Document Control

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Version	Date Issued	Status	Comment/ Change/ approval
V1.0	17/07/20	Draft	Sent to Dr Phuoc Duong + Dr Gavin Clearly updated and recommendations to reference SHARE Guidelines
V2.0	23/07/20	Draft	V2.0 – V2.4 Document formatted and Flow chart re-formatted and Dr. A Thirumurugan identified as origonal autor
V2.5	24/07/20	Draft	Document to be sent to Emily Willis (Consultant Rheumatologist at MFT) for comment – received comments back 16/08/2020
V3.0	27/08/20	Draft	Addition of Erythema/induration at site of BCG scar (pg 5) Flow chart Pg 10 updated – removed reference to other diagrams
V4.0	18/09/2020	Draft	GC comments: Defer inmmunisations for 6 mths + steroid therapy as per SHARE Guideline
V5.0	21/09/2020	Draft	Further clarifications from Dr Gavin Cleary + Dr Emily Willis. Re-formating of flow charts and addition of Dr

			Khodaghalian – involved in re-write in May 20. Removal of Dr Caroline Jones
V6.0	09/10/2020	Draft	Feedback from Andrew Riordan. Changes made to wording about bacterial infections and steroid dosing. Advised clarification of Varicella vaccine and Kobayashi score
V7.0	07/12/2020	Draft	r/v by GG: Changes to: timing of ECHO, Kobayashi score deleted, Changes to convalescent phase, information re Varicella vaccine removed
V8.0	08/12/2020	FINAL	GC recommendations: Change name of treatment flow chart on page 13 and changes to the flow chart

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Superseded Documents:
Original document written by Dr Arumugavelu Thirumurugan

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Stakeholders Consulted (list all)

- **Dr Caroline Jones (Consultant Cardiologist, Clinical Lead, Alder Hey NHS Foundation Trust)**
- **Dr Gordon Gladman (Consultant Cardiologist, Cinical Director, NW CHD Network)**

Approved By: NWCHDN RT&FG (Paeds) on behalf of the CHD Board

Date: 27/01/2021

Comments:
21/09/20: Dr Caroline Jones recommended removing her from the contributor list and adding in Dr Khodaghalian who had been involved in re-writing the guideline in May 2020

Kawasaki's Disease – Guidelines for Diagnosis & Management

Date: 21/09/2020:

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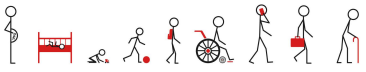


Introduction

- Kawasaki's disease (KD) is an acute systemic inflammatory vasculitic disease of unknown origin involving medium sized arteries.
- Affects predominantly children below the age of five.
- Most concerning complication of KD is coronary artery aneurysm.
- Early recognition and early suppression of inflammation prevents morbidity and mortality related to coronary artery aneurysm.

Epidemiology

- Affects 8.1/100,000 children under the age of 5 years in the UK.
- Second commonest vasculitic illness of childhood after Henoch- Schonlein Purpura.
- More common in boys, with an ethnic bias towards Asian children (highest incidence in Japanese or Japanese immigrants).
- Peak incidence in winter and spring months.
- Approximately 85% of children with KD are younger than 5 years of age, with peak age incidence at 18-24 months.

Diagnosis

- There are no diagnostic tests for KD.
- Diagnosis rests on combination of clinical criteria and laboratory findings.

Diagnostic criteria

A. Fever – duration of 5 days or more, sudden onset and swinging, often up to 40ºC

PLUS

B. Four out of five of the following:

1. Conjunctivitis – bilateral, bulbar, non-suppurative
2. Lymphadenopathy – cervical, often >1.5cm, often unilateral
3. Rash – polymorphous, no vesicles or crusts
4. Changes in lips or oral mucosa – red, cracked lips, 'strawberry' tongue, or diffuse erythema of oropharynx
5. Changes of extremities – initial stage: erythema and oedema of palms and soles. Convalescent stage: peeling of skin from fingertips

Further diagnostic considerations:

- Diagnosis of 'incomplete KD' cases depends on a high level of suspicion in children presenting with some of the KD features and evidence of systemic inflammation (eg elevated ESR, CRP or leukocytosis).
- Diagnosis of KD should not be delayed, and treatment instituted even when the fever is less than 5 days old if:

- Five out of above six diagnostic criteria of KD are present before day 5 of fever
- coronary artery aneurysm or coronary dilatation are present

- evidence of persistent elevation of inflammatory marker with no other explanation in patients where there remains clinical suspicion of KD.
  - Seek expert Cardiologist/Rheumatologist advice in such cases.
- Irritability is an important sign which is nearly always present.

Other Common Clinical Findings

- Arthritis, aseptic meningitis, pneumonitis, uveitis, gastroenteritis, meatitis, dysuria and otitis. Erythema/induration at site of BCG scar is a fairly common clinical finding and a useful sign to look for in uncertain/incomplete cases.

Other Uncommon Clinical Findings

- Hydrops of the gallbladder, gastrointestinal ischaemia, jaundice, cranial nerve palsy, renal involvement, (pyuria, proteinuria, tubular disturbances, tubulointerstitial nephritis and renal failure), petechial rash, shock syndrome, febrile convulsions and encephalopathy or ataxia.

Differential diagnosis

- Streptococcal infection (Scarlet fever and Toxic Shock like Syndrome (TSS)).
- Staphylococcal infection (TSS or Scalded Skin syndrome).
- Viral infection
  - Measles
  - Rubella
  - Roseola infantum
  - EBV infection
  - Influenza A & B
  - Adenovirus
- Mycoplasma Pneumonia infection.
- Stevens-Johnson Syndrome.
- Systemic onset idiopathic juvenile arthritis.
- Haemophagocytic lymphocytic histiocytosis (HLH).
- Diagnostic pitfalls include mistaking:
  - Rash and mucosal changes for an antibiotic reaction
  - Sterile pyuria for partially treated Urinary Tract Infections
  - CSF pleocytosis for viral meningitis

*Kawasaki Diease is **less** likely in the presence of:*

- exudative tonsillitis
- purulent conjunctivitis
- discrete intraoral lesions
- bullous or vesicular rash

- splenomegaly
- generalized lymphadenopathy

It is important to note that evidence of bacterial infection may be present in patients with KD (for example, evidence of recent Streptococcal infection) and clinicians may need to treat infection alongside KD. Children may also present with KD and co-existing viral infection for example (but not limited to) rhinovirus or enterovirus.

Incomplete KD

Diagnosis of incomplete KD requires a high degree of suspicion and should be considered in any child with a fever of ≥ 5 days. Many patients do not have all of the classical clinical features or clinical features may be transient.

In a child ≤ 6 months with fever for ≥ 7 days with evidence of systemic inflammation on laboratory investigations (CRP ≥ 30mg/L or ESR ≥ 40 mm/hour) KD should be considered even in the absence of any other clinical features.

Other possible clinical findings in KD

(Adopted from Newburger et al. Diagnosis, Treatment, and Long-Term Management of Kawasaki Disease: A Statement for Health Professionals From the Committee on Rheumatic Fever, Endocarditis, and Kawasaki Disease, Council on Cardiovascular Disease in the Young, American Heart Association. *Pediatrics* 2004;114(6):1708–33.)

Cardiovascular	Myocarditis, pericarditis, valvular regurgitation, shock
	Coronary artery abnormalities
	Aneurysms of medium-sized non coronary arteries
	Peripheral gangrene
	Aortic root enlargement
Respiratory	Peri-bronchial and interstitial infiltrates on chest x-ray
	Pulmonary nodules
Musculoskeletal	Arthritis, arthralgia
Gastrointestinal	Diarrhoea, vomiting, abdominal pain
	Hepatitis, jaundice
	Gallbladder hydrops
	Pancreatitis
Nervous system	Extreme irritability
	Aseptic meningitis
	Facial nerve palsy
	Sensorineural hearing loss

Genitourinary	Urethritis/meatitis, hydrocele
Other	Desquamating rash in groin
	Retropharyngeal inflammation
	Anterior uveitis on slit lamp examination
	Erythema and induration at BCG site

Clinical course

The course of KD can be described in three clinical phases:

- **Acute phase**: lasts 7 – 14 days, characterized by fever and inflammatory changes.
- **Subacute phase**: typically lasts from approximately day 10 to day 25 after onset of illness. Fever, rash and lymphadenopathy resolve, but irritability, anorexia and conjunctival injection persist. Desquamation of finges and toes appear, may have arthritis and arthralgia or myocardial dysfunction. Thrombocytosis is common.
- **Convalescent phase**: Begins when all clinical signs disappear and continues until acute phase reactants return to normal, usually six to ten weeks after onset.

Complications

- Coronary artery aneurysms (CAA) or coronary artery dilatation usually occurs within 6-8 weeks of onset of the illness. The prevalence of CAA in untreated cases of KD in children is 18 – 23%. Patients who develop CAA are at risk of coronary artery thrombosis, myocardial infarction and sudden death. Angiography may be required to diagnose subsequent regression of CAA.
- Additional rare complications of KD include macrophage activation syndrome (secondary haemophagocytic lymphohistiocytosis characterised by fever, hepatosplenomegaly, lymphadenopathy, rash, pancytopenia), and syndrome of inappropriate antidiuretic hormone secretion resulting in hyponatraemia.

Investigations

Investigations are aimed at identifying alternative diagnoses and assessment of complications.

- FBC, ESR, CRP
- U&Es, LFTs, Amylase
- Consider ferritin if HLH suspected
- Blood culture
- CSF MC&S if signs of meningitis
- Urine dipstick, MC&S
- Throat swab
- ECG

  - ST segment depression
  - T wave inversion
  - Conduction disturbances Eg. Heart block
- Echocardiogram
  - Myocarditis
  - Pericardial effusion
  - Coronary artery aneurysm

- Consider ASOT level, viral titres and mycoplasma serology
- Not all of the inflammatory markers may be abnormal at first presentation, and repeat blood testing should be undertaken if there is diagnostic uncertainty.
- Thrombocytosis occurs towards the end of the second week of the illness and therefore, may not be helpful in the early stages. Acute thrombocytopenia or low/normal platelet count may occur and may be associated with a poorer prognosis.
- LFTs may be deranged. Hypoalbuminaemia is common.
- Sterile pyuria and CSF pleocytosis (predominantly lymphocytes) representing aseptic meningitis also occur.

Timing of Echocardiogram

Echocardiogram should be performed

- At presentation.
- At 10-14 days of disease onset even if the initial echo was normal.
- Echo should be performed weekly in those with aneurysm detected on initial echo and with ongoing active inflammation to monitor aneurysm size progression, or the development of thrombus formation.
- At 6-8 weeks after disease onset.
- Consider need for further echocardiography depending on presence/absence of coronary artery aneurysms (6-12 month review?). No aneurysms ever identified, normal echo findings, discharge 6-12 months. Aneurysms identified consider need for long-term follow up/investigation (see flow chart end guideline).

Treatment

Acute phase

- 2 g/kg of intravenous immunoglobulin (IVIG) over 10-12 hours as a single infusion. Refer to NHSE IVIG commisioning criteria (http://igd.mdsas.com/).
- Patients with IVIG resistance or relapse (ongoing fever and/or persistent inflammation) within 48 hours may be given a second dose of IVIG of 2g/kg. These patients should be discussed with regional paediatric rheumatology service.

- Aspirin 30 – 50 mg/kg/day in four divided dose during the acute phase of illness, and dose reduced to an antiplatelet dose of 3-5 mg/kg/day once fever and inflammation subsides.
- Corticosteroid is recommended in conjunction with IVIG in high risk cases:
  - patients resistant to IVIG treatment with ongoing fever, and /or persistent inflammation or clinical signs greater than 48 hours after receiving IVIG as a single dose of 2 g/kg
  - Patients with features of most severe disease (and therefore the greatest likelihood of developing CAA)
    a. Very young patients (less than 1 year old)
    b. Those with markers of severe inflammation, including persistently raised CRP despite IVIG, liver dysfunction, hypoalbuminaemia and anaemia
    c. Features of haemophagocytic lymphohistiocytosis (HLH)
    d. Features of shock
  - Patients who already have evolving coronary and/or peripheral aneurysm with ongoing inflammation at presentation or extracoronary manifestations such as mitral regurgitation or pericardial effusion.

Dose of Corticosteroids

There is no consensus on the optimal regime of corticosteroid in KD. Based on the European consortium (SHARE guidelines) two treatment regimens are considered reasonable. Treating clinicians will need to determine the corticosteroid regimen for individual patients.

Regime 1: IV methylprednisolone 0.8 mg/kg BD for 5-7 days or until CRP normalizes; then convert to oral prednisolone 2 mg/kg/day (maximum per dose 40 mg)
Oral prednisolone should then be weaned slowly over next 2-3 weeks.

Or

Regime 2: IV methylprednisolone 10-30 mg/kg (maximum of 1 gram/day) once daily for three days; then convert to oral prednisolone 2 mg/kg/day (maximum per dose 40 mg) until day 7 or until CRP normalizes
Oral prednisolone should then be weaned slowly over next 2-3 weeks.

Individual cases should be discussed with paediatric rheumatology if there is

uncertainty about the most appropriate corticosteroid regime.

Biologics

Patients with KD resistant to treatment with IVIg, aspirin and corticosteroids should be assessed for anti TNF or anti IL-1 treatment. . Please discuss with the tertiary Rheumatology team and consider transfering to regional centre.

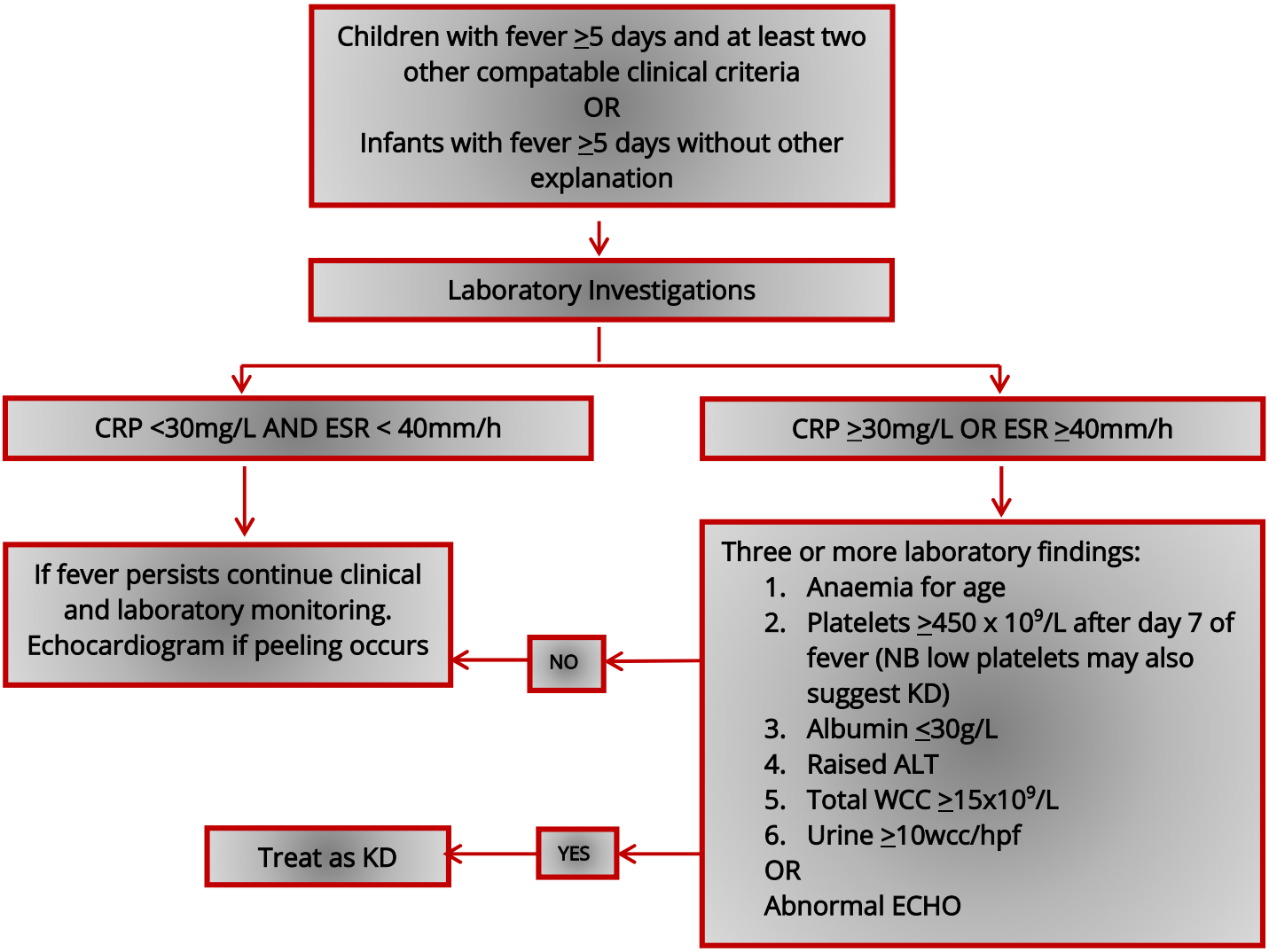
Convalescent phase

- If coronary aneurysm has been identified, antiplatelet therapy, 2-5 mg/kg of aspirin should be continued until the aneurysm resolves.
- In the presence of giant aneurysm (>8 mm internal diameter; for infants Z score > 7 based on Montreal normative data) lifelong aspirin 2-5 mg/kg is recommended. In addition, anticoagulation with warfarin and/or heparin is indicated and should be discussed with regional cardiology unit and regional paediatric haematology unit.
- Aspirin may be stopped at 6-8 weeks if the initial echocardiogram was normal and repeat echo at 6-8 weeks is normal.

PLEASE NOTE

- Treatment can be commenced before 5 days of fever as outlined above in the Diagnosis section, at the point a diagnosis of KD is made. Concomitant treatment of sepsis may also be indicated until sepsis excluded.
- Treatment should also be given if the presentation is greater than 10 days from fever onset if there are signs of persistent inflammation.

Management of suspected incomplete KD



Adopted from McCrindle et al, Diagnosis, treatment, and long-term management of Kawasaki disease: A scientific statement for health professionals from the American Heart Association. Circulation 2017;135(17):927-99, and De Graeff et al. European consensus-based recommendations for the diagnosis and treatment of Kawasaki disease-the SHARE initiative. Rheumatol (Oxford) 2019;58(4):672–82.

Follow-Up

- Review in second week of illness to ensure no symptoms or signs of evolving cardiac failure and to repeat ECG, Echo and review results of serology etc.
- Repeat echocardiogram in out-patient clinic at 2 weeks and then 6-8 weeks.

- If evidence of coronary artery aneurysm at any stage, refer to cardiologist for long term follow up into adult life. See flow chart.

Immunisation

Live vaccines should be delayed for at least 6 months following treatment with IVIg, due to the potential lack of effectiveness following IVIg. Thereafter,all vaccines should be adminstered as per Department of Health schedule. It should be considered whether to delay the MMR vaccine by a longer period of at least 11 months as IVIg suppresses the response to the measles vaccine (4). Children with high risk of exposure to measles do not need to wait for 11 months, but re-vaccination should be considered if serological response is suboptimal.

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Treatment of Kawasaki's Disease

High Risk Features i.e.

1.Severe disease: the very young (<12 mo); those with markers of severe inflammation (including: persistently elevated C reactive protein despite IVIG, liver dysfunction, hypoalbuminaemia and anaemia
2.Features of HLH or shock
3.Already having evolving coronary and/or peripheral aneurysms with ongoing inflammation
4.IF IN DOUBT SEEK EXPERT CARDIOLOGIST/RHEUMATOLOGIST ADVICE

No

- >IVIG 2g/kg as a single infusion over 12 hours
- >Aspirin 30-50 mg/kg/day in four divided doses
- >Perform echocardiography and ECG as soon as possible but do not delay therapy while awaiting echo

Yes

- > IVIG 2g/kg; aspirin (as per non-high risk group)

AND Corticosteroid administered using the following regimes at discretion of treating clincian:

- > Methylprednisolone 0.8 mg/kg BD IV for 5-7 days OR until CRP normalizes; then convert to Prednisolone 2mg/kg/day PO and wean off over next 2-3 weeks

OR

- > Methylprednisolone 10-30 mg/kg for 3 days, followed by Prednisolone 2mg/kg/day PO until day 7 **OR** until CRP normalizes; then wean over next 2-3 weeks

Disease defervescence (fever settled for 48 hours, clinical improvement and falling CRP Reduce Aspirin to 2-5 mg/kg/day and continue for a minimum of 6 weeks

No Disease defervescence within 48 hours, or disease recrudescence

Seek expert Cardiologist/Rheumatologist advice to consider:

- > Corticosteroids as above if not already received.
- > Second dose of IVIG at 2g/kg over 12 hours
- > Infliximab (6 mg/kg) IV 1-2 doses (2 weeks apart if 2 doses)
- > Other immunomodulators
- > Weekly Echo until clinical features and inflammatory markers have settled

If first echo is normal and CRP within normal range at one week after IVIG and no clinical concerns of systemic inflammation. (Otherwise, seek expert advice)

Repeat echocardiography at 2 weeks and 6 weeks (P.S. If first Echo abnormal, seek expert Cardiologist/Rheumatologist advice and follow local guideline re. frequency of Echo; Consider weekly echo

No CAA (coronary artery aneurysm)

Stop aspirin at 6 weeks

Follow up at 6-12 months and discharge if well after that

CAA ≤ 8mm, no stenoses

- >Continue aspirin until aneurysms resolve
- >Repeat echocardiography & ECG at 6 monthly intervals
- >Consider stopping aspirin if aneurysms resolve
- >Consider exercise stress test
- >Lifelong follow up and advice on reduction of cardiovascular risk factors
- >Consider Imaging by MR or CT angiogram

CAA > 8mm; or for infants Z score >7; and/or stenoses

- >Lifelong aspirin 2-5 mg/kg/day
- >Warfarin (with initial full heparinisation to prevent paradoxical thrombosis
- >Consider coronary angiography (catheter, MR or CT; if catheter wait at least 6 months from disease onset), and exercise stress test
- >Repeat echocardiography & ECG at 6 monthly intervals
- >Lifelong follow up and advice on reduction of cardiovascular risk factors

Kawas

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