Scottish Paediatric & Adolescent Rheumatology Network

Guideline for management of Kawasaki disease

NOTE

This guideline is not intended to be construed or to serve as a standard of care. Standards of care are determined based on all clinical data available for an individual case and are subject to change as scientific knowledge and technology advance and patterns of care evolve. Adherence to guideline recommendations will not ensure a successful outcome in every case, nor should they be construed as including all proper methods of care or excluding other acceptable methods of care aimed at the same results. The ultimate judgement must be made by the appropriate healthcare professional(s) responsible for clinical decisions regarding a particular clinical procedure or treatment plan. This judgement should only be arrived at following discussion of the options with the patient, covering the diagnostic and treatment choices available. It is advised, however, that significant departures from the national guideline or any local guidelines derived from it should be fully documented in the patient's case notes at the time the relevant decision is taken.

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Contents:

Guideline checklist

Process	Done	N/A	Date	Initials
Literature search and review of available evidence	□	□		
Review national and international guidance	□	□		
Review previous guidelines/ask other centres if appropriate	□	□		
Consult key stakeholders: Medical staff Specialist Nurses Physiotherapists Pharmacy Patients and Families Other	 □ □ □ □ □ □	 □ □ □ □ □ □		
Collate information and produce draft guideline	□	□		
Ensure guideline contains review date (max 3 years hence)	□	□		
Submit to SPARN steering group for review (see Appendix 1)	□	□		
Decision made by SPARN steering group	□	□		
Guideline re-drafted and submitted to SPARN steering group	□	□		
Final guideline accepted	□	□		
Guideline posted on SPARN website & review date noted	□	□		

Background

Kawasaki disease (KD) is an acute self-limiting systemic vasculitis of unknown cause predominantly affecting young children. It is the second most common vasculitis in childhood (IgA vasculitis being the most common) affecting 8.9/100 000 children under the age of 5 years in the UK(1)(2).

KD affects males more than females with male to female ratio of 1.5:1. The incidence of KD is higher in children of non-white ethnicity, with the highest incidence in patients from north-eastern Asia ancestry, especially from Japan and Korea, and is also higher in more deprived socioeconomic groups(1).

Classic features include fever, rash, conjunctivitis, lymphadenopathy, changes to the lips or oral mucosa, and peripheries, with initial swelling and erythema followed by desquamation in the second week.

KD is associated with systemic vasculitis particularly affecting the coronary arteries, causing coronary artery aneurysms (CAA) in 15–25% of untreated patients. In untreated KD, there is a 2–3% mortality due to coronary vasculitis(3)(4)(5). The British Paediatric Surveillance Unit survey reported 19% of treated patients in the UK with KD developed coronary artery aneurysms increasing to 39% in those aged under 1 year despite intravenous immunoglobulin(6). KD is the leading cause of acquired cardiac disease in developed countries.

Current standard treatment includes intravenous immunoglobulin (IVIG), alongside aspirin. There remains clinical equipoise if corticosteroids as part of primary therapy reduces coronary artery aneurysms in unselected cases, but they are advised to be added to primary treatment for high-risk cases as well as patients with Kawasaki shock syndrome. In IVIG-resistant cases, other medications which may be of benefit include tumour necrosis factor (TNF)-alpha inhibitors (e.g., infliximab), interleukin (IL)-1 inhibitors, (e.g., anakinra), or ciclosporin(7).

There are no internationally agreed guidelines for the management of KD. This guideline provides an approach for managing KD patients in the SPARN network, based on the American Heart Association (AHA) 2017 and the Single Hub and Access Point for Paediatric Rheumatology in Europe (SHARE) recommendations(8)(9).

Scope:

This guideline has been developed as a collaboration between Rheumatology, Infectious Diseases, Cardiology and Haematology for the management of Kawasaki disease throughout Scotland.

Referral pathway

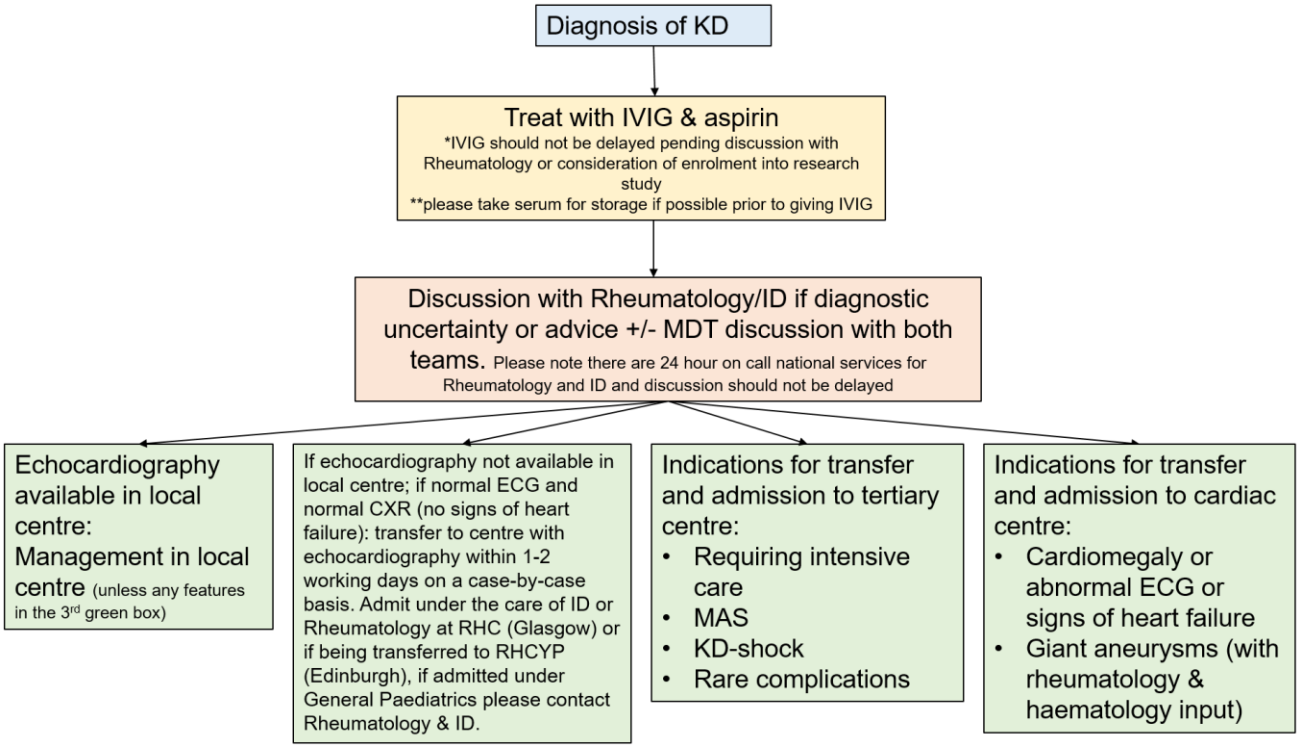

Figure 1: Pathway for referral and transfer to tertiary/cardiac centre for patients with KD

If transfer from local centre to RHC, Glasgow, transfer is arranged by ID or Rheumatology team and not by Cardiology team. These patients will be admitted under the care of ID or Rheumatology who will then contact the cardiology registrar or consultant to discuss arrangements for inpatient cardiology consultation and echocardiogram. If transferred to RHCYP (Edinburgh), they may be admitted under General Paediatrics, but the Rheumatology and ID teams should also be contacted.

If patient is being transferred to the tertiary centre due to MAS, KD-shock or other complications, Rheumatology should be involved.

If there is diagnostic uncertainty or for further advice on investigations or management we would encourage MDT discussion with ID and Rheumatology, which can be facilitated on a Teams call.

Clinical features

KD typically presents in children <5 years of age as an acute, self-limited febrile disease and is characterized by a combination of several characteristic clinical signs, which include polymorphic rash, non-purulent conjunctival injection, oropharyngeal and lip mucositis, tongue papillitis, erythema and oedema of the hands and feet, as well as unilateral cervical lymphadenopathy. Older children can also be affected with KD, and are at increased risk of CAA(10).

Clinical stages(7)

Clinically, the course of untreated KD follows the stages below:

Acute febrile stage (weeks 1-2)

• Fever, irritability, cervical adenitis, conjunctivitis, rash, mucosal erythema, painful erythema of the hands and feet, arthralgia or arthritis, possible myocarditis, and pericarditis.

Subacute stage (weeks 2-4)

• Fever, rash, and lymphadenopathy have resolved; if fever persists there is an increased risk of cardiac complications; persistent irritability, poor appetite, and conjunctival injection; desquamation of extremities begins at this stage.
• The patient may be completely asymptomatic if given intravenous immunoglobulin (IVIG). Periungual desquamation may be the only apparent clinical manifestation.
• Cardiac abnormalities (coronary artery ectasia or aneurysms) may develop during this stage, and rarely, later in patients treated with IVIG.

Convalescent (weeks 4-8)

• All signs of inflammation have receded, and acute phase markers normalise.
• If present, coronary artery ectasia or aneurysms may persist and enlarge.

Chronic stage (variable)

• If present, coronary artery dilation may resolve.
• However, coronary artery aneurysms may persist through adulthood. Such patients are at risk of subsequent coronary artery thrombosis, rupture, and myocardial infarction.

Diagnosis(8)

KD should be considered in any child with a febrile illness with a rash, especially in the context of a fever which persists longer than 4 days.

Complete KD

Complete KD is diagnosed in the presence of fever for 5 days or more (the day of fever onset is taken to be the first day of fever) together with at least 4 of the 5 clinical features:

Table 1: Clinical features of KD

Fever of 5 days or more, plus four of five criteria:
• Conjunctivitis: bilateral, bulbar, conjunctival injection without exudate
• Lymphadenopathy, cervical, often >1.5cm, usually unilateral
• Rash: Maculopapular, diffuse erythroderma or erythema multiforme
• Changes of lips or oral mucosa: red cracked lips, strawberry tongue or diffuse erythema of oropharynx
• Changes to extremities: erythema & oedema of palms and soles in acute phase and periungal desquamation in subacute phase

These features do not need to be present at the same time and may be elicited in the history.

In the presence of ≥4 principal clinical features, the diagnosis of KD can be made earlier before 5 days of fever. Diagnosis or treatment should not be delayed especially if:

- Five out of the six diagnostic criteria are present before day 5 of fever
- CAA (Z score ≥ 2.5) or coronary dilatation (Z score >2 but < 2.5)
- Evidence of persistent inflammation with clinical suspicion of KD with no alternative diagnosis

Incomplete KD

As per the AHA 2017 criteria(8), the diagnosis of incomplete (sometimes referred to as *atypical*) KD should be considered in any infant or child with:

- Fever for 5 days or more with only 2-3 criteria
- Infants under 12 months with fever for 7 or more days and no other explanation

Early echocardiography may confirm coronary vasculitis confirming the diagnosis in these children, although a normal echocardiogram does not exclude KD.

If considering KD in these cases please undertake the investigations in Table 4.

The following algorithm adapted from the American Heart Association guidance is recommended for diagnosis of incomplete KD., as per Figure 2 and Table 2.

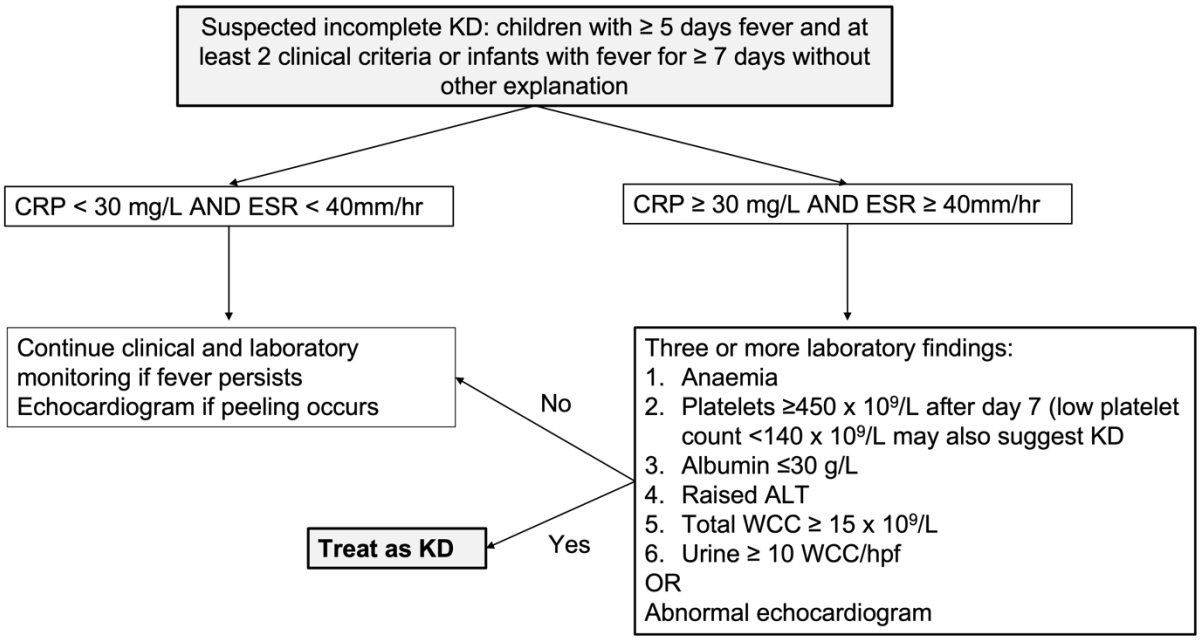

Figure 2: Diagnosis of suspected incomplete KD based on the AHA 2017 and SHARE guidelines(9)(8)

Infants are at higher risk of CAA and poorer outcomes and are more likely to present with incomplete KD. A low threshold for MDT discussion is advised for these patients.

Table 2: Guide for diagnosis of 'Incomplete KD'

Modified AHA criteria for 'Incomplete' KD				
< 1 yr			> 1 yr	
≥ 7 days fever			≥ 5 days fever & ≥ 2 KD criteria	
and				
CRP ≥ 30 or ESR ≥ 40				
And ≥ 3 of the following:				
Anaemia for age	PLT <140 or > 450	Alb < 30	Elevated ALT	WCC > 15
Or				
Abnormal Echo compatible with KD (but not established CAA (criteria given)				

Table 3: Other clinical findings associated with KD (adapted from AHA 2017 guidelines(8)):

Cardiovascular • Myocarditis, pericarditis, valvular regurgitation, shock • Coronary artery abnormalities or peripheral medium-sized non-coronary arteries • Peripheral gangrene • Aortic root enlargement	Gastrointestinal • Diarrhoea, vomiting, abdominal pain • Hepatitis, jaundice • Gallbladder hydrops • Pancreatitis
Respiratory • Peri bronchial and interstitial infiltrates on CXR • Pulmonary nodules	Musculoskeletal • Arthritis, arthralgia (pleocytosis of synovial fluid)
Nervous system • Extreme irritability • Aseptic meningitis (pleocytosis of cerebrospinal fluid) • Facial nerve palsy • Sensorineural hearing loss	Other • Desquamating rash in groin • Retropharyngeal phlegmon • Anterior uveitis by slit lamp examination • Erythema and induration at site of BCG
Genitourinary • Urethritis, hydrocele	

Table 4: Differential diagnoses of KD

Differential Diagnosis(8) (includes infectious and non-infectious)		
Infections: • Sepsis • Staphylococcal and streptococcal toxin-mediated diseases (eg, scarlet fever, acute rheumatic fever, toxic shock syndrome) • Measles • Other viral infections (eg, adenovirus, enterovirus)	Inflammation: • Systemic onset juvenile idiopathic arthritis • Other systemic vasculitides • Macrophage activation syndrome/secondary HLH • PIMS-TS/MIS-C (see separate guideline)	Others: • Drug hypersensitivity reactions, including Stevens Johnson syndrome

With epidemiologic risk factors: • Rocky Mountain spotted fever or other rickettsial infections • Leptospirosis		

Caveats to be aware of when considering the diagnosis:

- Strict adherence to the diagnostic criteria should be avoided; especially in infants, who may present without few additional features and are at risk of CAA development.
- The diagnosis should be considered in infants with prolonged fever and raised inflammatory markers.
- Although not part of the diagnostic criteria, irritability and erythema/induration of the BCG scar should raise suspicion of the diagnosis.
- The clinical features may not all be present at the same time and are significant if are present at any time during the illness.
- KD can be triggered by infection; a positive viral/bacterial result does not exclude the diagnosis and should not delay treatment with IVIG and aspirin.
- Patients with KD may also be treated with antibiotics if there is concern about infection.
- Sterile pyuria is classic feature of KD and does not indicate UTI in this context

Initial investigations

The diagnosis of KD is unlikely in the absence of significant systemic inflammation. Certain laboratory parameters may help stratify the severity of KD and thus help inform therapeutic decisions.

Table 5: First line investigations(9) [* to be considered on an individual basis or if there is suspicion of hyperinflammation]

Table below shows features which may be seen in KD; not all these abnormalities are expected to be present.

FBC & film	Anaemia, leucocytosis; thrombocytosis in the second week, usually normalises by week 4-6. Initial thrombocytopenia or low/normal platelet count may be associated with poorer outcomes
Urea & electrolytes	Hyponatraemia
Liver function tests	Transaminitis. Hyperbilirubinaemia. Hypoalbuminaemia
CRP	Significantly raised during the acute stage. CRP levels normalise quicker than other biomarkers. CRP can be used to guide management decisions.
ESR	Raised. ESR is only useful prior to IVIG therapy and should not be used to determine response, since ESR may be elevated post-IVIG as a consequence of binding to red blood cells.
Ferritin*	Especially if concern about macrophage activation syndrome
Coagulation profile (including fibrinogen)	As clinically indicated or if concern about macrophage activation syndrome
Troponin, NT-proBNP*	NT-proBNP may indicate myocardial involvement and should be considered if myocardial dysfunction or cardiogenic shock
D dimers*	
LDH*	
Serum for storage*	Consider storing prior to IVIG Additional serum bottle can be sent to the local immunology lab along with an email to the immunology lab team (Immunology.Labs@ggc.scot.nhs.uk if local immunology lab is at RHC, Glasgow)
Infection screen: - Blood cultures - Urine culture - Throat swabs (viral & bacterial) - Stool virology if relevant	- Mild sterile pyuria of urethral origin in 50% of patients - Some patients with KD may have aseptic meningitis

- Consider lumbar puncture	- Treatment should not be delayed pending microbiology/virology results

Echocardiography:

- During the acute stage, a baseline echocardiogram is important to rule out coronary artery abnormalities and identify evidence of myocarditis, valvulitis, or pericardial effusion, **but should not delay initial treatment (aspirin, IVIG)**
- The initial echocardiogram should be undertaken as close as possible to the time of diagnosis and no later than 2 weeks after the onset of fever
- Indications for urgent early echocardiogram during the first week include clinical signs suggestive of heart failure, cardiomegaly on chest X-ray and ECG abnormalities
- If there are no abnormalities on initial echocardiogram, the echocardiogram should be repeated 2 weeks following administration of IVIG (if possible) and 6-8 weeks after diagnosis

Organising Cardiology follow up and Echocardiograms:

- 2 week echocardiogram: discuss with the on call Cardiology registrar or consultant;
- 6-8 week echocardiogram (RHC): referring team to email the referral letter to the on call Cardiology Consultant to organise 6-8 week follow-up Cardiology clinic review and Echocardiogram;
- DGH follow-up: email the referral to the on call Cardiology consultant to organise follow-up in outreach Cardiology clinic or in their own clinic in RHC

For RHCYP (Edinburgh): contact the on call Cardiologist at RHC Glasgow and cardiology service administrator in Edinburgh on nathan.pedersen@nhslothian.scot.nhs.uk

ECG: To evaluate for pathological Q waves, conduction and repolarisation (ST/T) abnormalities.

Other imaging to consider:

- Chest x-ray to evaluate cardio-thoracic ratio or investigate intercurrent infection
- Abdominal XR or abdominal ultrasound
- Galbladder ultrasonography: May be necessary if liver or gallbladder dysfunction suspected. May detect gallbladder hydrops in some patients.
- Ultrasonography of the testes: Epididymitis may be observed in boys with KD. In case of testicular involvement, a scrotal ultrasound should be considered in case of testicular torsion.

Treatment

- Treatment of KD should started as soon as Kawasaki disease is diagnosed and should not be delayed by speciality discussion, echocardiogram or recruitment to a research study.
- Initial treatment involves IVIG and aspirin unless there are high risk features and in these children corticosteroid should be included as part of initial management.
- High risk features are listed in figure 3 this includes infants < 12 months of age, evidence of severe inflammation, evidence of HLH or shock, evolving coronary or peripheral aneurysms or those who have already failed IVIG

Treatment pathway

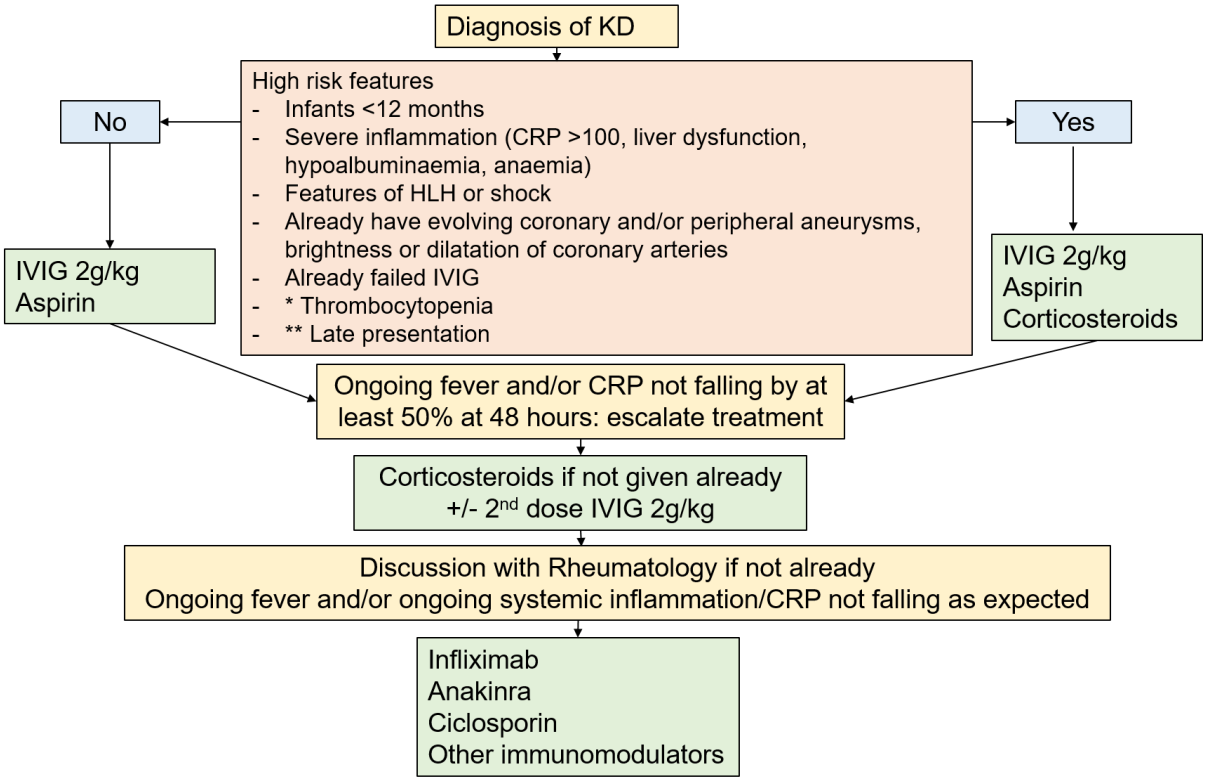

Figure 3: suggested treatment pathway for KD

* consider corticosteroids if thrombocytopenia especially if associated with other high risk features
** consider corticosteroids if late presentation especially if other high risk features

Antibiotics:

- It may be appropriate if the diagnosis is not clear to treat children with empirical antibiotics, until culture results are available. Seek ID advice if required.

IVIG:

Initial management includes IVIG 2g/kg for all children with KD(11)

- KD is a red indication for IVIG and therefore approval is not required prospectively
- Infusion rates should be as per local protocol depending of brand of IVIG used
- If fever recurs/ or does not settle by 48 hours or CRP at 48 hours remains >50% baseline, treatment should be escalated, adding in corticosteroids +/- a second dose of IVIG at the discretion of the clinician(9)
- If there is IVIG resistance a second dose of IVIG may not be of benefit
- IVIG resistance is associated with increased risk of coronary artery aneurysm(12)

Aspirin:

Appropriate aspirin dosing regimes are either:

- High dose initially ((30-50mg/kg/day usually 10mg/kg QDS) and continued until the child has been afebrile for 48 hours and CRP is falling then switched onto low anti-platelet dose (3-5mg/kg OD max dose 75mg OD))

OR

- Low dose aspirin (3-5mg/kg/day max 75mg OD) which can be started from diagnosis at the discretion of the clinician

- There is currently insufficient evidence to recommend one dosing approach over the other.
- A retrospective cohort showed no advantage of high dose aspirin over low dose(13)(14), although SHARE and AHA guidelines still recommend high dose initially(9)(8)
- Aspirin can be stopped if the week 6-8 echocardiogram is normal
- Non-steroidal anti-inflammatory drugs (including ibuprofen) should be avoided due to interference with antiplatelet effect of aspirin
- In patients with coronary artery aneurysms(CAA), long term aspirin is recommended, and ongoing life-long aspiring administration should be considered(9). In patients with regressed CAA long term/lifelong aspirin should still be considered given the increased risk of coronary artery events in this population

Corticosteroids:

- Initial management with corticosteroids along with IVIG may reduce inflammation and risk of CAA(15)(16). Conflicting results may be explained by differing corticosteroid regimens used.
- Current practice pending results of clinical trials is to treat patients at higher risk of CAA with first-line corticosteroids along with IVIG (see figure 3)
- Patients with early vessel changes, such as brightness or dilatation, or extra-coronary manifestations, such as pericardial effusion or mitral regurgitation,

may be at increased risk of CAA and therefore may benefit from corticosteroids(10)

- The Kobayashi score has been validated in the Japanese population to predict those at higher risk of IVIG resistance and CAA but it is not validated in other populations(17)(18)(19) and is not used clinically in the UK
- There is accumulating evidence that concomitant corticosteroids, alongside IVIG, decreases progression of CAA if present at diagnosis, although results have been mixed to date(20)(21)

Appropriate corticosteroid regimens include:

- IV methylprednisolone 10-30mg/kg (max 1 gram/day) once a day for 3 days then oral prednisolone at 2mg/kg once a day until day 7 or until CRP normalises and wean over 2-3 weeks; OR
- Oral prednisolone 2mg/kg/day (or IV methylprednisolone equivalent) until day 7 or until CRP normalises; then wean over 2-3 weeks (a suggested regimen is 1mg/kg for 7 days, then 0.5mg/kg for 7 days then stop)
- Gastroprotection with omeprazole is usually prescribed alongside corticosteroids

Treatment of refractory KD

Refractory KD diagnosis:

- Re-assess 48 hours after initial IVIG or sooner if unwell/required; if remains febrile or if the CRP does not fall by at least 50% by 48 hours, this suggests refractory KD and treatment should be escalated
- Rheumatology should be involved in the care of the patient, if not already involved

Treatment:

- At the clinician's discretion a second dose of IVIG 2g/kg can be given
- If corticosteroids have not been part of initial management, then these should be started at the doses above
- TNF-α blockade with infliximab 10mg/kg single dose can be used if there is inadequate response to IVIG and corticosteroids
- Evidence has shown that anti-TNFs have a significant effect on reducing inflammation, fever and potential length of hospital stay(22). Emerging evidence has suggested an advantage of dosing of 10mg/kg over 5mg/kg infliximab(23)
- There is some evidence that infliximab may promote CAA healing and therefore adjuvant treatment with infliximab if CAA is present can be considered(24)(23)
- Further medications dependent on a case-by-case basis and discussion at MDT should be considered; these include ciclosporin, anakinra, or other immunomodulators
- Anakinra has been shown to have some efficacy in fever resolution, reduction of systemic inflammation and improvement in coronary artery dilatation in a small phase II study(25) and should be considered alongside high dose IV methylprednisolone in children with KD and MAS
- A phase III trial in Japan has shown benefit of ciclosporin alongside IVIG for patients predicted to be IVIG resistant(26)

Monitoring of disease activity:

- The therapeutic target for KD is 'zero fever, zero CRP'(27)
- The child should have regular observations, especially to identify if ongoing or recurrence of fever
- The CRP should be monitored at 48 hours; if CRP not < 50% of baseline this suggests inadequate response and escalation of treatment is indicated
- A full set of bloods should also be checked at 48 hours, with a CRP, FBC, U+Es, LFTs, bone profile (note ESR will not be helpful following IVIG).
- Further blood tests beyond this should be considered at the discretion of the treating clinician. CRP typically returns to normal values around 5 days after starting treatment in patients who respond well to treatment. Consider treatment escalation for patients with evidence of persisting inflammatory response.

Kawasaki disease shock syndrome:

- Kawasaki disease shock syndrome is a recognised complication of Kawasaki disease characterised by haemodynamic compromise and hypotension thought to affect around 7% patients with Kawasaki disease(28)
- It is associated with severe inflammation, a higher incidence of coronary artery aneurysms, left ventricular dysfunction and IVIG resistance(28)(29)(30)
- Fluid resuscitation, vasoactive drugs and intensive care support maybe required
- Children with Kawasaki disease shock syndrome should routinely be treated with corticosteroids in addition to IVIG and aspirin
- KD/KD-shock can present with a similar phenotype as PIMS-TS/MIS-C

Kawasaki disease with secondary haemophagocytic lymphohistiocytosis (HLH)/macrophage activation syndrome (MAS): (please see separate SPARN guideline for early recognition of MAS)

- Secondary HLH or macrophage activation syndrome (MAS) is a recognised complication of KD
- This hyperinflammatory complication can be recognised with persistence of fever, hyperferritinaemia, cytopenias, including thrombocytopenia, transaminitis, hepatosplenomegaly
- KD complicated by MAS is associated with a high incidence of coronary artery aneurysm and also mortality(31)
- If there is clinical concern about MAS the following blood tests should be carried out: FBC, CRP, U+E, LFT, ESR, LDH, coagulation including

fibrinogen, triglycerides and ferritin (this should be processed urgently which may require discussion with the out-of-hours laboratory staff)

- Early recognition of this complication is important and urgent discussion with Rheumatology is recommended with a low threshold for admission to intensive care
-

Echocardiograms in first 8 weeks after diagnosis of KD

- Baseline **echocardiogram,** as soon as practical within 2 weeks from the onset of fever, is needed to assess anatomy, function, presence of effusion and valvar regurgitation. Focus on all coronary arteries- left main, left anterior descending, circumflex, right coronary and the posterior descending artery and assess for aneurysm/dilatation/stenosis. Measurements should be made from inner edge to inner edge and compared with standardised Z-scores for body surface area(32). *[Please see this reference for further details: Dallaire F, Dahdah N. New Equations and a Critical Appraisal of Coronary Artery Z Scores in Healthy Children. Journal of the American Society of Echocardiography. 2011 Jan 1;24(1):60–74]*
- **DO NOT delay starting treatment whilst awaiting echocardiogram.** In cases of incomplete KD an echocardiogram may support the diagnosis and treatment should be initiated if not already.

Table 6: Definition of coronary dilatation, small, medium and giant CAA as per AHA 2017 recommendations

Coronary artery change as per AHA guidelines(8)	**Z score (internal coronary artery diameter Z score)**
Non-aneurysmal coronary dilatation	> 2 to <2.5
Small CAA	≥ 2.5 to <5
Medium CAA	≥ 5 to <10
Giant CAA	≥ 10 or absolute internal diameter ≥ 8mm

- **ECG** looking for: inflammatory changes (myocardial or pericardial involvement) such as prolonged PR interval, other conduction defects; repolarisation abnormalities or signs of ischaemia – ST/T changes. Severe KD can be associated with tachyarrhythmias. As a minimum an ECG is required at baseline for later comparison.
- **Patients with ongoing active inflammation** (increasing or persistently elevated CRP and/or persisting signs and symptoms), **ECG and echo** should

be performed as advised by the Paediatric Cardiologist on a case-by-case basis.

- Those with CAA or ectasia (dilatation) detected on initial echo, should be reviewed by the Paediatric Cardiologist, or the Paediatrician with Expertise in Cardiology (PEC), and follow-up echo should then be performed as advised by the Paediatric Cardiologist on a case-by-case basis.

Discharge plan, vaccinations

Children with KD may be considered for discharge when they are afebrile and well for at least 48 hours and inflammatory markers are improving. Parents should be counselled about the need to re-present if fever recurs.

Reye syndrome is reported in children who receive salicylates, usually with a varicella or influenza infection, and has also been reported in patients taking high-dose aspirin for a prolonged period after KD. Low-dose therapy used for antiplatelet effect has not been associated with the development of Reye syndrome. In a patient who presents with influenza and KD, administration of high-dose IVIG without aspirin and use of alternative antipyretic drugs (i.e. paracetamol) as needed should be considered. An alternative antiplatelet agent may be considered for a minimum of 2 weeks(8).

Concomitant use of ibuprofen antagonises the irreversible platelet inhibition induced by aspirin. Ibuprofen should be avoided in children with coronary artery aneurysms taking aspirin for its antiplatelet effects(8).

Immunisation with all live vaccines should be deferred for at least 3 months following an episode of KD treated with IVIG, mainly due to the potential lack of effectiveness following IVIG. Thereafter, all vaccines should be administered as recommended by national schedules(9).

Measles, mumps, and varicella immunizations should be deferred for 3 months after receiving high dose IVIG. However, children in whom risk of exposure to measles is high may receive vaccination earlier and then be re-immunised at least 3 months after IVIG administration if they have an inadequate serological response(8).

If the child is to remain on long term aspirin due to CAA, varicella immunisation should be considered owing to risk of Reye syndrome with varicella infection.

All children ≥6 months should receive a seasonal influenza vaccine, as should their family members. Only inactivated vaccine should be administered to children on aspirin therapy. Those who are taking chronic aspirin therapy should receive an annual inactivated influenza vaccine(8).

Patients who have had Kawasaki disease should be reminded that this is part of their medical history. General counselling around healthy lifestyle and activity should be promoted. Blood pressure, fasting lipid profile and body mass index should be monitored along with dietary advice, and advice to avoid smoking. Precautions with physical activity may be required for individual patients, for example if on anticoagulation therapy or with myocardial ischaemia or arrhythmias, as per cardiology advice(7)(33).

Patients and families may benefit from psychological support, especially during teenage and young adult life.

For patients who require transition to adult cardiology service, the acquired cardiac disease transition pathway should be followed, as per cardiology.

Anticoagulation

All patients with KD and documented coronary artery changes **must be referred to Cardiology or Paediatrician with Expertise in Cardiology (PEC)**. Patients with giant aneurysms should be managed as an inpatient until anticoagulation is established.

If Z scores are ≥ 5, anti-coagulation should be considered in consultation with Haematology and Cardiology.

For medium-sized aneurysms (Z score ≥5 -10) consider dual antiplatelet therapy e.g. clopidogrel (0.2-1.0mg/kg/day) plus aspirin 5 mg/kg OD.

For giant aneurysms (internal diameter ≥8mm or Z score ≥10) anticoagulation should be started with low molecular weight heparin, with a target anti-factor Xa of 0.5-1.0. In some children warfarin in addition to aspirin can be considered after initial heparinisation as per cardiology and haematology advice.

In the case of giant aneurysms, the haematology team will manage monitoring of anticoagulation, for patients throughout Scotland.

Longer term cardiac management & follow-up

Further follow up after 8 weeks should be guided by the extent of coronary artery involvement.

No aneurysms

If the initial echocardiogram is normal, with no evidence of ectasia or aneurysm, repeat the ECG and echocardiogram at 2 weeks and 6-8 weeks after diagnosis.

If no coronary artery aneurysms:

- Stop aspirin at 6-8 weeks
- Can discharge at this point if well

Coronary artery ectasia (dilatation) and coronary artery aneurysms (CAA) without stenosis/thrombus

- Coronary ectasia (Z score >2): a follow-up appointment at 6-12 months should be offered
- Patients with CAA should have life-long cardiology follow-up
- Continue aspirin at least until aneurysms/dilatation resolves, consider life-long aspirin.
- Frequency of follow-up/CT/MRI and stress imaging as advised by Paediatric Cardiologist.

Giant CAA aneurysms > 8mm or Z score ≥ 10,0 +/- stenosis +/- thrombus

- These patients are at high risk for cardiovascular events and require lifelong cardiology follow-up.
- Frequency of follow-up and additional imaging (CT/MRI/stress imaging) at the discretion of the Paediatric Cardiologist
- Continue aspirin 5mg/kg/day (max 75mg) indefinitely
- Add warfarin or LMWH until resolution of giant aneurysm

Appendix: Drug doses

Table 7 recommended drug doses used in KD [*consider in KD complicated by MAS]

Medication	Dose
IVIG	2 grams/kg This can be repeated if no resolution of fever within 48 hours
Aspirin	30-50mg/kg/day until afebrile, divided into 4 doses Followed by 3-5mg/kg/day aspirin until at least 6 weeks OR 3-5mg/kg/day from diagnosis Continuation thereafter depends on coronary artery status (as per cardiology)
Corticosteroids	Should be given to patients with severe KD Suggested regimens (decide on case-by-base basis): • Methylprednisolone 0.8mg/kg BD IV for 5-7 days or until CRP normalises; then convert to oral prednisolone 2mg/kg/day, then wean over next 2-3 weeks • Methylprednisolone 10-30mg OD (max 1 gram/day) for 3 days then oral prednisolone 2mg/kg/day until day 7 or CRP normalises, then wean over 2-3 weeks • Prednisolone 2mg/kg/day until CRP normalises then wean over 2-3 weeks
Infliximab* (TNF-α blockade)	10mg/kg. Single dose for refractory KD. In the case of large or giant aneurysms a longer course can be considered to promote healing
Ciclosporin*	2-3mg/kg BD orally with trough immediately before 4th dose and aim for levels of 100-150
Anakinra*	2-8mg/kg/day subcutaneously until clinical resolution and normalisation of CRP

Patient/parent information sheets:

Lauren Currie Foundation

11-kawasaki-disease-factsheet-2020.pdf (thelaurencurrietwilightfoundation.org)

Societii UK Kawasaki Disease Foundation

Societi - The UK Kawasaki Disease Foundation

Kawasaki disease-NHS

www.nhs.uk/conditions/kawasaki-disease/

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