# *Frequently Asked Questions about* **Kawasaki Disease**


***Kawasaki Disease** is the leading cause of acquired heart disease in UK children...*

**...faster diagnosis and treatment can change that!**

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# *Frequently Asked Questions about* **Kawasaki Disease**

**The following FAQ's have been prepared by the Scientific Advisory Board of Societi Foundation – who are NHS consultants, across paediatric specialisms, with specialist knowledge and experience in caring for children with Kawasaki Disease.**

**Thank you to our Scientific Advisory Board, in particular Professor Robert Tulloh, for valuable and expert input into this document.**

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# General

## What is Kawasaki Disease?

Kawasaki Disease is an inflammatory disease. It mainly affects young children (75% of patients are under 5 years) but it can affect people of any age. Kawasaki Disease has a range of symptoms including a characteristic and distinctively persistent high fever for five days or more. This fever often appears with two or more of the following symptoms: rash, bloodshot eyes, "strawberry" tongue, cracked, dry lips, redness of the fingers and toes, and swollen glands in the neck – sometimes very large and often just on one side.

Kawasaki Disease can present with some or all of these symptoms. If a child has a persistent fever with any of these symptoms, please THINK Kawasaki Disease.

Most of these symptoms occur in the first few days of the illness, although they are often not all present at the same time. There are also other typical features we see which are those of irritability (children with Kawasaki Disease are characteristically irritable!) This irritability is often disproportionate to the level of fever. Loss of appetite, moodiness, diarrhoea, reactivation the BCG scar, tummy ache, vomiting and jaundice can also be seen.

## What causes Kawasaki Disease?

There are lots of theories around the cause of Kawasaki Disease and much research ongoing across the globe to try and identify a cause. But at the moment, no-one is certain of the cause.

There is some evidence to suggest that some children have a genetic predisposition to being affected by Kawasaki Disease. Some researchers believe it could be a child's response to an infection or a number of infections, though no infectious cause has been found. There are theories too that suggest an environmental agent – perhaps something which is airborne or related to water bodies. Whilst there is much research ongoing, some of it appears contradictory – and the patterns of incidence of Kawasaki Disease are different in different places.

## Reported incidence is rising across the world. Is this because recognition is better?

Incidence is rising – because of increased disease, not simply increased awareness alone. In Japan, for example, where Kawasaki Disease is very common and awareness is very high, yet there is a continued and rapid rate of increase in cases. In the UK, awareness is low presently, yet incidence is also rising sharply. With increased awareness we'd expect to see increased correct diagnosis. Currently diagnosis is often delayed, demonstrating poor awareness – Kawasaki Disease is often arrived at as a diagnosis after, on average, 2 or 3 prior misdiagnoses (Societi Foundation Diagnosis Day research 2022). Please expect to see Kawasaki Disease. Be ready to treat it.

# Diagnosis

## What are the clinical features of Kawasaki Disease?

- **Persistent fever** – Can be unremitting with anti-pyretics, may be spiking and may come and go. Parent/carer reports of very high fever should form part of the case history.
- **Polymorphous rash** – Can take many forms. Could appear like eczema and in eczema locations. Can appear as 'sun burn'. Can be fleeting – case history is important.
- **Oropharyngeal changes – 'strawberry' tongue, cracked lips:** Lips can be cracked and dry, so called 'lipstick sign' and painful and sore. Sore throat, dry mouth, 'strawberry tongue' – which is often shown in images to be bright red, may in fact present as white 'strawberry tongue' with bumps initially.
- **Bilateral non-purulent conjunctival injection – non exudative:** Bloodshot, non-sticky conjunctivitis. Remember red eyes do not appear in Scarlet Fever – this is a key differentiator. Limbic sparing - area of pallor adjacent to the iris, typical of the conjunctival injection which can be part of the immune response with Kawasaki Disease.
- **Changes in peripheral extremities, redness and swelling:** Erythema – reddened hands and feet with swelling. Can be very distinctive and cause discomfort. Puffy hands and feet sometimes referred to as indurative oedema.
- **Cervical lymphadenopathy – often just one side:** will be pronounced and enlarged - may be very large.
- **Additional signs:** include perineal rash, BCG scar reactivation, tummy ache, Disproportionately irritable, diarrhoea/abdominal pain, aseptic meningitis, urethritis, uveitis, hydrops of gallbladder.
- **Cardiac signs:** Echo can show inflammation of coronary arteries and coronary artery aneurysms, pericarditis, valvulitis or myocarditis. Do not delay treatment pending echo findings!

## What is the target population where Kawasaki Disease starts to be considered as a possible diagnosis? And at which timepoint?

Kawasaki Disease should be considered in ANY child with persistent fever for 5 days with no obvious cause. The other symptoms may not be present when the child is examined. Around 25% of cases occur in children over the age of 5, 75%

are under 5 years. Infants and young children are especially vulnerable to severe heart damage – possibly linked to delayed diagnosis and late treatment as the disease is often not considered soon enough. Older children also often experience diagnosis delay and poorer outcomes as a result. Consider Kawasaki Disease in ANY child with persistent fever for 5 days.

## What are the differential diagnoses?

Any of the following can be mistaken for Kawasaki Disease or can occur prior to a case of Kawasaki Disease:

**Scarlet fever** – remember you will NOT see red eyes in scarlet fever but you might in Kawasaki Disease.

**Virus** – runny nose typically associated with viral infection is not a feature of Kawasaki Disease. Remember Kawasaki Disease can be present with a comorbid infection – do not rule out Kawasaki Disease simply based on the presence of another infection.

**Meningitis** – if this is suspected, treat but stay alert to the possibility of Kawasaki Disease which can present with fever and few other symptoms, especially in infants. If child is non-responsive to antibiotics / treatment – maintain a high index of suspicion for Kawasaki Disease.

Persistent fever, disproportionate irritability and failure to respond to treatment for earlier diagnosed conditions should trigger continued suspicion. If Kawasaki Disease is suspected – DO NOT DELAY – treat.

Other important differential diagnoses, particularly when the illness persists beyond what might be expected for 'typical' Kawasaki Disease include systemic onset juvenile idiopathic arthritis; other rare chronic vasculitides such as polyarteritis nodosa or Takayasu arteritis; malignancy (we have seen lymphoma present initially like Kawasaki Disease); other connective tissue disease e.g. SLE.

## Are there any tests for Kawasaki Disease?

No, as yet there is no specific test to diagnose Kawasaki Disease. Although non-specific for diagnosis, the following laboratory findings may be helpful in the diagnosis of Kawasaki Disease.

Complete blood count (CBC) may reveal:

- Normocytic normochromic anaemia
- Thrombocytosis
- Platelets may be low initially then ≥ 450×103/μL (450 × 109/L) after the first week and typically peaking to 700×103/μL and normalising after 4-6 weeks of onset of acute episode of Kawasaki Disease
- Leucocytosis, white blood cell count ≥ 15,000/μL (15.0 × 109/L)
- Lipid profile - may demonstrate hypertriglyceridemia

- Elevated erythrocyte sedimentation rate
- Elevated C-reactive protein
- Hypercoagulation profile - may or may not demonstrate evidence of hypercoagulability
- Panel should include thrombomodulin, tissue factor, tissue factor pathway inhibitor, Von Willebrand factor, coagulation factor VII, activated factor VII, prothrombin fragment 1 + 2, and D-dimer
- Elevated liver enzyme levels
- Hypoalbuminemia ≤ 3.0g/dL (30g/L)
- Electrolyte study may reveal hyponatraemia
- Urine analysis may demonstrate sterile pyuria

Echocardiogram may show coronary artery abnormality. Decreased left ventricular (LV) contractility, mild valvular regurgitation (most commonly mitral regurgitation), and pericardial effusion also may be seen in an echocardiogram of a patient with acute Kawasaki Disease.

As most episodes of acute Kawasaki Disease occur in young children, assessment for coronary artery involvement is by serial transthoracic echocardiography, at least at diagnosis, 2 weeks and 6 weeks following onset of the disease. If abnormal, more frequent echocardiography will be required (up to twice weekly) to identify rapidly progressive coronary involvement and/or coronary thromboses.

## *Does the fever have to be continuous for the 4-5 days?*

In Kawasaki Disease, a characteristic symptom is a persistent high fever which typically is unresponsive to antipyretics. Fevers may also spike and become very high or come and go. Continuous fever is typical but a child with a history of prolonged fever or 5 days with no obvious cause should raise suspicion of Kawasaki Disease.

## *In terms of incomplete presentation in infants, how many symptoms should we be looking for before considering Kawasaki Disease?*

Fever plus rash is a common presentation in infants. However, a persistent high fever with no obvious cause is not common and should always raise a suspicion of Kawasaki Disease. In Kawasaki Disease in infants, persistent fever may be accompanied only by a rash on presentation – but history is critical. Discuss the appearance (even if fleeting) of other symptoms with parents/carers and remain alert to the likelihood of Kawasaki Disease. 39% of infants (under 1 year) currently develop coronary artery aneurysms from Kawasaki Disease and will need lifetime specialist care. Giant coronary artery aneurysms are seen in this patient group – this is a life changing and life-threatening condition. Delay in diagnosis and treatment in infants is linked to these poor outcomes. Rapid treatment is key.

# Treatment

## How is Kawasaki Disease treated?

Treatment of the acute illness is with intravenous immunoglobulin (IVIG) and aspirin, this reduces the risk of CAA and is now the standard recommended treatment. However, c.15% of patients are unresponsive to IVIG, these patients may be treated with corticosteroids, infliximab or other immunosuppressive agents.

If there are giant aneurysms, then the patient may need intravenous heparin to reduce the risk of thrombosis in the coronary arteries.

A trial called KD-CAAP is looking at the addition of oral prednisolone to IVIG in the treatment of Kawasaki Disease. Research in other countries indicate that this might improve outcomes. The trial concludes recruiting during 2024.

## Can IVIG be started very early if all features are present?

Yes. If Kawasaki Disease is suspected or confirmed based on clinical presentation, do not delay treatment – treat urgently, as early treatment (before 7 days of illness) reduces the risk of heart damage. If treatment is started early, be prepared to give a second dose of IVIG since this is more likely.

## Is there any harm in giving IVIG if we are not clear?

If there is suspicion of Kawasaki Disease – treat. There are some risks associated with the administration of IVIG as a blood product, therefore the balance of the risk of treatment versus non-treatment (and risk of lifetime heart damage) must be considered.

There are however very significant risks of delayed treatment, or non-treatment, for a child with Kawasaki Disease. If Kawasaki Disease is suspected – treat.

# Long term management

## If the coronaries appear normal on echo, how long should we continue antiplatelet agents?

Undertake an echo at 6 weeks (following acute illness) and if coronaries are normal, aspirin can be stopped.

If coronary artery aneurysms persist beyond six weeks, even if they later remodel (resume normal size) aspirin should be continued (for life) as risk of major cardiac events in later life, including stenosis, are raised in this patient group.

## If the coronaries appear normal on echo, can the patient be discharged? And if so, at what point post presentation?

Undertake an echo at 6 weeks (following acute illness) and if coronaries are normal, aspirin can be stopped. It's good practice to see the patient again at 6 months and 12 months – to answer questions and discuss concerns with parents. If there are no new issues, discharge to Primary Care. An annual check-up for discussion of any new concerns, blood pressure check, dietary and lifestyle advice (including avoidance of cardiovascular risk factors) should be arranged.

## How can you reassure families of children with Kawasaki Disease and no coronary artery aneurysm in terms of their long term health? Some families are asking about angiograms/MRI's etc?

Following Kawasaki Disease, those patients with coronary artery aneurysms which persist beyond the acute phase (even where they remodel later) need lifetime specialist care by a clinician with expertise in Kawasaki Disease.

However, there is no current evidence to indicate that patients who have no lasting cardiac damage following the acute phase will experience subsequent cardiac complications linked to Kawasaki Disease, following resolution of their acute illness. Current guidance is that this low-risk group with no coronary artery aneurysms persisting beyond the acute phase should be discharged at 12 months to Primary Care. They should have an annual check-up for discussion of any new concerns, blood pressure check, dietary and lifestyle advise (including avoidance of cardiovascular risk factors) should be arranged. See Societi Long Term Issues leaflet for information on non-cardiac issues which may arise.

# What are the potential long-term effects?

Although the acute febrile and exanthematous illness resolves spontaneously, 19% of children overall and 39% of those aged under 1 year, still develop coronary artery aneurysm despite IVIG, partly related to delayed diagnosis and treatment. Such children are at long-term risk of coronary thrombosis, acute coronary syndrome and progressive coronary stenoses.

Where children have severe coronary artery damage, there may also be aneurysms in non-coronary arteries.

# What are the cardiovascular consequences of Kawasaki Disease?

All cardiac tissues are involved in the acute inflammatory phase of the disease. Vasculitis causes destruction of the normal arterial architecture and is followed by aneurysmal dilatation, particularly affecting the proximal coronary arteries. Pathological studies in patients with previous Kawasaki Disease reveal widespread changes including inflammatory cell infiltration of the arterial wall, disruption of the intima and media, intimal myofibroblastic proliferation and replacement of myocytes with fibroblasts and connective tissue.

Fibrotic changes occur in the myocardium even in regions not closely related to aneurysms, probably reflecting widespread cardiac inflammation. Arterial remodelling occurs and may progress over months to several years with the development of coronary stenoses, particularly at the junction between the aneurysm and normal artery. Later calcification is common in the aneurysmal arterial wall. Aneurysms of non-coronary arteries (axillary, ilio-femoral, renal and popliteal arteries for example and rarely in visceral and cerebral arteries) may also occur and should be considered and investigated, particularly when coronary involvement is extensive.

Serial echocardiographic studies in acute Kawasaki Disease show that coronary artery dilation may be visible early in the illness, but maximal development is usually in the second and third week of the acute illness. Those with persistent coronary artery aneurysm, defined as a Z score≥2.5 after 6 weeks (Z score=the internal dimension of the coronary artery expressed as the number of standard deviation units normalised for body surface area) are considered to have suffered permanent arterial damage.

The risk of thrombotic and stenotic complications is related to aneurysm size. Large or giant aneurysms (≥8 mm in diameter or Z score ≥10) are the least likely to undergo resolution, and within 30 years after the initial illness are associated with up to a 50% risk of thrombotic coronary occlusion, progressive stenoses requiring revascularisation or acute coronary syndrome or even heart transplant. Even though the risk of coronary events is lower in those with smaller aneurysms longer-term follow-up is still needed. Heart failure and serious arrhythmias may also occur later in life.

# How should patients with Kawasaki Disease be followed up?

On the basis of echocardiography, patients are classified into defined risk groups each requiring different follow-up.

The table below shows the risk level and required follow up:

| Risk level | Description of coronary arteries | Follow-up interval | Imaging required to assess for inducible ischaemia (stress echo or stress MRI) | PSP | Regional specialist Kawasaki Disease clinic |
|---|---|---|---|---|---|
| 1 | No involvement at any time point (Z score <2) | 2 weeks<br>6 weeks<br>6 months<br>12 months<br>Discharge if normal at 12 months | None | No | No-annual cardiac and general health review with GP recommended* |
| 2 | Dilation only (2<Z scores<2.5): resolves within 1 year | 2 weeks<br>6 weeks<br>6 months<br>12 months<br>Discharge if normal at 12 months | None | No | No-annual cardiac and general health review with GP recommended* |
| 3 | Small aneurysm (2.5≤Z score<5):<br>(a) current or persistent,<br>(b) decreased to normal or Z score <2.5 | 2 weeks<br>6 weeks<br>6 months<br>12 months<br>Annual review | Coronary angiography (preferably CT) at 12 months as baseline.<br>Consider stress imaging for inducible myocardial ischaemia every 2 years.<br>Imaging (echo) for coronary surveillance annually | Yes | Yes |

| Risk level | Description of coronary arteries | Follow-up interval | Imaging required to assess for inducible ischaemia (stress echo or stress MRI) | PSP | Regional specialist Kawasaki Disease clinic |
|---|---|---|---|---|---|
| 4 | Medium aneurysm (5≤Z score<10): (a) persistent aneurysm, (b) decreased to normal or Z score<2.5 | 2 weeks<br>6 weeks<br>6 months<br>12 months<br>Annual review | Coronary angiography (preferably CT) at 12 months as baseline.<br>Consider stress imaging for inducible myocardial ischaemia annually.<br>Imaging (echo, CT† or MRI) for coronary thrombus surveillance annually. | Yes | Yes |
| 5 | Giant aneurysm (Z score≥10 or ≥8 mm): (a) persistent giant aneurysm, (b) persistent aneurysm (but regressed to medium or small aneurysms), (c) regressed to normal dimensions | 2 weeks<br>6 weeks<br>3 months<br>6 months<br>9 months<br>12 months<br>Then every 6 months | Coronary angiography (preferably CT) at 6–12 months as baseline.<br>Consider stress imaging for inducible myocardial ischaemia annually.<br>Imaging (echo, CT† or MRI) for coronary thrombus surveillance 6 monthly. | Yes | Yes |

**GP review should include clinical examination, blood pressure measurement, general health discussion and advice on avoidance of cardiovascular risk factors and lifestyle choices—including maintaining a healthy weight, reducing risk of diabetes, avoiding smoking and taking regular exercise. This provides the opportunity to discuss any parent or patient questions and concerns.*

*†CT should not be used repeatedly if possible. Use MRI or ultrasound where possible, to reduce radiation exposure.*

*ADP, Adenine di-Phosphate; AHA, American Heart Association; FBC, Full blood count; GP, General Practitioner; PSP, person-specific protocol*

# Are there national guidelines for the management of Kawasaki Disease?

Currently there are no evidence based national guidelines from the National Institute of Health and Care Excellence (NICE) regarding diagnosis or treatment of Kawasaki Disease. However, Kawasaki Disease does feature in NG143 Fever in under 5s: assessment and initial management (2021).

Recommendations are:

1.2.25 Be aware of the possibility of Kawasaki Disease in children with fever that has lasted 5 days or longer. Additional features of Kawasaki Disease may include:

- Bilateral conjunctival injection without exudate
- Erythema and cracking of lips, strawberry tongue, or erythema of oral and pharyngeal mucosa.
- Oedema and erythema in the hands and feet
- Polymorphous rash
- Cervical lymphadenopathy.

1.2.6 Ask parents or carers about the presence of these features since the onset of fever, because they may have resolved by the time of assessment.

1.2.7 Be aware that children under 1 year may present with fewer clinical features of Kawasaki Disease in addition to fever but may be at higher risk of coronary artery abnormalities than older children.

An expert consensus for the lifetime management of patients with previous Kawasaki Disease has been agreed and the paper can be found here.

# What is a person-specific protocol?

All patients with a history of Kawasaki Disease at high risk of future coronary events require a person-specific protocol (PSP). This is a guidance document held by the patient, parents and school (if a child) the Congenital Cardiac Surgical Centre (children)—or Heart Attack Centre (adults) and their emergency medical services (including Ambulance Services). This means they have prior knowledge of the patients' Kawasaki Disease history and can act quickly in the event of a suspected cardiac emergency. The PSP highlights the specific instructions to the Ambulance Service regarding the specialist centre to which the patient should be transported, where the necessary age-appropriate expertise, facilities and imaging are available without delay.

It is recommended that the patient should hold a copy of their most recent ECG and their coronary imaging (either digitally or as printed copy), to facilitate decision making in an emergency situation. The PSP should be agreed with the patient (if adult) or parents/carers (if child) and should include direct phone contact numbers (24 hours) for a specialist Kawasaki Disease service, and clear instructions regarding who to contact for advice out of hours. It should be agreed by the local hospital and ambulance services and should be provided to the patient and, as relevant, the patient's school/university and/carers parents.

## How might patients with long term effects of Kawasaki Disease present with a cardiac emergency?

Patients with new onset chest pain, exercise induced chest pain or (particularly in young children) unusual pallor, restlessness, breathlessness, poorly localised pain or unexplained crying or collapse should be transported urgently to the designated Heart Attack Centre (adults) or nearest paediatric cardiac surgical centre - or as specified as their PSP.

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, whether persistent or remodelled, should always be evaluated at a Heart Attack Centre (adults) or paediatric cardiac surgical centre, as specified on their PSP.

## What is the atypical presentation of myocardial ischaemia in patients with coronary artery aneurysm(s) after Kawasaki Disease?

The classical presentation of myocardial ischaemia in adults (chest pain, arm or jaw pain, decreased exercise tolerance, breathlessness) may be absent in young children, whose symptoms may be non-specific, including poorly localised pain, unexplained crying, restlessness, unusual pallor or sweating.

Children and young adults with stenotic CAA may have well-developed collaterals, a greater tolerance for ischaemia and may present with atypical symptoms even when extensive thrombus is present in the CAA.

In all patients with a previous history of Kawasaki Disease, an initial ECG and troponin may be unremarkable, even with significant myocardial ischaemia.

Thrombosis within aneurysms can occur in children and adults even when taking anticoagulant and antiplatelet agents.

For these reasons, a high index of suspicion is needed in all patients with a prior history of Kawasaki Disease, with persisting or resolved aneurysms, whenever new symptoms occur that could represent myocardial ischaemia, as potentially life-threatening coronary thrombosis may be the cause. Rapid access to urgent expert assessment and imaging is needed.