Acute cardiovascular management of patients with previous Kawasaki disease

Guidance for London hospitals, clinicians and London Ambulance Service

Executive summary

- Those who have a past history of Kawasaki disease (KD) are at life-long risk of future cardiovascular events, particularly acute coronary syndromes.

- The risk of such events is related to the severity of residual cardiac pathology (particularly coronary aneurysms) after the initial illness.

- Every adult or child who is under follow-up for the cardiac consequences of KD assessed as risk level 3 or higher should have a person specific protocol (PSP) written.

- Acute coronary syndromes may present with atypical symptoms, and in the absence of typical changes in the electrocardiogram (ECG) or cardiac enzymes.

- Any adult or child with a history of prior KD, presenting with any symptoms or signs which could be due to an acute coronary syndrome, should be taken directly by London Ambulance Service (LAS) to a heart attack centre (as in their PSP). Those who self-present to a local hospital should be transferred to a HAC (for adult patients) for assessment and further management. Children should be transported to a paediatric centre offering paediatric emergency services, paediatric cardiology and adult HAC expertise on the same site.

- All patients who had signs of coronary artery injury (persistent coronary artery dilatation or aneurysm) beyond the initial 6 weeks should have lifelong follow up by a cardiology team with specialist interest in KD.

- The likely number of people requiring such follow up in London means that experience should be concentrated in no more than two specialist centres.

- Transition of care from a paediatric to adult service should be seamless and well-coordinated.

Background

Since its first description in Japan in 1967, KD has emerged as a common illness affecting young children, with a global distribution. It may occasionally occur in older children or adults. The incidence ranges from over 100 per 100,000 children under five in Japan and South East Asian countries to 8-14 per 100,000 children under five in Europe and USA. In the UK, approximately 300 new cases occur annually. The cause of KD is unknown, but epidemiological features strongly suggest a common infectious agent causing an acute disease in genetically predisposed individuals. Although the acute febrile and exanthematous illness resolves spontaneously, 30 per cent of untreated patients develop coronary artery aneurysms (CAA). Treatment of the acute illness with intravenous immunoglobulin (IVIG) reduces the risk of CAA to 5-10 per cent, and is now the standard recommended treatment. However 10-15 per cent of patients are unresponsive to IVIG, and are at increased risk of CAA, as are those in whom treatment is delayed due to late presentation or failure to diagnose early. Despite current optimal management it is estimated that 5-10 per cent of children with acute KD still develop CAA, significantly increasing their long-term risk of coronary thrombosis and consequent myocardial infarction. They are also at risk of progressive coronary stenosis due to vascular remodelling, often years after the initial illness.

Increasing numbers of patients who were affected by KD in early childhood are now entering adult life. This
Cardiovascular consequences of Kawasaki disease

All cardiac tissues including pericardium, myocardium, valves and coronary arteries (CA) are involved in the acute inflammatory phase of the disease. After resolution of the acute inflammation, the major site of persistent injury is the coronary arteries. Inflammatory vasculitis causes destruction of the arterial intima and media and is followed by aneurysmal dilatation, particularly affecting the proximal coronary arteries. Aneurysms of the axillary, carotid, femoral, coeliac and renal arteries are very rare but may also occur.

Serial echocardiographic studies in acute KD show that CA dilatation may be visible early in the illness, but their maximal development is usually in the second and third week of the acute illness. Dilatation may resolve in some cases by six weeks, but those with persistent CA dilatation visible on echocardiography are considered to have suffered long-term arterial damage. Large or giant aneurysms (>8mm in diameter) are those least likely to undergo resolution and are at greatest risk of longer term complications. Patients with giant CAA have a greater than 50 per cent risk of thrombotic coronary occlusion, stenosis requiring revascularisation, or myocardial infarction within the first 30 years after the initial childhood illness. The risk of coronary artery adverse events in those with smaller aneurysms is lower, but longer term follow up of these patients is still needed. Patients with previous aneurysms who undergo resolution of the aneurysm remain at risk of developing late stenotic lesions, despite apparently normal coronary artery dimensions on imaging studies.

Assessment of cardiovascular risk

As most episodes of KD occur in young children, assessment of whether coronary artery damage has been sustained during the acute KD illness is undertaken by serial echocardiography. While echocardiography is currently the preferred modality for diagnosis of coronary artery dilatation and aneurysms in children, it is less helpful in older children and adults. For the occasional KD case occurring in teenagers and adults, MRI or CT angiography may be needed to define any coronary artery injury.

All children with acute KD currently undergo echocardiography at specialist paediatric cardiology centres, to identify coronary artery involvement, with a minimum of three staged echocardiography studies (acute, two weeks and six weeks following onset of the disease). Coronary aneurysms are measured as coronary z-scores, to adjust for body surface area. On the basis of these studies patients can be classified into the following five risk groups according to the 2004 American Heart Association classification, each requiring different levels of active follow up.

Risk level I

Normal coronary arteries on all imaging studies - Antiplatelet therapy (low dose aspirin) is given only for six to eight weeks after disease onset, and there is no restriction of activity after this point. Counselling on cardiovascular risk factors (such as smoking, lack of exercise, poor diet) is recommended every five years because of possible subclinical coronary injury. No invasive cardiac tests are warranted.

Risk level II

Transient coronary artery ectasia or dilation that resolves by eight weeks after disease onset - Management is similar to that of risk level I.

Risk level III

Small to medium coronary artery aneurysms (3-6mm or z-score of 3 to 7 SD units) - Low-dose aspirin is continued beyond the first eight weeks, at least until the aneurysm regresses. Physical activity is not limited beyond the first eight weeks for children in the first decade of life. Annual echocardiography and electrocardiography by a paediatric cardiologist are recommended, and angiography undertaken if abnormalities are noted on a stress test. Stress myocardial perfusion imaging or exercise ECG testing should
be performed in the second decade, approximately every two years and before participation in competitive sports. Patients in this and higher risk levels should transition to adult cardiology care for long-term follow-up, as this group of patients is at risk of later coronary stenosis and thrombosis.

**Risk level IV**

**Large (≥6 mm) aneurysms, and coronary arteries with multiple complex aneurysms without obstruction** - Long-term antiplatelet therapy is indicated for these patients, and warfarin should be added for patients with giant aneurysms (≥8mm or z-score ≥ 10 SD units). Annual stress myocardial perfusion imaging or exercise ECG testing will help inform advice about physical exercise. Collision and high-impact sports should be avoided because of anticoagulant therapy. Echocardiography and electrocardiography should be performed every 6-12 months. In older children, teenagers and adults MRI is preferable to echocardiography and should be the preferred modality for regular follow up in view of the absence of radiation risk, and better definition of coronary artery status. The frequency of other invasive or non-invasive imaging studies (such as CT angiography) is determined by the severity of the lesions and considerations of radiation risk. Invasive angiography should be reserved for those patients in whom coronary intervention is being considered, or in whom additional data is needed for clinical decision making (such as fractional flow reserve or use of intravascular ultrasound).

**Risk level V**

**CAA associated with obstruction documented on MR, CT, or invasive angiography** - Recommendations are similar to those of risk level IV, with the addition of beta-adrenergic blocking agents. For those with abnormal stress myocardial perfusion imaging, unstable angina, or acute myocardial infarction, cardiac catheterisation is important to evaluate patients for thrombolytic therapy, catheter intervention, or possible coronary artery bypass surgery.

**Patients with a history of KD but uncertain coronary artery status**

Some adults and children may present to medical services with a past history of KD, but without adequate or recent documentation of their cardiac status. This group may be at risk of myocardial ischaemia and should be considered for cardiac investigation (stress myocardial perfusion scanning or exercise ECG, CT calcium score and angiography or cardiac MRI). A formal cardiac reassessment should be undertaken particularly if symptoms or clinical concerns develop.

**Management (see Appendix 1)**

Patients with persistent aneurysms should be managed according to the AHA guidelines using aspirin as an antiplatelet agent (3-5 mg/kg/day) for those with small to moderate aneurysms (< 8 mm). Other anti-platelet agents, such as clopidogrel, are also added to aspirin therapy at some centres. Anticoagulation with warfarin in addition to aspirin has been associated with improved survival in meta analysis of published data and is now recommended for all patients with giant CAA, despite the well-known risks of bleeding. The choice of antithrombotic medication should be discussed with the patient and relatives. The new oral anticoagulants such as apixaban, dabigatran and rivaroxaban are increasingly used in other conditions, and may offer advantage in terms of reduced does monitoring, however there is no data at present on which to base their use instead of warfarin for patients with giant CAA.

Patients whose aneurysms have regressed, and have normal coronary artery diameters on echocardiography, MRI or CT angiography remain at risk of developing late stenosis. It is not clear whether continued aspirin therapy is beneficial once the coronary artery diameter has normalized. However patients with regressed aneurysms require continued follow up and repeated reassessment as for those with persistent aneurysms.

**Percutaneous coronary interventions**

Percutaneous coronary interventions may be necessary if stenosis causes myocardial ischemia. Due to the severity of vessel wall thickening and associated calcification high balloon inflation pressures may be needed, sometimes leading to neo-aneurysm formation. There is limited experience with the use of covered or drug-eluting stents in this patient population. Rotational atherectomy may be appropriate for heavily calcified stenosis which are not amenable to balloon dilatation.

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**Surgical coronary revascularization**

Surgical coronary revascularization both venous and arterial grafts have been used in this patient population

Arterial grafts have a much higher rate of graft patency over time compared to venous grafts. Cardiac transplantation has been successfully performed for the rare KD patient with end-stage cardiomyopathy and inoperable multivessel coronary artery disease. Decisions on whether to exclude aneurysms, and the risk of competitive flow through the aneurysms, need to be considered and as surgical experience with KD is limited, elective interventions should be planned after discussion with international experts.

**Psychological considerations**

Patients with large CAA are at considerable risk of psychological disorders due to the stress of adjusting to teenager and young adult life with the constant threat of life threatening coronary ischaemic events. Care teams have to balance providing honest advice on the risks and need for urgent action in the event of changing symptoms, with the value of reassurance and helping families to live as normal a life as possible. Multidisciplinary team involvement, including access to counselling and psychological support should be part of the specialist service provided to KD patents.

**Management of suspected acute coronary syndromes**

**Presentation out of hospital or calls to ambulance services**

1. Every adult or child who is under follow-up for the consequences of KD should have a person specific protocol (PSP) written (see Appendix 2), to guide the London Ambulance Service in the actions they should take if the individual presents with ANY symptoms that might be caused by CAA thrombosis, embolization, or myocardial ischemia.

2. Importantly, the classical symptoms, ECG changes and troponin levels conventionally used to identify myocardial ischemia in adults with coronary artery disease should not be relied upon to exclude CAA thrombosis or myocardial ischaemia in KD patients. Children with CAA and stenotic lesions as a result of KD may have well developed coronary collaterals, and a greater tolerance for myocardial ischemia than the usual older adult population, and may present with atypical features.

3. Any patient with known CAA, (or a history of KD where cardiac status is unknown) presenting with chest or abdominal pain, breathlessness, exercise intolerance, unusual pallor, restlessness, vomiting or discoloration of the skin suggestive of embolization should be suspected of having a KD related cardiac event (thrombosis within CAA, embolization, myocardial ischaemia) and should be transported to a heart attack centre (HAC). Children should be transported to a paediatric centre offering paediatric emergency services, paediatric cardiology and adult HAC expertise on the same site.

**Presentation to accident and emergency departments**

1. Unless presentation is clearly due to a non-cardiac condition (such as acute gastroenteritis, bacterial infection, acute abdomen, epilepsy or trauma) patients with known CAA should always first be evaluated at a HAC to exclude a cardiac cause.

2. As discussed above, the usual clinical signs of myocardial ischemia may be unreliable in young patients with KD related coronary disease, due to the well-developed collaterals. Rises in troponin and creatine kinase (CK) levels may occur late, so CAA thrombosis should always be excluded by imaging in any patient with persistent symptoms, even if initial ECG and troponins are normal. Any patient with known CAA, (or a history of KD where cardiac status is unknown) presenting with chest or abdominal pain, breathlessness, exercise intolerance, unusual pallor, restlessness, vomiting or discoloration of the skin suggestive of embolization should be suspected of having a KD related cardiac event (thrombosis within CAA, embolization, myocardial ischaemia) and should be transported to a Heart Attack Centre (HAC) for assessment irrespective of initial ECG and troponin. Children should be transported to a paediatric centre offering paediatric emergency services, paediatric cardiology and...
adult HAC expertise on the same site.

3 Management of patients too ill to transfer, or in whom delay in transfer to a HAC is likely, should be discussed with a HAC consultant to determine whether intravenous thrombolysis is initiated prior to later transfer or imaging. Once a decision is made to offer thrombolysis it should be delivered as soon as possible.

**Presentation to a heart attack centre**

1 Any person with a past history of KD admitted or transferred to a HAC with a suspected acute coronary syndrome should receive urgent review by a consultant interventional cardiologist, who should be aware that:

   a. The presentation of an acute coronary syndrome may not be with typical symptoms.
   b. Significant intracoronary thrombus may be present without obvious ECG change and without a rise in serum troponin.
   c. Urgent imaging (CT, MRI or coronary angiography) is advisable in order to determine the extent and severity of any coronary disease and the presence of any thrombus. The choice of invasive or non-invasive imaging will depend on the immediate availability of MRI or CT angiography, and the patient’s condition. Most patients with giant CAA will be under regular follow up and comparison with previous MRI or CT images may enable any new thrombus within the CAA to be detected.
   d. The size of coronary aneurysms and the presence of dense calcification may make the use of coronary stents inappropriate unless rotational atherectomy is used to pre-treat the vessel.
   e. The use of intravascular ultrasound (IVUS) may often help inform clinical management when there is extensive thrombosis that makes the diameter of the true coronary lumen difficult to determine.
   f. The use of intravenous thrombolytic and glycoprotein IIb/IIIa anti-platelet inhibitors should be considered.
   g. Discussion with a cardiac surgeon regarding appropriate revascularisation may be helpful in cases where myocardial ischaemia persists and percutaneous treatment is not appropriate. Consultation with UK and international experts (see contact list after references) may be helpful prior to surgical intervention.

**Non-cardiac acute complications**

1. *Thrombosis within extra cardiac aneurysms*
   Patients with aneurysms of extra cardiac arteries (most commonly axillary and iliac/femoral) are at risk of thrombosis within extra-cardiac aneurysms. This may present with features of peripheral ischaemia such as claudication, pallor, pain, loss of pulses, or discoloration of peripheral limbs or digits. Any acute symptoms compatible with thrombosis should lead to discussion with a vascular specialist and imaging studies to exclude thrombosis or occlusion should be considered.

2. **Bleeding**
   Patients with giant CAA on warfarin and antiplatelet agents are at risk of external or internal bleeding, spontaneously or following trauma. Internal bleeding may present with swelling over limbs or joints, GI bleeding, or haemorrhagic stroke. New symptoms or lesions should undergo imaging by ultrasound or CT, and INR should be checked. Any CNS symptoms with or without a history of trauma such as persistent headache, impaired consciousness or neurological signs requires imaging to exclude haemorrhagic or thrombotic stroke.
References


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Appendix 1: Management of Kawasaki disease: Flowchart

- Those who have a past history of Kawasaki disease (KD) are often at lifelong risk of future cardiovascular events, particularly acute coronary syndromes.
- The risk of such events is related to the severity of residual cardiac pathology (particularly coronary aneurysms) after the initial illness.
- Every adult or child who is under follow-up for the consequences of KD and is in cardiac risk category 3 or more should have a person specific protocol (PSP) written.
- Acute coronary syndromes may present with atypical symptoms, and in the absence of typical changes in the electrocardiogram (ECG) or cardiac enzymes.
- A person with a history of prior KD, who presents with any symptoms or signs which could be due to an acute coronary syndrome, should be taken directly by London Ambulance Service (LAS) to a heart attack centre. Children should be taken to a designated paediatric centre offering on site paediatric emergency care, paediatric cardiology and adult HAC expertise.
- Those who self-present to a local hospital should be transferred to a HAC for assessment and further management.
- Unless there is good evidence that coronary vasculitis associated with the initial KD episode has resolved completely without cardiac abnormality, patients should have lifelong follow up by a cardiology team with specialist interest in KD.

![Flowchart Image]

- The size of coronary aneurysms and the presence of dense calcification may make the use of coronary stents inappropriate unless rotational atherectomy is used to pre-treat the vessel.
- The use of intravascular ultrasound (IVUS) may often help inform clinical management when there is extensive thrombosis that makes determination of the true lumen difficult.
- The use of thrombolytic and intravenous glycoprotein IIb/IIIa anti-platelet inhibitors should be considered.
- Discussion with a cardiac surgeon regarding appropriate revascularisation may be helpful in cases where myocardial ischaemia persists and percutaneous treatment is not appropriate.
- As cardiac centers in the UK have little experience of the surgical problems presented by Giant CAA, consultation with the Japanese and USA experts, with experience of the disorder should be considered, time permitting, prior to surgical intervention.
This protocol has been specifically prepared for the patient named below and details the treatment to be given in specified circumstances.

Patient's Name:  
Date of Birth: 

NHS No.:  

Address:  

Reason for protocol:  

Specific Treatment / Instructions:  

If required please transport to the nearest XXX  

All other aspects of clinical care remain unchanged.  

If required contact the Clinical Hub for advice  

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Name of Responsible Clinician:  

Date of Issue:  

Review (Renew) Date: