Guidance on Kawasaki disease diagnosis, management, follow-up and referral

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Signature of ratifying Group Chair	John Pappachan-Chair of Children's Services Review Group
Author(s) and title	Dr Norah Yap, Paediatric Cardiology SpR Dr Tara Bharucha, Consultant Paediatric Cardiologist Dr Alan Magee, Consultant Paediatric Cardiologist Dr Nick Hayes, Consultant Paediatric Cardiologist Dr Sanjay Patel, Consultant Paediatric Infectious Disease Dr Alice Leahy, Consultant Paediatric Rheumatology Dr Roy Sievers, Consultant Paediatrician
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No

Contents

Flowchart

Kawasaki Disease Algorithm
Guidance on diagnosis, management, follow-up and referral

Features suggestive of Kawasaki disease? [2]

If no, consider differential diagnosis [3]

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1st line investigations [4.1]

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Start IV ceftriaxone 80mg/kg IV

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If remains febrile by 24-48 hours, and no alternative diagnosis reached.
If reaching day 10 of fever, may need to consider IVIG treatment more urgently

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Classical features of Kawasaki disease

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- Start IVIG 2g/kg and high dose aspirin
- Recommend discussion with UHS ID/ rheumatology team if risk factors for IVIG resistance- haemodynamic instability, age <1 year, deranged LFTs (ALT >100), Platelets <100

Timing for first echocardiogram [6.1]

- Classical feature of Kawasaki disease and responded to IVIG: Non-urgent echo i.e 2 weeks after onset of illness
- Risk factors for IVIG resistance (haemodynamic instability, age <1 year, deranged LFTs (ALT >100), Platelets <100) / features of incomplete Kawasaki disease: Urgent echo but **DO NOT delay treatment** whilst waiting for an echocardiogram

Incomplete Kawasaki disease

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- If no response/ partial response to IVIG, recommend discussion with UHS ID/ rheumatology teams
- Perform 2nd line investigations [4.2]
- Recommend discussion with UHS ID/rheumatology team regarding differentials and need for ***urgent echocardiogram**

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Echocardiography Timeline and Follow-Up for Kawasaki Disease

Normal Echo [8.1.1]

- Repeat echocardiography and ECG at 6 weeks from fever onset
- If remains normal, stop maintenance dose aspirin
- Follow up by PEC or UHS cardiology clinic

- Repeat echo in 1 year
- If remains normal, discharge from follow-up with healthy lifestyle advice

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Abnormal Echo at diagnosis

- Coronary artery dilatation or aneurysm but no stenosis [8.1.2]

- Continue on maintenance dose aspirin until dilatation/aneurysms resolve
- Repeat echocardiography and ECG at 2 weeks and 6 weeks
- Subsequent echocardiography at minimum 6 monthly intervals
- Consider imaging of the coronary arteries by CT/MRI or angiogram
- Other investigations to consider: Stress Imaging, CT calcium score (during late follow up)
- ETT if clinically indicated i.e symptoms of chest pain/ breathlessness
- Healthy lifestyle advice to minimise cardiovascular risk factors
- Lifelong follow-up

- Giant coronary artery aneurysm ≥8mm or infant Z score >7 [8.1.3]

- Lifelong maintenance dose aspirin
- Add in Warfarin (with initial full heparinisation to prevent thrombosis). Target INR 2-2.5
- Weekly echo initially or at the discretion of consultant paediatric cardiologist
- Subsequent follow-up at the discretion of consultant paediatric cardiologist
- Consider further imaging of the coronary artery by CT/MRI or angiogram
- Other investigations to consider: Stress imaging, CT calcium score
- Avoid high intensity exercise
- Healthy lifestyle advice to minimise cardiovascular risk factors
- Lifelong follow-up

1 1.1 Introduction

This guideline applies to all paediatric patients (under 16 years).

Kawasaki disease is the second most common systemic vasculitis in childhood and is the commonest cause of acquired heart disease in the UK through a predilection for the coronary arteries. Kawasaki disease is:-

- most commonly seen in children from 6 months to 5 years (peak 8 to 24 months)
- more common in winter and spring,
- more common in boys
- more common in East Asian populations.

1.2 Scope

This guidance has been developed to aid the diagnosis and management of children with possible Kawasaki disease in Wessex using available skills and network links.

1.3 Purpose

Early recognition and appropriate treatment may reduce the risk of coronary involvement and subsequent complications from up to 25% to nearer 3%. Diagnosis is reliant on clinical features and may be difficult as there is no diagnostic test and there may be considerable overlap with other conditions at initial presentation (see section 3). Some children are at risk of IVIG resistance and rapid evolution of coronary artery aneurysms (see section 6). Therefore, discussion with Southampton ID or rheumatology teams is recommended if risk factors are present for IVIG resistance or the patient is unresponsive to the 1st dose of intravenous immunoglobulin (IVIG), to decide if adjuvant immunosuppressive therapy, such as steroids, is required in addition to IVIG.

2 Definition

Diagnosis of Kawasaki disease

Clinical feature	usual characteristics/notes
Fever for more than 5 days…	Sudden onset Swinging Above 40 degrees Poor response to antipyretics and/or antibiotics
1. Cervical Lymphadenopathy	Non-tender Non-supperative Solitary Often > 1.5 cm diameter
2. Oral changes	Cracked lips Erythema of lips Strawberry tongue
3. Rash	Starts in first few days Lasts around 1 week Often more marked in groin area which may peel Many forms but not usually vesicular or crusting
4. Conjunctival injection	Bilateral Non-purulent Limbic sparing
5. Extremity changes	Oedema Erythema Periungual desquamation

Other clinical features and complications
Other features may support the diagnosis and relate to the complications of the condition. For example:

Non-cardiac complications and associated clinical features	
Aseptic meningitis	**Irritability is common**
Gallbladder hydrops (10%)	Abdominal mass, pain, jaundice, or deranged LFT
Diarrhoea (20%)	
Hepatitis	
Pancreatitis	
Myositis Arthralgia and arthritis (30%)	Muscle and joint pains (week 2 to 8)
Urethritis or Meatitis	Dysuria and sterile pyuria
Aneurysmal arteries	May occur in axilla or groin
Pro-inflammatory state	BCG scar induration (if present)

If patients do not meet the classic criteria they may either have atypical/incomplete Kawasaki disease or an alternative diagnosis (see section 3). Atypical Kawasaki disease is more common in infants and in children over 7 years[1] and these groups have a high risk of coronary complications if not treated. In up to 90% the absent cardinal feature is cervical lymphadenopathy, and in up to 50% the rash may not be present. It is appropriate to treat children with atypical Kawasaki disease. In such children the presence of additional clinical features (see section 2.), supportive lab investigations (see section 4) and findings on early echocardiography (see section 6) are aids to making a diagnosis. Such cases should be discussed with the Southampton ID or rheumatology teams.

It is suggested that all children presenting with suspected Kawasaki disease are started on ceftriaxone 80mg/kg on admission. Resolution of fever following commencement of IV antibiotics makes a diagnosis of KD extremely unlikely.

Note: a diagnosis of Kawasaki disease can be made and treatment started if there is fever of *less than* five days accompanied by all of the five features AND persistent elevation of inflammatory markers without alternative cause. Treatment of such cases at less than 5 days of fever should be discussed with the Southampton ID or rheumatology teams.

3 Differential diagnosis

Many childhood illnesses may be confused with Kawasaki disease on initial presentation. These include: -

- Gp A streptococcal infection +/- toxin mediated disease
- Staphylococcus aureus infection +/- toxin medicated disease
- Viral infections – Adenovirus**,** enterovirus, measles, EBV
- Stevens-Johnson syndrome
- Systemic juvenile idiopathic arthritis.

However, with careful attention to the evolution of the clinical picture, results of investigations, and response to 24 - 48 of antibiotic therapy the diagnosis is likely to be

clarified. In order to treat Kawasaki disease effectively it is important to reach a diagnosis and commence treatment before the 10th day of the illness.

4 Investigations

4.1 First line investigations during acute illness

There are no diagnostic tests for Kawasaki disease and the diagnosis relies on clinical criteria, supported by evidence of inflammation, whilst ruling out other differential diagnoses. There are some characteristic laboratory findings in Kawasaki disease which may help in atypical cases. Other investigations may be helpful in clarifying an alternative diagnosis where there is uncertainty.

(4.1) In all patients where Kawasaki disease is considered likely:

Investigation		expected findings	additional notes
FBC and film	Hb	normal in week 1	
		reduced from week 2	normochromic normocytic
	WCC	elevated	neutrophilia with band forms in week 1
			lymphocytosis by week 2
	Platelets	normal in week 1	
		rapid rise from day 10	approx. range 600 - 1000
CRP	CRP	30 mg/l or greater	until week 4-6 untreated
U&E			
LFT		mild hepatitis common	Bilirubin elevation and AST/ALT elevation
		low albumin common	
Blood culture		Age <1 month 0.5ml 1-36 months >1ml >36 months 4ml	
ASOT			Streptococcal infection may co-exist with KD and does not exclude KD diagnosis but may warrant treatment. ASOT/antiDNAseB B remains elevated for a number of months following Gp A strep infection.
antiDNAse B			
Bacterial throat swab			
Throat swab for resp viruses inc enterovirus			
Urine dip and micro		May have sterile proteinuria & haematuria	But if significant proteinuria consider other diagnoses eg PAN

4.2. Second line investigations during acute illness

If no response to IV antibiotics by 24- 48 hours, remains febrile and no alternative diagnosis reached, suggest proceeding to 2nd line investigations. Recommend discussion with Southampton ID or rheumatology team in such cases in order to review need for urgent echocardiogram.

Investigation		Additional notes
Connective tissue / vasculitis investigations	C3/C4 ANA / ANCA Ferritin	Systemic JIA clinical picture is of 2 weeks of fever with at least one of: painless lymphadenopathy, rash, hepatomegaly, serositis. May or may not have arthritis. Significantly raised ferritin is characteristic
Viral titres	EBV serology	
	CMV serology	
	Parvovirus serology	
	Measles PCR	Temperature falls after day 5 and Koplik spots present
Mycoplasma titres		
Stool for enterovirus		
Abdominal USS		Look for hydrops of gall bladder
CXR		
LDH, VMAs etc		Consider malignancy, may need discussion with haem/oncology regarding the need for bone marrow aspirate

5. Treatment of Kawasaki disease

Following diagnosis patients with Kawasaki disease should be commenced on treatment with intravenous immunoglobulin and aspirin.

Treatment with intravenous immunoglobulin within the first 10 days of the onset of the illness reduces the complications, mortality and morbidity of Kawasaki disease. There may still be limited benefit of treatment from 10 to 60 days if there are ongoing active signs of inflammation.

Immunoglobulin should be prescribed on an intravenous fluid chart as Normal Immunoglobulin for Intravenous Use **at a dose of 2 g/kg given over 12 hours**. If there are features of heart failure (disproportionate tachycardia, gallop rhythm, liver enlargement, breathlessness) then discuss the rate of administration with the duty consultant due to the risk of cardiac decompensation.

If risk factors for IVIG resistance (age <1 year, plts <100, liver derangement - ALT>100), to discuss with UHS ID or rheumatology team regarding need for adjuvant immunosuppression (oral prednisolone 2mg/kg for 3 days followed by wean over 2 weeks) in addition to first dose of IVIG and role of urgent echocardiogram. If shock/haemodynamic instability, consider adding methylprednisolone with first dose of IVIG.

Immunoglobulin side effects include chills, malaise, fever, haemolytic anaemia, aseptic meningitis and rarely anaphylaxis.

Administration issues with immunoglobulin

- Consent forms are not required.
- Record batch number and product name in notes.
- Different manufacturers / products have specific instructions on infusion rates – see the package insert.

- Please note that this is a "red" indication for immunoglobulin and the necessary local immunoglobulin request paperwork will need to be completed

(5.2) Aspirin

Although aspirin is normally contraindicated in children under 16 years due to the risk of Reye's syndrome it is recommended in children with Kawasaki disease. Aspirin treatment is started at high dose (for anti-inflammatory effects), and reduced to lower dose (for anti-platelet effects) once the fever and inflammatory markers have settled. The low dose is continued until the coronary arteries have been shown to appear normal.

(6.2.1) High dose aspirin should initially be prescribed on the drug chart (and discharge medication sheet) **at a dose of 7.5 to 12.5 mg/kg four times a day**, equivalent to a total daily dose of 30-50 mg/kg. This dose is administered by dispersing 75 mg tablets in 5 mls of water (equivalent to 15 mg/ml) and drawing up the appropriate volume. (Note that 300 mg tablets are also available but their use should be avoided to prevent confusion). This should be continued until the fever and inflammation have subsided. If the temperature has settled at this point the dose should be reduced as follows (6.2.2). If the temperature has not settled a careful clinical review and consideration of alternative causes should be made prior to continuing high dose aspirin until at least 48 hours of temperature normalization.

(6.2.2) Low dose aspirin should be prescribed on the discharge medication sheet **at a dose of 2 to 5 mg/kg once daily**, with instruction to change from high dose to this lower dose once the fever and inflammation have subsided. This dose is administered by dispersing 75 mg tablets in 5 mls of water (equivalent to 15 mg/ml) and drawing up the appropriate volume. (Note that 300 mg tablets are also available but their use should be avoided to prevent confusion). Ensure that the family and GP are aware that repeat prescriptions will be needed. **Low dose aspirin should continue until at least the 6-8 week echocardiogram.**

(5.3) Warfarin

Patients with giant coronary artery aneurysms with or without stenosis are at the highest risk for coronary thrombosis due to abnormal flow conditions. In addition, the presence of chronic thrombus in the aneurysms can amplify the thrombotic cascade. Therefore, warfarin should be commenced for patients with giant coronary artery aneurysms with initial full heparinisation to prevent thrombosis. **Aim for an INR range of 2-2.5.**

5.4. Expected response to therapy

80-90% respond to above treatment within 36 hours with a settling of temperature. If symptoms persist at 48 hours or recur within 2 weeks of initial treatment and there is no alternative diagnosis identified then discuss with Southampton paediatric ID or rheumatology teams regarding differential diagnoses, the role of an urgent echocardiogram and whether 2nd line treatment should include adjuvant steroids along with a second dose of IVIg.

6. Cardiac involvement in Kawasaki disease

Transthoracic echocardiography has high sensitivity and specificity for identifying cardiac involvement in Kawasaki disease. Coronary artery abnormality is the commonest complication of untreated Kawasaki disease but other cardiac involvement includes:

i) Valvar regurgitation,
ii) Pericardial effusion suggesting pericarditis

iii) Papillary muscle brightness and impaired left ventricular systolic function suggesting myocarditis
iv) Aortic root dilatation (usually mild)

However, **timing of echocardiography should not delay** the initiation of IVIG.

If Kawasaki disease is strongly suspected in patients who do not fulfill all the clinical criteria for diagnosis of Kawasaki disease, an urgent echocardiography can be diagnostic. Presence of coronary artery abnormality on echocardiography is diagnostic of incomplete Kawasaki disease.

A baseline ECG should be obtained in all patients treated with Kawasaki disease.

6.1. Echocardiography assessment

Patients with diagnosis of Kawasaki disease who have received IV immunoglobulin need follow-up echocardiography and ECG on at least 2 occasions, at 2-3 weeks and 6-8 weeks after diagnosis **(see 8. Follow-up arrangement).** Coronary artery dilatation can be difficult to assess in the acute phase of Kawasaki disease. Therefore, all patients with the diagnosis of Kawasaki disease must be referred to the paediatric cardiologists at UHS for an echocardiographic assessment.

Children with Kawasaki disease are usually very irritable and may not tolerate echocardiography. Sedation with chloral hydrate or midazolam (see local sedation protocol) may be required for detailed echocardiographic studies. In a distressed child, imaging of the coronary arteries is given priority to sequential segmental imaging. Coronary arteries are assessed using multiple views before concluding the presence or absence of coronary artery involvement.

Features of abnormal coronary arteries in Kawasaki disease are:

i. Perivascular brightness
ii. Dilatation (z score >2)
iii. Aneurysm
    a. Saccular
    b. Fusiform
iv. Lack of tapering of the distal coronary vessel

In order of highest to lowest frequency, common sites of coronary aneurysms are:

i. Proximal left anterior descending (LAD)
ii. Proximal right coronary artery (RCA)
iii. Left main coronary artery (LMCA)
iv. Left circumflex (LCx)
v. Distal RCA
vi. Junction between the RCA and posterior descending coronary artery

Coronary artery measurements should be taken from the inner edge to inner edge of the vessel wall. In addition to the coronary arteries, left ventricular (LV) function should also be routinely assessed in patients with Kawasaki disease.

LV systolic function should be assessed using a combination of techniques i.e M-mode, 2-D approach and Simpson biplane technique and not only rely on visual assessment. These techniques allow quantification of fractional shortening (FS), fractional area change (FAC) and ejection fraction (EF) which are useful in long-term follow-up.

Definition of abnormal coronary arteries

i. Diameter of the coronary arteries with Z score of >2
ii. Giant coronary artery aneurysm- CA ≥ 8mm or infant Z score of > 7
iii. Perivascular brightness or lack of tapering of the distal coronary artery may also suggest coronary artery involvement in Kawasaki disease

7. Discharge arrangements

The following criteria are a guide prior to discharge:

- 36 hours or more has elapsed since the completion of intravenous immunoglobulin
- Fever has settled (less than 37.5 for at least 24 hours)
- There are no other active clinical signs of inflammation
- Aspirin is tolerated orally
- The child's family understand the regime of aspirin treatment
- The child's family understand the need to obtain repeat prescription of aspirin from GP
- The discharge letter includes advice that live vaccines should be deferred until at least 3 months following immunoglobulin therapy.

8. Follow-up arrangements

Kawasaki disease-related vasculopathy is characterized by myointimal proliferation with or without layering of thrombus which may lead to progressive coronary artery stenosis. Patients with coronary artery aneurysm carry a lifelong increase risk of coronary artery thrombosis and stenosis which may results in myocardial ischaemia, infarction and sudden death. Therefore, children with Kawasaki disease with coronary artery involvement should be follow-up.

Follow-up recommendations:

8.1.1 Normal coronary artery and no other cardiac involvement

- For **non-urgent echo** and ECG at 2 weeks after onset of illness and repeat echo in 6 weeks
- Follow up in the local joint cardiac clinic or paediatric cardiology clinic in University Hospital Southampton
- Discontinue maintenance dose of aspirin at 6 weeks if echo remains normal
- Review again in 1 year and if continue to have normal coronary artery, discharge from clinic
- Offer healthy lifestyle advice to minimize cardiovascular risk factors- No smoking, moderate alcohol consumption and regular exercise.

8.1.2 Coronary artery dilatation (Z score >2.0) /aneurysm but no stenosis

- Repeat echo and ECG at 2 weeks and 6 weeks after diagnosis
- Subsequent echo at 6 monthly to 1 yearly interval
- Continue on aspirin until dilatation or aneurysm resolved
- Consider imaging of the coronary artery with CT/MRI or angiogram
- Other investigations to consider:
    - Stress imaging
    - CT calcium score
    - Exercise tolerance test (ETT) if clinically indicated i.e chest pain or breathlessness
- Advice to inform paediatric cardiologist urgently if develop chest pain
- Healthy lifestyle advice to reduce cardiovascular risk factors (see above)
- Refer to interventional cardiologist for lifelong follow-up

8.1.3 Giant coronary artery aneurysm (CAA ≥ 8mm or infant Z score >7)

- Lifelong maintenance dose of aspirin
- Add Warfarin (Target INR 2-2.5). Heparin should be started to prevent thrombosis.
- Weekly echocardiography to monitor progression of aneurysm size or thrombus formation
- Frequency of further follow-up is at the discretion of consultant paediatric cardiologist
- Imaging of the coronary artery using CT or MRI to monitor progression of and assessment for coronary artery stenosis
- Other investigations to consider:
    - Coronary artery angiography (wait at least 6 months from acute presentation)
    - Stress imaging
    - ETT if clinically indicated (see above)
- Exercise restriction advice (avoid high intensity exercise)
- Advice to inform paediatric cardiologist urgently if develop chest pain
- Healthy lifestyle advice to reduce cardiovascular risk factors
- Refer to interventional cardiologist for lifelong follow-up

9 Implementation

This guideline will be displayed on the PIER network website, accessible to all paediatrician working within the Wessex region.

10 Process for Monitoring Effectiveness

Audit results will be circulated and presented at the multidisciplinary audit meetings, identified in the monitoring table. Any areas of non compliance or gaps in assurance that arise from the monitoring of this guideline will result in an action plan detailing recommendations and proposals to address areas of non compliance and/or embed learning. Monitoring of these plans will be coordinated by the group/committee identified in the monitoring table. The resulting actions will be reviewed or followed up at the subsequent multidisciplinary audit meeting(s).

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12 Appendices

Appendix A

Documentation of regional consultation:

Trust	Name of person consulted* (print)	Designation	Signature
Dorchester	Will Verling		
Hampshire Hospitals Foundation Trust	Katie Yallop/Ayo Kadri		
Poole	Steve Wadhams		
Portsmouth	Amanda Freeman		
Salisbury	Nick Brown		
Southampton	Sanjay Patel		
IOW	Arun Gulati		

*this person agrees they have read the guidelines, consulted with relevant colleagues and members of MDT, managers and patients, young people & their families as appropriate. Any queries raised during consultation and review process should be documented with responses and any changes made to the guideline.

Appendix B

Coronary artery	Echocardiography view
LMCA	• Parasternal short axis (slight clockwise rotation maybe needed) • Parasternal long axis sweep between the aorta and pulmonary artery • Subcostal left ventricle long axis
LAD	• Parasternal short axis (slight clockwise rotation maybe needed) • Parasternal long axis sweep between the aorta and pulmonary artery
LCx	• Parasternal short axis (slight clockwise rotation maybe needed) • Parasternal long axis sweep between the aorta and pulmonary artery • Apical 4 chamber views will show the LCx in the left atrioventricular (AV) groove • Subcostal
Proximal RCA	• Parasternal short axis with probe moving slightly to the right • Parasternal long axis • Subcostal short axis at level of AV groove
Mid-RCA	• Parasternal short axis • Apical 4 chamber • Subcostal LV long axis • Subcostal short axis at level of AV groove
Distal RCA	• Apical 4 chamber views with probe pointing posterior will show the distal RCA in the right atrioventricular groove
Posterior descending CA	• Apical 4 chamber view with probe pointing posterior • Parasternal long axis with probe pointing posterior and tangential to image the posterior interventricular groove