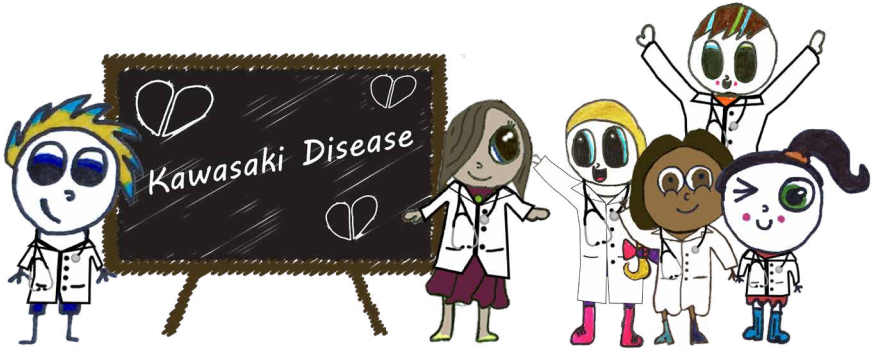
The little book of



Kawasaki Disease

Published by Societi Foundation, the UK Foundation for Kawasaki Disease
May 2023

For more information, go to www.societi.org.uk

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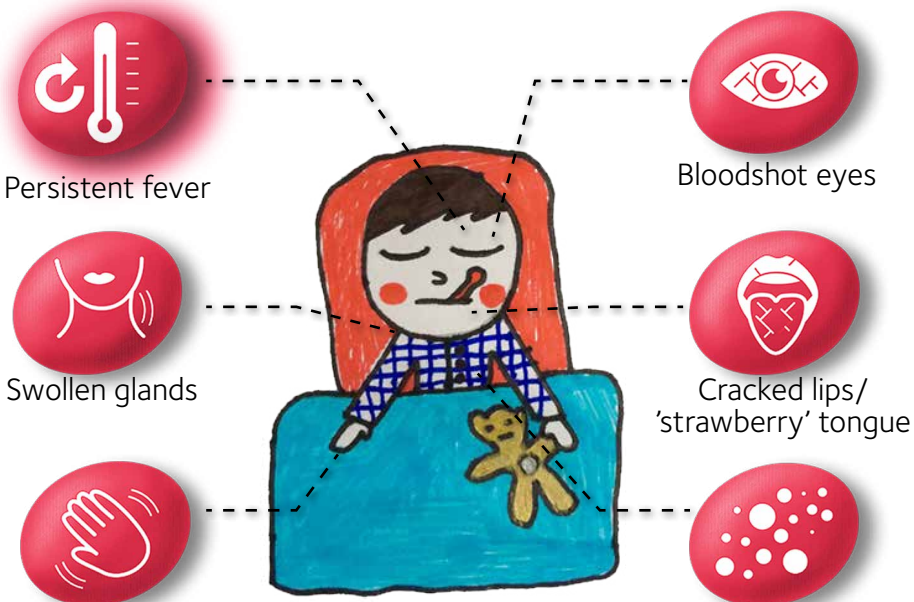
Kawasaki Disease symptoms



If a child has a **persistent high fever** *for 5 days or more, with TWO or more of these symptoms please* **THINK Kawasaki Disease**

NB! Symptoms may appear in series and not all at the same time. Not all children show all symptoms and children often have other symptoms besides.

About our little book...

We are passionate about sharing knowledge and facts on every aspect of Kawasaki Disease. It's such an important illness for **EVERY** doctor who sees children to know.

...we made it for you!

We've created this lovely little book of Kawasaki Disease... which we hope you'll enjoy. It's packed with lots of information, including things we think you'll already know about Kawasaki Disease and perhaps things that you won't (yet!)

It's aim is to help you quickly and easily, and we hope enjoyably, get the in-depth understanding of Kawasaki Disease that children need you to have.

Thank you to our experts...

We want to record our gratitude and sincere thanks to **Dr Jethro Herberg, Dr Filip Kucera** and **Prof Robert Tulloh** for authoring the clinical content of our booklet, and to our Founder, Rachael McCormack, who led the project.

Things we feel sure you already know...

Remember TEMPERS

Children with **Kawasaki Disease** *are characteristically irritable!*

If a child has a **PERSISTENT FEVER** *& two or more of these symptoms* **THINK Kawasaki Disease!**

T Temperature - **Persistent high fever**

E Erythema - reddened hands and feet with swelling

M Mouth - dry, sore mouth, cracked lips 'strawberry tongue

P Pace - **treat early** to reduce potential heart damage

E Eyes - bloodshot, non-sticky conjunctivitis

R Rash

S Swollen glands in neck, often just one side

Case history

Case history is important in **Kawasaki Disease** *- symptoms can appear over time. NB: Not all symptoms appear in all children*

Differential diagnosis

When ruling out the many other causes of fever in children...

~~*Scarlet Fever?*~~

~~*Virus?*~~

~~*Meningitis?*~~ ~~*Tonsillitis?*~~

Please...
THINK Kawasaki Disease

~~*Slapped cheek?*~~

~~*Strep Throat?*~~ ~~*Measles?*~~

Persistent fever

Kawasaki Disease *should always be considered in any child with unexplained* **persistent fever**

Increasingly common

Hospital admissions are rising: doubling every 10 years

EXPECT *to see it,*
BE READY *to treat it*

Babies under 1

Babies under 1 *may have fewest symptoms but* **39% develop coronary artery aneurysms**

Treatment time[1]

Refer **URGENTLY** *for* **treatment within 5 days** *from onset of fever*

BPSU[1] study findings show children treated early had a lower risk of lifetime heart damage than children treated later

EARLY TREATMENT IS KEY *to reduce risk of heart damage*

...PLEASE DON'T DELAY!

[1] BPSU Kawasaki disease: a prospective population survey in the UK and Ireland from 2013 to 2015, Professor R Tulloh et al

Questions and answers

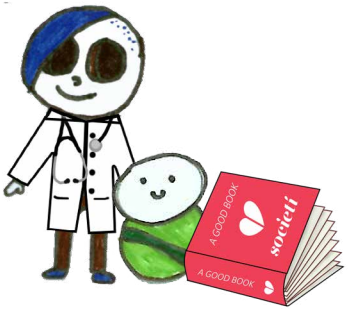
The following series of questions and answers have been compiled with the clinical guidance of doctors who are expert in Kawasaki Disease. With more doctors knowing more about this increasingly common disease, we hope to improve the speed of diagnosis and treatment for all children affected by Kawasaki Disease, and reduce their risk of lifelong heart disease.

Many of the questions are taken from our film *Acute Kawasaki Disease – an expert-led discussion,* which you can watch here – just click the button below:

Watch it here

Endorsed by RCPCH Royal College of Paediatrics and Child Health *Leading the way in Children's Health*

You'll find a host of *'true or false'* questions on the pages that follow too – will you know the correct answers to these common myths about Kawasaki Disease? We'd love to know how you get on...!



Q1: *What causes Kawasaki Disease?*

A1: It's one of the big enigmas in paediatrics. We don't know what the cause of Kawasaki Disease is. It could be that there is a single pathogen trigger, there may be multiple triggers in different people, there's some evidence that there's a genetic predisposition in some children and there may be environmental triggers. Right now, we don't know the cause though!

True or FAlse?

There is a treatment window for IVIG of 10 days

FAlse – There is no "window" or cut off point for IVIG. If clinical benefits are possible and inflammation is ongoing (fever, elevated CRP) - TREAT! And do not delay IVIG assuming a 10 day window for effective treatment. Current treatment times are too slow. Aim to treat at 5 days (ASAP) after fever onset - early treatment is key to reduce risk of heart damage!

Q2: *What's the adverse outcome from Kawasaki Disease, that by spotting it quickly and treating, you're looking to avoid?*

A2: You're looking to diagnose and treat quickly to reduce the likelihood of damage to the coronary arteries. Kawasaki Disease is the leading cause of acquired heart disease in children in the UK.

Numbers to Remember[1]

39% *of treated infants develop coronary artery aneurysms*
19% *of treated children overall develop coronary artery aneurysms*
#1 *cause of acquired heart disease in UK children*

True or FAlse?

A characteristic symptom of Kawasaki Disease essential for diagnosis is peeling of fingers/soles of feet.

FAlse – If skin peeling occurs - and it only appears in some patients - this will only occur after 10-21 days. Never dismiss a case on the basis of skin peeling being absent.

Q3: *How do you make a diagnosis of Kawasaki Disease?*

A3: Making a diagnosis of Kawasaki Disease can be difficult, because there isn't a diagnostic test that we can use at the moment. The textbooks and the Kawasaki Disease guidelines describe a classical set of features in combination with prolonged fever and they are important to know because they can help you make the diagnosis but they're not sufficient to make a diagnosis in everyone who has Kawasaki Disease. And they can distract you from patients who've got Kawasaki Disease who are being missed.

The features are traditionally five days of fever - plus at least four out of five of having conjunctivitis, inflammation of the oral mucosa, adenopathy, rash and inflammation to the hands and feet, typically red and swollen in the early parts of the illness. 14-21 days later on, you can get skin peeling – but if you see this, you've probably missed the acute stage!

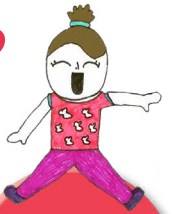
Kawasaki Disease does not fit to a single type. Every patient comes with a slightly different set of symptoms. **Symptoms may appear in series and not all at the same time. Not all children show all symptoms and children often have other symptoms besides**. So, you have to have a high index of suspicion to catch this disease.

True or FAlse?

Kawasaki Disease has no characteristic symptoms

FAlse – The strongest defining symptom which should always trigger suspicion of Kawasaki Disease is a persistent, high unremitting fever for 5 days

Q4: *You must have had a persistent fever for 5 days to consider a diagnosis of Kawasaki Disease – is this true or false?*



Find out the answer

A4: FALSE! The classical description of Kawasaki Disease was to have five days of fever plus certain other features. We know that if you treat Kawasaki Disease earlier, you're more likely to have a good outcome. In parts of the world like Japan where Kawasaki Disease is more common than it is in the UK, the median day of diagnosis is less than five days of fever.

You do not need to wait for five days of fever if you've got strong suspicion of Kawasaki Disease because you can actually start treatment and prevent damage. Do not wait for five days before you feel you're entitled to make a diagnosis!

True or FAlse?

IVIG treatment reduces heart damage from 25% to 5%

FAlse – 19% of all children develop permanent heart damage and 39% infants develop coronary artery aneurysms **despite IVIG,** linked to delayed treatment[1]. Early treatment is critical! And new treatments for Kawasaki Disease are urgently needed.

Q5: *Who is affected by Kawasaki Disease?*

A5: Kawasaki Disease is a disease of children and there is a peak in quite a young age. But it's important to be open to the idea that any child you see coming in with a fever may have Kawasaki Disease. Kawasaki Disease is something that can affect all ages of children, all races of children, boys and girls. There are some differences, but these are not important at the point of making a diagnosis. We see Kawasaki Disease from first weeks of life through to older children, even teenagers.

The BPSU study[1] found that 19% of children with Kawasaki Disease had a diagnosis with an aneurysm or coronary artery damage after the illness. Even more shockingly, in the under ones, the rate of coronary artery damage was 39%, which is incredibly high. And we can really change that by being better able to recognise the disease more quickly and being ready to treat it optimally.

True or FAlse?

Kawasaki Disease rarely causes heart damage

FAlse – In the UK, 28% of affected children have heart damage, 19% have lasting coronary artery aneurysms. 39% of infants develop coronary artery aneurysms[1]. Late treatment is linked to poorer outcomes.

Q6: *What blood tests can be used to support a diagnosis of Kawasaki Disease?*

A6: Kawasaki Disease generally, though, not always, is associated with high CRPs, typically above the 100 milligrams per litre range with changes in blood count, such as neutrophilia. We can also see a low haemoglobin and a low albumin which goes down as the illness sets in.

Platelets can be low in the early part of the disease and then they can get to a high level later on in the disease. None of these things are particular only to Kawasaki Disease but they can be clues to help you think about it.

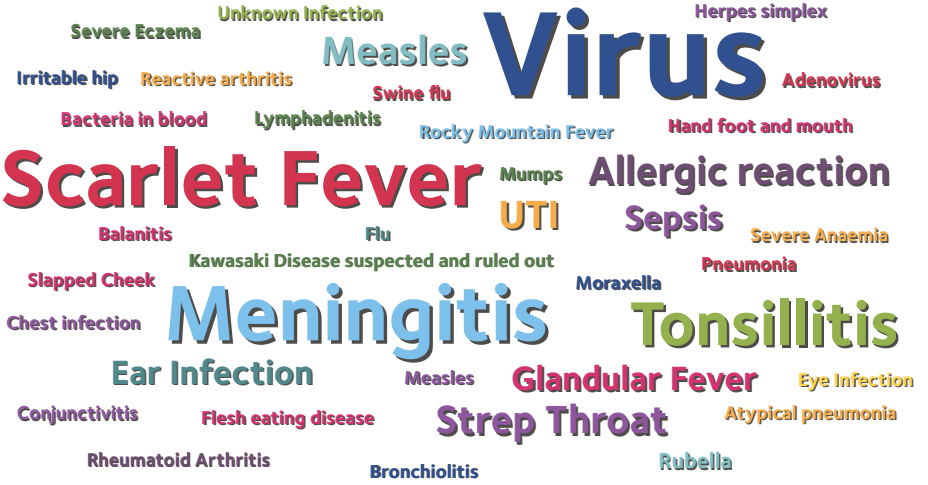
True or FAlse?

Persistent fever plus all 5 symptoms must all be present to confirm a diagnosis of Kawasaki Disease

FAlse – 47%[1] of UK/Ireland cases are incomplete i.e. do not have all symptoms. Kawasaki Disease can be diagnosed with fewer symptoms - not all patients exhibit all symptoms and symptoms can appear in series. If a child presents with persistent fever and 2 or more Kawasaki Disease symptoms, always THINK Kawasaki Disease

Q7: *What are some of the important differential diagnoses that clinicians should consider when a child presents with these features?*

A7: You can think about Kawasaki Disease as a child with a high fever and high inflammation. So, there's a long list of differential diagnoses. In particular, there are a few conditions which actually mimic those classical clinical features of Kawasaki Disease. So, in terms of infections, bacterial infections with Group A streptococcus, or toxic shock syndrome can mimic Kawasaki Disease and there are viral infections that can mimic it too, particularly measles and adenovirus. Plus, there are other inflammatory illnesses.



R McCormack et al Diagnosis Day study 2022.

The above image represents the findings from Societi Foundation research in 2022, exploring the incorrect prior diagnoses families received before getting a correct diagnosis of Kawasaki Disease. The larger the word, the more often this is an incorrect prior diagnosis.

Q8: *How do you differentiate between PIMS-TS and Kawasaki Disease?*

A8: PIMS-TS is paediatric inflammatory multi-system syndrome temporarily associated with SARS-CoV-2. It's a new condition that we've seen following the COVID 19 pandemic where children have presented, among other problems, with persistent fevers, rash, conjunctivitis, abdominal symptoms. So, some similar features to Kawasaki Disease, but there are also distinct features.

On clinical presentations in PIMS-TS there's a prominence of gastrointestinal symptoms. The epidemiology is also slightly different with older age groups being affected in PIMS-TS, usually around 10 to 12 year olds. And research studies looking at gene expression or immunophenotyping have shown that while there are similarities, that actually these two conditions are very different.

True or FAlse?

After coronary artery aneurysms have 'resolved', patients can be fully discharged from care

FAlse – All patients with heart damage which persist beyond the acute phase (even if it 'resolves' later) require lifelong specialist care and are at increased risk of major cardiac events

Q9: *What are the possible cardiac complications from Kawasaki Disease?*

A9: Kawasaki Disease is a vasculitis - an inflammation of blood vessels and particularly medium sized blood vessels. A very important set of medium sized blood vessels are the coronary arteries that give the heart muscle its blood supply. And that is the point at which we are most interested in looking at Kawasaki Disease, but it is not the only set of arteries that can be affected by Kawasaki Disease.

The damage can lead to coronary artery aneurysm formation. The remodelling can later on lead to stenosis and inadequate blood supply to the heart muscle. So coronary arteries are a particular site of concern of Kawasaki Disease, but it affects all areas of the heart muscle, and you can see myocarditis and pericarditis too. And you can also have valvular problems. So, it's a pan cardiac disease. The involvement of the heart, though, is really what drives the need to treat and diagnose Kawasaki Disease quickly. Because the quicker you treat, the less likely you are to get coronary artery damage. And therefore, careful examination of the heart is an essential part of the work-up in Kawasaki Disease.

True or FAlse?

Child is too young / too old for Kawasaki Disease

FAlse – You will see Kawasaki Disease in very young and older children. It can be most severe in infants (under 1yr) and c.25% of those affected are older than 5 years[1].

Q10: *How important is it to get an early echo in the management of Kawasaki Disease?*

A10: Firstly – it is essential to know that you don't need to have an abnormal echocardiogram (or any echo) to make a diagnosis of Kawasaki Disease. You should expect to make a diagnosis, often without having had the benefit of an echo. Secondly, if you do get an echo, and it's normal, it doesn't mean the child hasn't got Kawasaki Disease, it means you're doing well because you're treating before there is visible damage.

An echo should therefore not be seen as an essential part of the diagnostic criteria. However, it's a really important investigation to be done early in Kawasaki Disease, because it does help you seal the diagnosis if you find changes, but more importantly perhaps, it allows you to stratify your Kawasaki Disease patient according to what's going on. If there's significant coronary artery involvement, you may need to be thinking about additional treatments earlier, including anti-inflammatory treatments, and maybe further treatments to prevent blood clotting. So, echo is important early in the disease but shouldn't be relied on for diagnosis.

True or FAlse?

The only lasting damage from Kawasaki Disease is to the heart

FAlse – Kawasaki Disease is a systemic disease and effects can be wide ranging. It can affect hearing, sight, kidneys, joints and cause hydrops of the gallbladder. It can also cause behavioural issues.

Q11: *If you find a cause for an infection in a patient with Kawasaki Disease features, does that mean that they don't have Kawasaki Disease?*

Find out the answer

A11: No! It doesn't mean that they don't have Kawasaki Disease. To the contrary. In fact, we often do find pathogens that can cause disease in patients with Kawasaki Disease symptoms. And it may not be entirely independent - we don't know what the cause of Kawasaki Disease is.

You can have an infection and Kawasaki Disease. And that is often the case - 20% of children or more have an infection and Kawasaki Disease - and you'll need to treat both!

True or FAlse?

Echocardiograms are a useful way to confirm a Kawasaki Disease diagnosis

FAlse – Echo is very useful to confirm heart damage but Kawasaki Disease if treated early, does not always lead to heart damage. Echo can help diagnose an atypical case. Never delay treatment awaiting access to an echo if Kawasaki Disease is suspected

Q12: *What are the treatment options for Kawasaki Disease?*

A12: You should start the patient with treatment with intravenous immunoglobulin – IVIG: 2g/kg, so a long infusion. There's good data to show that this can reduce the risk of aneurysm formation as long as you give it early in the illness. The second treatment, which is also standard, is aspirin. Aspirin is actually given at different dosages at different stages of the disease. High dose aspirin is given early in the disease for its anti-inflammatory effect. Once the inflammation is controlled, aspirin is reduced to an anti-platelet dose. So, all patients get IVIG and aspirin.

There are other things we could also consider giving as a first line treatment. There's particular interest in giving steroids alongside IVIG in the initial treatment. There's been a number of studies of this, particularly in Japan, and indeed there's a trial ongoing in Europe called KD-CAAP and the results are awaited – this trial may help us determine whether or not it goes into the into the textbook as the standard adjunctive treatment at the beginning.

True or FAlse?

There are no known future health risks for patients

FAlse – Patients with lasting cardiac damage are known to be at higher risk of artery stenosis and calcification. Lifetime specialist care is essential. See lifetime cardiac management guidance for clinical follow up regime

Q13: *How would you assess if a patient is responding well to your first line treatment?*

A13: A child with Kawasaki Disease will have a set of clinical features, they'll have abnormal blood tests, they'll probably be very irritable or have fever. There's no one of those things that is better when the child responds to treatment, they all have to be better. This is important! A patient has only responded to first line treatment, if all the clinical features are either better or quickly improving, if the irritability is gone, if the fever has stopped, and if the blood tests are either normal, or on a sharp gradient down towards normal.

If any of those things don't apply, then you need to be thinking about a second line treatment. It's important to know that this isn't a rare situation, c. 20% of patients need to have second line treatment. Act quickly - if you think that there hasn't been a full response to your first line treatment. This is a moment in this child's life, which if you get it wrong, can lead to a lifelong problem.

True or FAlse?

A past patient history of Kawasaki Disease is an irrelevant clinical consideration later in life

FAlse – Adverse cardiac events with atypical presentation can occur in patients with a past history of Kawasaki Disease and this history should always inform clinical care

Q14: *What sort of agents are available for second line treatments?*

A14:

A second line treatment is considered when you still have inflammation. Your goal is shutting off the inflammation. How you do it is probably less important than what you use. Steroids, anti-TNF drugs like infliximab, anti IL-1 drugs like anakinra, and anti T-cell drugs, such as cyclosporine are all used, they've all got trial evidence for their use.

IVIG can also be used (a second dose) but this is expensive - it's also a medicine that's in short supply and it's a blood product. It's potentially preferable to use another medicine with a different mode of action (for example steroids) if the initial IVIG treatment did not fully resolve the inflammation.

True or FAlse?

Kawasaki Disease is very rare, you'll never see it

FAlse – Kawasaki Disease is increasingly common. Cases are doubling every 10 years, globally. In England, hospital admissions for Kawasaki Disease increased fourfold in the decade to 2018. 1,000+ cases will be seen in the UK each year. Please EXPECT to see it and be READY to treat it

Q15: *When discharging a patient with Kawasaki Disease, what needs to be considered?*

A15: An important message for doctors to give their patients is that they should expect to get better. This is a self-limiting illness, and all the nasty aspects of the condition when it first comes including the fever, should get better. It may take some time, but they will get better.

Also – think about immunisations. IVIG can impact on how well you respond to vaccines, and it's recommended that you delaying live vaccines for six months after IVIG. It's also recommended that subunit vaccines are delayed for a few months after IVIG.

Immunosuppressive drugs (if given) can have an impact for a few months until they've left the patients system, in terms of susceptibility to for instance, measles, and varicella.

Essential - before someone goes home after Kawasaki Disease, there must be robust cardiology follow up in place. That's the cornerstone of good after Kawasaki care is to make sure that the heart is being looked at with an echo at least, normally in an uncomplicated Kawasaki case, at two weeks and six weeks and then with follow up to at least six months or a year before it's possible to discharge the child – or refer on, where there is severe heart damage, for long term cardiac follow-up.

Societi Foundation have produced 2 helpful leaflets which you can give to your patients too - scan the QR codes below for the *Family and carer guide to Kawasaki Disease* and *Long-term issues* leaflet.

Family and carer guide to Kawasaki Disease

Access

Long-term issues leaflet

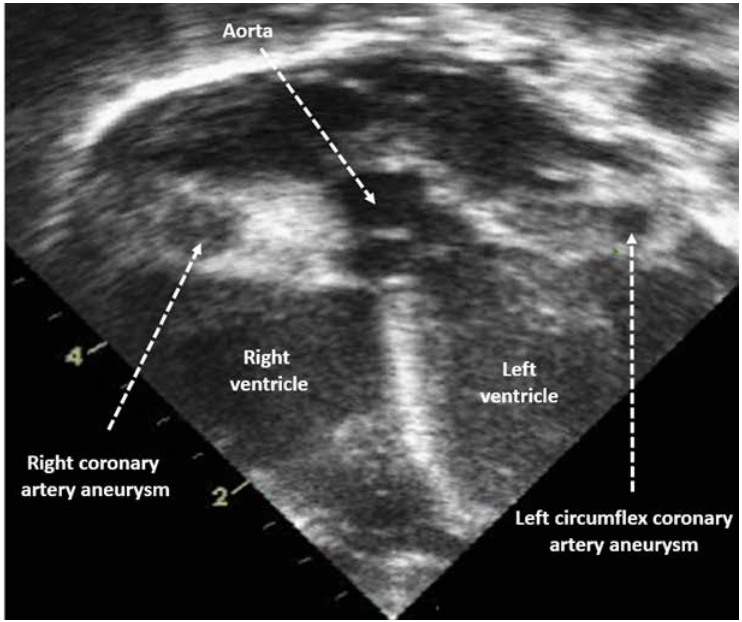
Access

Ready for a challenge...?

Are you ready for a stretch?! On the following pages we've included a few more questions to really put you through your paces! We hope you enjoy working out these tricky Kawasaki Disease questions!

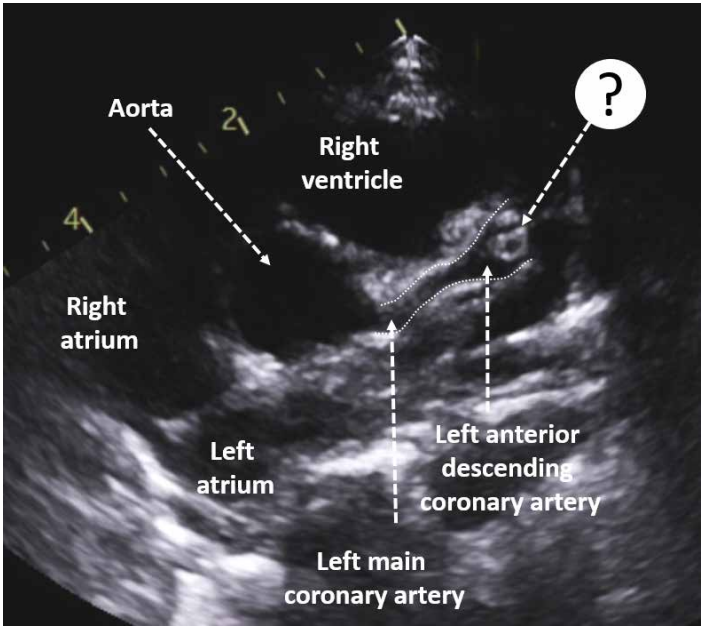
Q16: *Which echo view is the easiest and most routine view for imaging the proximal coronary arteries?*

A16: The *parasternal short axis view* is the easiest and most routine view for imaging the proximal coronary arteries. However, don't forget to use all the other views to see the coronaries in different planes. In addition to parasternal views, apical and subcostal views may provide valuable information, especially about the mid- and distal coronary artery segments, and should always be part of routine echocardiographic examination. In some patients, quality imaging can only be achieved with the use of sedation, especially in young children. Coronary CT angiography may be required in patients with poor acoustic "windows".



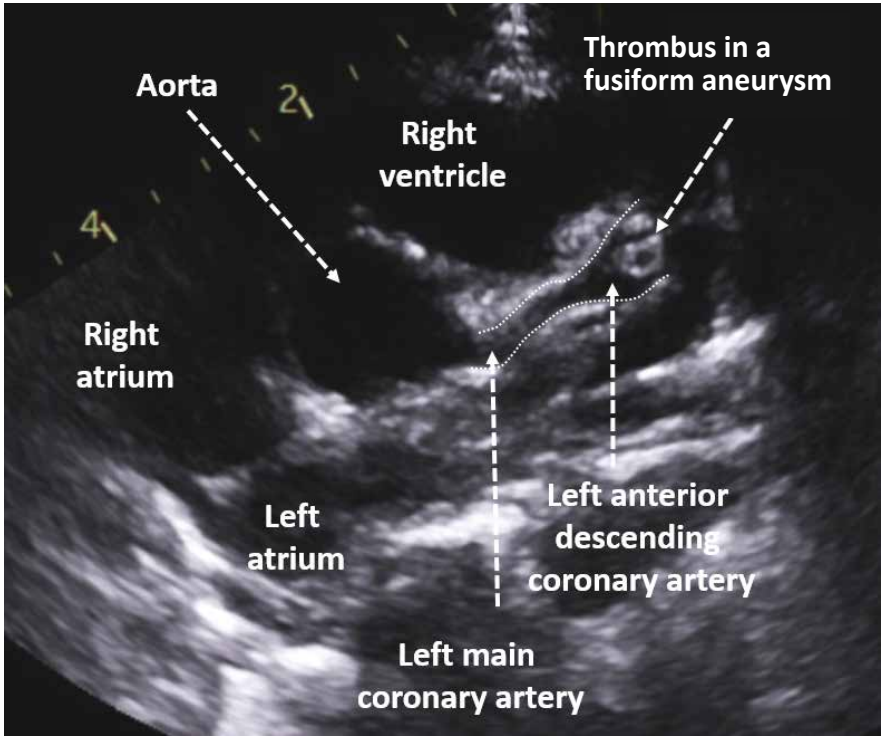
Courtesy: Kucera F
Personal library

Q17: *Which Kawasaki Disease features are shown?*



Courtesy: Kucera F
Personal library

A17: When reviewing findings from echocardiography, as well as considering size and overall appearance of the coronary arteries, it is also important to look for the possible presence of coronary thrombi. This example demonstrates a thrombus in a fusiform aneurysm of the left anterior descending coronary artery.



Courtesy: Kucera F, Personal library

Q18: *What features may suggest a patient could be at high risk of developing coronary artery aneurysms?*

A18: There are no firm and fast criteria here - and as 28%[1] of all children develop some heart damage, it's reasonable to consider *any child with Kawasaki Disease as being at high risk.*

Research is underway to find better adjunctive treatments which could become standard in the future, such as the KD-CAAP European trial looking at whether adding in corticosteroids to initial treatment reduces the number of children who go on to develop coronary artery aneurysms.

In the absence of a definitive patient risk assessment method for children of European descent, what we know from observation is that high risk patients can be those who:

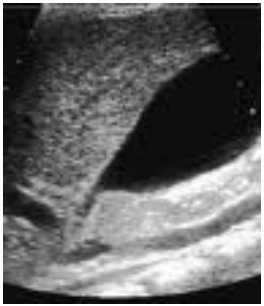
1. Have been treated with IVIG and this first line treatment has failed
2. Are very young - less than 12 months old
3. Have few clinical features
4. Are being treated later than five days following onset of fever
5. Have severe inflammation, with very high CRP, low albumin and anaemia
6. Have features of Hemophagocytic Lymphohistiocytosis (HLH) or shock
7. Already have evolving coronary artery or peripheral artery aneurysms/ changes

Q19: *What other signs and symptoms can you look for as clues, to help you make a diagnosis of Kawasaki Disease?*

A19: Irritability – *irritability* – irritability! Remember TEMPERS! Children with Kawasaki Disease are characteristically and disproportionately irritable, much more so than you'd expect to see in a febrile child with, say, common viral illness.

Also look out for:

- Perineal rash
- BCG scar inflammation
- Diarrhoea / abdominal pain
- Aseptic meningitis
- Urethritis
- Uveitis
- Hydrops of gallbladder



Hydrops of gallbladder
Courtesy Tulloh R, Personal library

Remember TEMPERS

Children with **Kawasaki Disease** *are characteristically irritable!*

If a child has a **PERSISTENT FEVER** *& two or more of these symptoms*
THINK Kawasaki Disease!

T – **T**emperature – **Persistent high fever**

E – **E**rythema – reddened hands and feet with swelling

M – **M**outh – dry, sore mouth, cracked lips 'strawberry tongue

P – **P**ace – **treat early** to reduce potential heart damage

E – **E**yes – bloodshot, non-sticky conjunctivitis

R – **R**ash

S – **S**wollen glands in neck, often just one side

Q20: *What are the consequences of diagnosis and treatment delay in Kawasaki Disease?*

A20:

Too many children currently experience DELAY in diagnosis and treatment! In the UK, children being diagnosed on average at 7.8 days after fever onset – this is TOO LATE!

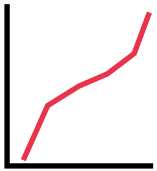
Kawasaki Disease is a medical emergency – and treatment should be started urgently in any child who is suspected of having Kawasaki Disease.

The *adverse consequences of delay include*[1]:

- Children treated late have increasing risk of cardiac damage
- Risk increases proportionately with increasing delay
- 28% children have some heart damage
- 39% infants develop coronary artery aneurysms
- 19% all children affected develop coronary artery aneurysms

These patients – need LIFELONG specialist cardiac care
These patients – increased risk of major cardiac events in later life
These patients – increased risk of sudden death

Kawasaki Disease is increasingly common



Hospital admissions are rising: doubling every 10 years

EXPECT *to see it,*
BE READY *to treat it*

Thank you...

Phew! That's it! How did you do? Brilliantly we hope!

And we really hope too that you've enjoyed our *little book of Kawasaki Disease*. Our goal, which we know you will share, is to get Kawasaki Disease really well known, so we can reduce the number of children who go on to suffer serious heart damage from Kawasaki Disease.

Armed with the knowledge this little book contains, you're brilliantly well placed to spot it, quickly, treat it urgently - and protect tiny hearts from serious harm. Thank you!

Get in touch!

If you have any feedback or would like to get involved in our work, would like more copies of this booklet - or for absolutely anything else to do with Kawasaki Disease, please get in touch - *info@societi.co.uk or fill out our contact form here:*

Contact us

[1] BPSU Kawasaki disease: a prospective population survey in the UK and Ireland from 2013 to 2015, Professor R Tulloh et al

Many of the questions in this booklet are taken from our RCPCH endorsed film *Acute Kawasaki Disease - an expert-led discussion*. Just click the button below to watch it:

Access

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Royal College of Paediatrics and Child Health
Leading the way in Children's Health

Randal
Charitable Foundation

Funding generously donated by the **Randal Charitable Foundation** made the production of these resources possible – powering our work to protect tiny hearts.

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The UK Foundation for Kawasaki Disease
www.societi.org.uk
info@societi.co.uk