
- To quantify coronary changes in proven KD.
- To look for other cardiac complications like myocarditis and cardiovascular collapse (5%), valvular regurgitation (*e.g.*, mitral regurgitation), pericardial effusion [1,8,9].
- To assess response to therapy by serial echocardiography (regression, persistence or progression of aneurysm, myocarditis and valvular dysfunction).

- To look for myocardial ischemia secondary to coronary involvement, usually seen in giant/large aneurysms.
- Rarely rupture of aneurysm with cardiac tamponade especially in acute phase with rapid enlargement of aneurysm.
- Prognostication and counselling of family.
- Long term follow-up of KD with persistent CAA.

Echocardiographic Changes in KD

The cardiac involvement in KD can be grouped into a) Early changes b) Subacute Changes c) Late changes.

a) *Early changes (1st week of fever)*: Coronary changes are uncommon in the first week. The important clues are myocarditis (prevalence 50-70%), pericarditis, small pericardial effusion and transient mild to moderate mitral regurgitation (23-27%). We recommend use of advanced echo modalities like myocardial performance index and tissue Doppler to document myocarditis in addition to standard parameters like Ejection Fraction (EF) and Fractional Shortening (FS) [14,15].

7% of children with KD may present with cardiovascular collapse (KD shock syndrome). The unique features of KD myocarditis are 1) it presents early 2) precedes coronary arteritis, 3) transient and resolves earlier than other causes of myocarditis as inflammation and myocardial edema subside. In doubtful cases, serum NT pro BNP may be used as a surrogate marker, although it is nonspecific and cut off values yet to be clearly defined [13,16,17].

We reiterate that normal coronaries in the first week do not exclude KD.

b) *Subacute changes (after 1st week of fever)*: The highlight of this phase is detection of coronary involvement and its aftermath.

Some tips and clues for successful echo in KD child are given in **Box III**. The coronary involvement as per z score classification is as follows [1]:

- No involvement: z score always <2
- Dilatation only: 2 to < 2.5

Aneurysms as per size:

- Small CAA: ≥ 2.5 to <5
- Medium CAA: ≥ 5 to <10 and absolute dimension <8mm
- Large /Giant CAA: ≥ 10 or absolute dimension ≥ 8 mm

Aneurysms as per shape: saccular or fusiform

The Heart beyond the Coronaries

Apart from early phase, ECHO during the subacute and long term phases should focus also on:

- Aortic root dilatation and aortopathy
- Cardiac valves: Late onset regurgitation is attributed to fixed damage to valve apparatus by the inflammatory mechanism.

- Myocardial function: Both global and regional wall motion abnormalities (RWMA) perfused by particular coronary territories are to be reported. Abnormal RWMA is a clue of myocardial ischemia and prompts further analysis by CT or direct coronary angiography.

How frequently should one repeat Echo in a child with KD?

- At diagnosis.
- Uncomplicated patients: 1-2 weeks and also 4-6 weeks after treatment. This is because dilatation is unusual beyond 6 weeks. Normal coronaries may be discharged from cardiology care after 12 months but the medical records should permanently mention the diagnosis of KD.
- For significant and evolving coronary abnormalities: At least twice per week till luminal dimensions stabilize and we should look specifically for thrombus. After that at 2 weeks, 4-6 weeks, 3 months and then every 6 -12 months till parameters normalize.
- To detect coronary artery thrombosis it may be reasonable to perform echocardiography for patients with thrombus at diagnosis, expanding large or giant aneurysms twice per week while dimensions are expanding rapidly and at least once weekly in the first 45 days of illness, and then monthly until the third month after illness onset, as failure to escalate thromboprophylaxis is a primary cause of morbidity and mortality.

Long term cardiac assessment in KD

Long-term status is when the patient is stable after the acute illness and the coronary artery luminal dimensions are not increasing or progressing (usually within 15 to 45 days).

- 5% of acute coronary syndrome in US has been attributed to “missed KD in childhood” [18, 19].
- Normal coronaries at initial presentation usually have no long term sequelae.
- Small or moderate aneurysms usually demonstrate normalization of luminal dimensions, infrequently stenosis may happen. Development of late aneurysms especially with coexistent stenosis is also reported especially with repeat KD or suboptimal initial treatment.
- Coronary artery events (thrombosis, stenosis, intervention, MI, death) occurred in 1% of those with an aneurysm Z score <10 and an absolute dimension <8 mm, in 29% of those with a Z score ≥ 10 but an absolute dimension <8 mm, and in 48% of those with both a Z score ≥ 10 and an absolute dimension ≥ 8 mm [20, 21].
- Subclinical functional impairment (fibrofatty changes, necrotic core and calcification) of these coronaries have been observed with advent of intravascular ultrasound (IVUS) and optical coherence tomography (OCT). Interestingly, wall thickening was found more in those coronaries where aneurysms normalized on longitudinal follow up. PET scan shows increased uptake in these areas [22-24]. Clinically these translate to impaired myocardial flow and reduced response to traditional coronary vasodilators like nitroglycerin. This poses a risk to myocardial infarction in KD survivors.

Limitations of echocardiography: Despite its primary position as a diagnostic modality for KD, echocardiography has some limitation:

- Abnormal coronaries are seen in only 20- 25% of KD. Hence, a normal echo does not preclude KD [1].
- Coronary artery aneurysms usually appear after 1st week. It must be repeated in all KD patients after 2 & 6 weeks [1].
- Cardiac sequelae in classical and incomplete KD are same. So, cardiologist has to be more meticulous while imaging suspected atypical KD because diagnosis rests on 2 D echo and laboratory findings.

Role of Other Cardiovascular Imaging Modalities

- *Acute phase:* Echocardiography is the best modality.
- *Medium and long term phase:* As the child grows, transthoracic echocardiography may not be able to visualize especially the distal coronary segments. Apparent normalization of coronary diameters may also be due to intimal calcification and fibro fatty changes. So, use of CT coronary angiography, PET scanning, cardiac MRI and documenting inducible myocardial ischemia (Dobutamine stress echocardiography, stress thallium scan, PET) to assess myocardial function and ischemia in older children, adolescents and adult survivors is recommended. Exercise TMT alone is not sufficient to detect these changes. If any of these are positive, direct coronary angiography as a planner for subsequent angioplasty or bypass surgery is to be done.

Differential Diagnosis (Table 1)

- *Infections:* Bacterial (Streptococcal, Leptospirosis, Rickettsia), Viral (measles, adenovirus, Epstein Barr virus).
- *Toxin related:* Staphylococcal Scalded Skin Syndrome, toxic epidermal necrolysis
- *Inflammatory:* Systemic Juvenile idiopathic arthritis
- *Drug hypersensitivity:* Steven-Johnson syndrome, Drug reaction with eosinophilia and systemic symptoms (DRESS), mercury hypersensitivity.

Gastrointestinal features like paralytic ileus, gall bladder hydrops, greenish diarrhea, jaundice and raised transaminases may mimic other gastrointestinal infections or surgical conditions. Sterile pyuria and CSF pleocytosis can masquerade as urinary tract infection or aseptic meningitis.

A fever that does not appear to respond to antimicrobials should always raise the consideration of alternate pathologies like inflammatory or vasculitic illness like KD.

TREATMENT

Acute Kawasaki Disease

The goal of treatment is to control the acute inflammation and prevent long term coronary sequelae. IVIg and high-dose aspirin are the cornerstones in the management of KD, although the role of high-

dose aspirin in the acute stages is debatable. Treatment should be initiated promptly and must not be delayed awaiting echocardiography, when the clinical features are suggestive of KD.

Single dose of IVIg 2g/kg administered over 12-24 hours should be given within 10 days of illness, preferably in the first 7 days [1]. Timely administration of IVIg reduces the development of CAAs from 15-25% to 3-5%, and the risk of giant aneurysms to 1% [1].

IVIg should be considered even in patients with >10 days of illness with persistent fever, systemic inflammation evidenced by elevated ESR or CRP (>3.0 mg/L), or presence of CAAs. IVIg may not be needed in patients who had resolution of fever with normal inflammatory parameters and normal echocardiography findings [25].

Dose of aspirin used in the acute stages is 30-50 mg/kg/day in 3-4 divided doses, that is continued until the patient is afebrile for 48 hours. The dose of aspirin (ASA) is reduced to 3-5 mg/kg/day and continued for 6-8 weeks and stopped if CAAs are not detected in the 6th week echocardiography. The anti-platelet dose of aspirin is continued in patients who have persistent CAAs until the normalization of coronary artery dimensions. Patients on long-term aspirin need influenza vaccination yearly to reduce the risk of Reye's syndrome.

Multiple studies have come up recently, demonstrating the beneficial use of corticosteroids along with IVIg in children predicted to have an increased risk of CAAs and IVIg resistance [3]. Addition of glucocorticoids (prednisolone) to IVIg has been shown to reduce the risk of CAAs, duration of fever, and inflammation in Japanese children who are at a high risk for resistance to IVIg therapy. A recently published Cochrane database systemic review has even suggested that a long course of steroids along with IVIg should be considered in all children with KD until further evidence are available [26].

Recommended use of steroids in KD: Oral prednisolone (2mg/kg/day) to be initiated with IVIg and gradually tapered over 15 days after normalization of CRP levels.

In IVIg responsive patients, fever usually subsides by 36-48 hours along with decrease in inflammatory parameters. Patients with recurrent KD, defined as a repeat episode of KD after complete resolution of the first episode, should receive standard therapy with IVIg and ASA.

Anticoagulation in Kawasaki disease is indicated in the following situations:

- a. Giant aneurysm, multiple or complex aneurysms, presence of thrombus
- b. Associated stenosis
- c. Peripheral gangrene

It is prudent to initiate with LMW heparin followed by oral warfarin to maintain INR of 2-2.5. However in view of the difficulty of maintaining the target INR in children on oral anticoagulants, one may consider continuing long term thromboprophylaxis with LMW heparin only after proper parental counselling.

For arterial thrombosis/peripheral gangrene- thrombolytic therapy has been tried in addition to anticoagulation.

Treatment of incomplete KD: Incomplete forms should be treated in the same manner as complete KD.

Resistant KD

Children who have persistence or recurrence of fever 36 hours after the end of IVIg infusion are considered to be IVIg resistant [1]. Around 10 to 20% of patients are IVIg resistant [27]. Prolonged fever and unresponsiveness to the first dose of IVIg are significant risk factors for CAAs.

Risk scores for predicting non response to IVIg: Egami [28], Sano [29] and Kobayashi [30] scoring systems are some of the scoring systems that have been shown to predict IVIg resistance.

There is no established consensus on the pharmacologic treatment of refractory KD. Various therapeutic options available -

- *IVIg retreatment:* Many experts recommend retreatment with second dose of IVIg 2g/kg. Rate of refractoriness to the second dose IVIg is around 22-49% [31].
- *Corticosteroids:* Furukawa et al compared the effectiveness of second dose IVIg and IV prednisolone in patients with IVIg resistant KD. They found that incidence of CAA and treatment failure were similar between 2 groups, however, the steroid group had a faster defervescence of fever and improvement in inflammatory markers [32] The AHA recommends that a short duration of high-dose glucocorticoids could be a reasonable treatment option in patients with IVIg resistant KD [1].
- *Infliximab:* Infliximab is a chimeric monoclonal anti TNF α antibody. Dose is 5 mg/kg given intravenously over 2 hours. Studies have not demonstrated superiority of infliximab over others in IVIg-resistant KD in terms of coronary artery outcomes though fever and other constitutional features resolve well. The AHA recommends the use of infliximab as a substitute for a 2nd dose IVIg or steroids in resistant KD [33,34].
- *Cyclosporine:* Cyclosporine inhibits lymphocyte activation by blocking the NFAT-calcineurin pathway that is thought to influence disease susceptibility and development of CAAs in KD [35]. The AHA recommends the use of cyclosporine as a possible third or fourth-line therapy in patients with KD.
- *Plasma exchange:* Used rarely for children who have active inflammation despite multiple doses of IVIg, corticosteroids, and infliximab.
- *Cytotoxic agents:* Cyclophosphamide is used to treat other severe vasculitides, but the risks of cytotoxic agents limits its use.
- *Statins:* Statins, hydroxymethylglutaryl coenzyme A-reductase inhibitors, have been shown to reduce cholesterol levels as well as improve surrogate markers of atherosclerosis and cardiovascular disease. Huang, *et al.* [36] reported that short-term (3 months) statin treatment

(simvastatin, 10 mg/day as a single dose at bed-time) in KD patients complicated with CAL. Chronic vascular inflammation is also significantly improved, as well as endothelial dysfunction, with no adverse effects. However, long-term and randomized control trials are needed before further conclusions can be made.

It has been recently reported that atorvastatin is able to inhibit critical steps (T cell activation and proliferation, production of the pro-inflammatory cytokine TNF- α , and up-regulation of matrix metalloproteinase-9 and an elastolytic protease) known to be important in the development of coronary aneurysms in an animal model of KD, suggesting that statins may have therapeutic benefits in KD patients [37]. Taken together, statins may be beneficial as an adjuvant therapy in KD patients with CAL.

Management of Cardiovascular Sequelae

Coronary artery aneurysm is a potential serious cardiac complication of KD. With giant coronary artery aneurysm, there is increased risk of thrombosis, stenosis, ischemia, infarction and death [38, 39]. The goals of long-term management are to prevent thrombosis and myocardial ischemia while maintaining optimal cardiovascular health [39].

Medical therapy for myocardial protection: β - blockers used are Carvedilol, Metoprolol or Bisoprolol. They decrease the risk of myocardial infarction and death by reducing myocardial oxygen demand. ACE inhibitors also protect against myocardial infarction and death. Statins in addition to their cholesterol lowering action have other pleiotropic effects in inflammation, endothelial dysfunction, oxidative stress, platelet aggregation, coagulation and fibrinolysis, which make them useful in the management of KD [37].

Thromboprophylaxis: Antiplatelet drugs like aspirin are commonly used in KD. In giant aneurysm or large distal aneurysms, a dual antiplatelet treatment with aspirin and Clopidogrel is preferred. Anticoagulation with Warfarin to achieve a target INR of 2-3 is used. LMWH is equally effective to Warfarin, used in young children in whom dosing with warfarin is difficult [1].

Surgical management: is rarely required in pediatric age group. It includes percutaneous coronary intervention or coronary artery bypass grafting [38].

Macrophage activation syndrome (MAS) is a dreaded complication that may rarely occur characterized by persistent fever, pancytopenia, liver dysfunction, hepatosplenomegaly, hyperferritinemia, hypofibrinogenemia, elevated serum lactate dehydrogenase, and hypertriglyceridemia. Prompt treatment with pulse methylprednisolone along with IVIg may result in favorable outcome [1].

KD should be diagnosed and treated by primary care pediatricians. However, involvement of a pediatric rheumatologist is required in some circumstances (**Box IV**)

CONCLUSION

Kawasaki disease is the most common cause of acquired heart disease in children in the developed world. It is being increasingly recognized and treated in various parts of our country. Pediatricians must be aware of the varied manifestations of KD. Early diagnosis and prompt treatment can result in better outcomes.

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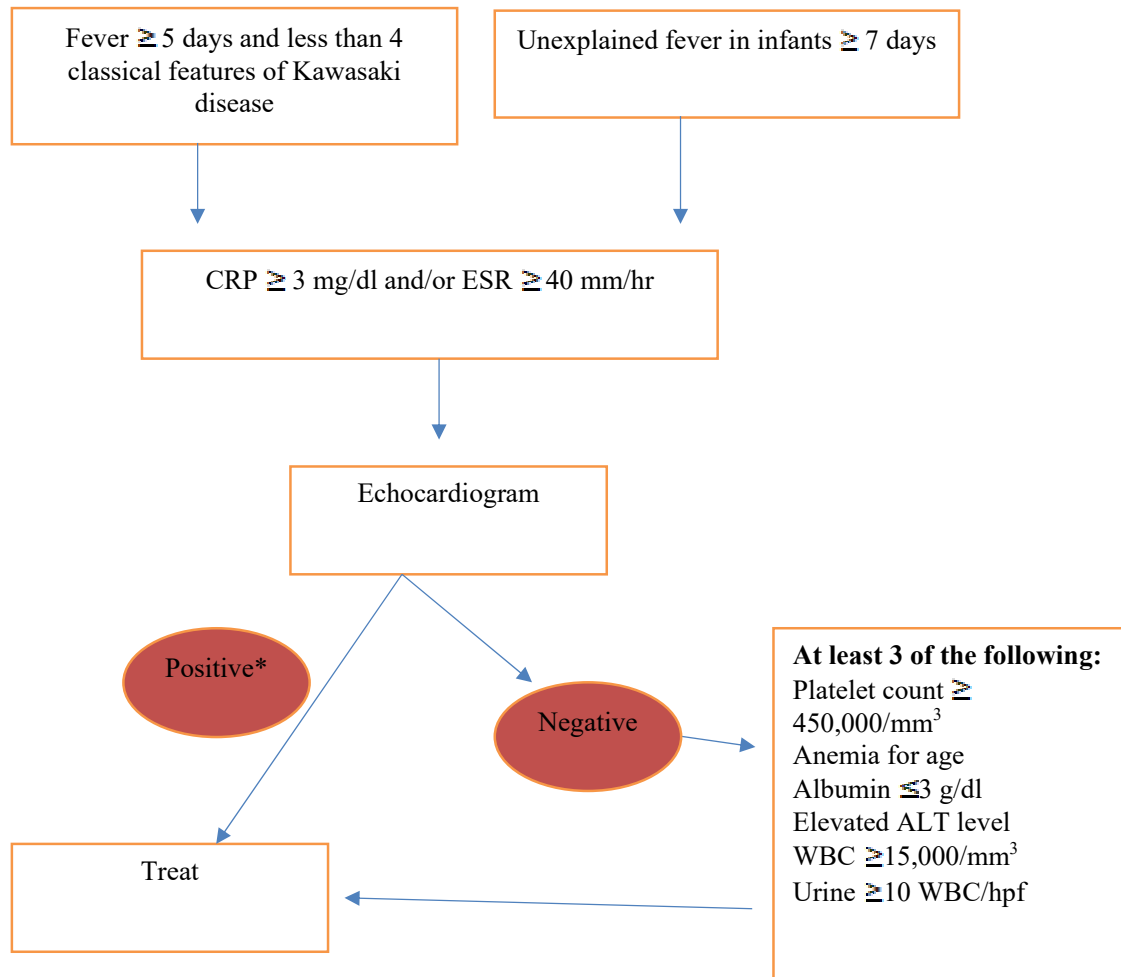
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Table I Differential Diagnoses of KD and differentiating features

	<i>KD</i>	<i>Scarlet fever</i>	<i>Measles</i>	<i>SJS</i>	<i>TSS</i>	<i>SJIA</i>
Strawberry tongue	Present	Present	Absent	Absent	Absent	Absent
Red eyes	Present (non-exudative)	Absent	Exudative conjunctivitis	Absent	Exudative conjunctivitis	Absent
Red lips	Present	Absent	Absent	Absent	Absent	Absent
Response to antibiotics	Does not respond	Brisk response in 48 hours	NC	NC	NC	NC
Peeling	Perineal and periungual	Generalised	NC	NC	Generalised	NR
Follicular tonsillitis	Usually absent	May be present	NC	NC	NC	NC
Edema of extremities	Present	Absent	Absent	Absent	Absent	Absent
Koplik spots	Absent	NC	Present	NC	NC	NC
Oral ulcers	Absent	NC	NC	Present	NC	NC
Hepato-splenomegaly	Absent	Absent	NC	NC	NC	Present
Hypotension /renal impairment	Absent	NR	NC	NC	Present	NC
Leukocyte counts	Elevated	May be elevated	Normal	NC	NC	Elevated
ESR and CRP	Elevated	May be normal	NC	NC	NC	Elevated

NC – Not common in comparison with features in KD, SJS – Stevens Johnson syndrome, TSS – Toxic shock syndrome, SJIA – Systemic juvenile idiopathic arthritis.



(*Positive echocardiogram – refer to the section on echocardiography,

CRP – C reactive protein, ESR – erythrocyte sedimentation rate, ALT – alanine transaminase, WBC – White blood cell count).

Fig 1 Evaluation of suspected Incomplete Kawasaki Disease

Box I Classical Diagnostic Clinical Criteria of Kawasaki Disease by the American Heart Association [ref]
<i>Fever persisting ≥ 5 day</i>
<i>History/presence of ≥ 4 principal features</i> Changes in extremities (pedal edema in acute phase, periungual peeling in sub-acute phase) Polymorphous rash Bilateral bulbar conjunctival injection without exudates Changes in lips and oral cavity Cervical lymphadenopathy (>1.5 cm diameter)
<i>Exclusion of other diseases with similar findings</i>
<i>All manifestations may not be present at the same time in a given child, as they are often transient. However, a thorough history is likely to elicit findings which maybe currently absent</i>

Source: _____

Box II Definitions used in Diagnosis of Kawasaki Disease

Complete KD: Patients with fever of at least 5-day duration with presence/history of 4 or more of the 5 principal clinical findings are labelled as typical or classic KD.

Incomplete KD: Presence of fever with less than 4 out of the 5 principal clinical criteria with compatible laboratory or echocardiography findings suggest incomplete KD. Often seen in infants ≤ 6 months and children >6 years of age, the incomplete clinical picture often delays the diagnosis. Approach to a child with suspected incomplete KD is shown (**Fig. 1**).

Atypical KD: Patients who along with the usual clinical features of KD also have few unusual clinical manifestations like pulmonary involvement, renal impairment are diagnosed to have atypical KD.

The terms atypical KD and incomplete KD are interchangeably used, but recent consensus is to use atypical KD in patients who have unusual clinical features and complications of KD.

Box III Tips for Successful Echocardiography in a Child With Suspected Kawasaki Disease

- Sedation should be used, as these children (especially infantile KD) are extremely irritable and toxic.
- To accurately identify coronary arteries, we recommend use of highest frequency echo transducers (10-12 Hz).
- The main coronary territories to be visualized are: left main coronary artery (LMCA) bifurcating into left anterior descending artery (LAD) and circumflex (Cx), right coronary artery (origin, mid and distal segments).
- The luminal diameter from inner edge to edge is taken in zoomed mode. Please note all measurements are to be compared with the child's body surface area. Weight and especially height are to be considered while interpreting coronary sizes. Z Scores are then calculated as per BSA.

Box IV Situations Where a Pediatric Rheumatologist Consultation May be Needed

- Incomplete/ atypical KD
- KD in infancy
- Presence of CAL at diagnosis
- IVIg resistant KD
- KD shock syndrome
- Suspicion of a macrophage activation syndrome