Kawasaki Disease
resource pack

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

...faster diagnosis and treatment can change that!

societi
The UK Foundation for Kawasaki Disease

societi.org.uk

Welcome to your **Kawasaki Disease** *resource pack*

Kawasaki Disease is the leading cause of acquired heart disease in children in the western world. Increasingly common, there are currently around 1,000 hospital admissions for Kawasaki Disease in the UK every year. Low awareness levels amongst the public and clinicians alike means Kawasaki Disease often gets initially misdiagnosed leading to delays in treatment and increased risk of heart damage in children.

This resource pack is intended as a learning resource for clinicians to help identify Kawasaki Disease and understand the issues surrounding it.

Included in this Kawasaki Disease resource pack are the following:

- **KD-CAAP clinical trial** - a brief introduction to the KD-CAAP clinical trial with access to further information and useful patient resources.
- **Spotting Zebras - Overcoming the challenges of Kawasaki Disease diagnosis** - A clinician information guide produced based on a RCPCH training webinar, given by Professor Robert Tulloh and Professor Paul Brogan.
- **NICE guidance for fever in under 5s** - The November 2019 guidance is based on the evidence reviewed by, and experience of, the appointed NICE committee. The updated guidance urges doctors to be aware of the possibility of Kawasaki Disease in children with fever that has lasted 5 days or longer.
- **Clinician Q&A** - Following many of the discussions we have had with clinicians during events, conferences and webinars, we have put together some frequently asked questions which we hope you find helpful.
- **Myths and Facts sheet** - This "Myths and Facts" summary has been prepared for clinicians with input from Professor Robert Tulloh, internationally recognised expert in Kawasaki Disease.
- **Lifetime cardiovascular management of patients with previous Kawasaki Disease** - This provides guidance on the long-term management of patients who have vascular complications of Kawasaki Disease and guidance on the emergency management of acute coronary complications.
- **Clinician & general awareness posters** - There are two different posters included in this pack - one designed as a clinic resource and a Kawasaki Disease awareness poster, intended as a waiting room resource for patients.

Kawasaki Disease *resource links*

As well as the information included within this pack, we have some really useful Kawasaki Disease learning resources that are freely accessible online. Just click the buttons below to access these.

- **RCGP Kawasaki Disease e-learning course**
  Accessible via the RCGP website, this course explores Kawasaki Disease, focusing on the need to consider it as a diagnosis and how essential it is to achieve early treatment.

- **Kawasaki Disease – Acute Management – An expert-led discussion** - Created by doctors for doctors as we work to get Kawasaki Disease known, Dr Jethro Herberg and Dr Harsita Patel from Imperial College London discuss how to spot and treat Kawasaki Disease in this expert led training film.

- **Kawasaki Disease – Four Family Perspectives**
  Watch our film to hear about the experiences of four different families as they tell their Kawasaki Disease stories.

- **Time to 'Think Kawasaki Disease' RCPCH-BPSU webinar** - This RCPCH webinar given by Professor Robert Tulloh and Professor Paul Brogan, provides an excellent training session for staff teams. The information in our Spotting Zebras booklet, included in this pack is based on the information within the webinar.

- **KNOW Kawasaki Disease awareness animation** - Watch our animation, created to raise awareness of Kawasaki Disease. Just a 90 second video, starring our much loved Societi Kids, is all it takes to better understand this serious childhood illness that is always a medical emergency - and that everyone needs to know.

- **Societi's website area 'For Clinicians'** - Societi has gathered together learning information and resources for clinicians, links to Kawasaki Disease research and Kawasaki Disease management resources - all in one handy place on our website, www.societi.org.uk.

The KD-CAAP Clinical Trial

Kawasaki Disease Coronary Artery Aneurysm Prevention trial, or KD-CAAP is a phase III multi-centre, randomised, open-label, blinded endpoint assessed, trial of corticosteroids plus intravenous immunoglobulin (IVIG) and aspirin, versus IVIG and aspirin for prevention of coronary artery aneurysms (CAA) in Kawasaki Disease.

Societi is patient and public involvement (PPI) lead and co-investigator for the KD-CAAP trial which is the single greatest opportunity for transformation in patient care, improving outcomes in Kawasaki Disease, in a generation.

What is the aim of the KD-CAAP trial?

The aim of the KD-CAAP trial is to determine whether adding immediate corticosteroid treatment to standard of care IVIG and aspirin will reduce coronary artery aneurysm (CAA) rates in unselected Kawasaki Disease patients across Europe compared with IVIG and aspirin alone.

Why do we need a clinical trial?

A number of recent studies conducted in different European countries (UK, Sweden, and Germany), Russia, and the United States have recently demonstrated alarmingly high rates of coronary complications despite IVIG. Coronary artery aneurysm (CAA) rates ranged from 16% in the Swedish study (45% in infants under 12 months), to as high as 42% in younger children in the German survey. In the UK, a recent survey (2013-2015) suggested that 19% of children with Kawasaki Disease still developed CAA despite IVIG; and, even more worryingly in that survey, 39% of patients under the age of 1 year developed CAA despite IVIG [7]. These high complication rates now emphasise the need for an urgent reappraisal of IVIG and aspirin as the primary therapeutic agents for Kawasaki Disease.

We have recently published evidence-based, consensus European guidelines for the diagnosis and treatment of Kawasaki Disease and in doing so clearly observed:

- Higher CAA rates than previously considered to be associated with IVIG-treated Kawasaki Disease;
- Important evidence gaps regarding lack of an appropriate clinical tool to stratify patients at highest risk of CAA outside of Japan, and hence who to target for more aggressive treatment; and
- Significant equipoise among the paediatric community across Europe regarding the use of adjunctive treatments for unselected Kawasaki Disease cases.

KD-CAAP | MRC Medical Research Council | Smarter Studies Global Impact Better Health | UCL | conect 4children COLLABORATIVE NETWORK FOR EUROPEAN CLINICAL TRIALS FOR CHILDREN | societi.co.uk

These observations have been important drivers for a trial to improve Kawasaki Disease outcomes across Europe. The KD-CAAP trial is a multi-centre randomised, controlled, open-label, blinded endpoint assessed, trial to explore the efficacy and safety of adjunctive corticosteroid therapy combined with IVIG/aspirin, versus IVIG/aspirin alone in unselected Kawasaki Disease cases across Europe.

Why Corticosteroids?

Corticosteroids are an effective treatment for virtually all forms of vasculitis, but they have not been adopted as first-line treatment of unselected Kawasaki Disease cases, for which there remains significant equipoise. Increasingly compelling evidence summarised above from randomised controlled trials and meta-analyses supports corticosteroid use as primary adjunctive treatment for patients with severe Kawasaki Disease, particularly for Japanese patients with a Kobayashi score ≥5, and for whom CAA risk is 20-30% despite IVIG. This does not, however, resolve the ongoing debate about which Kawasaki Disease patients should be considered as "severe" outside of Japan, since the Kobayashi score and other clinical severity-scoring systems have poor predictive value in non-Japanese patients. Given however, the aforementioned high CAA complication rates seen across Europe (16-45%), all Kawasaki Disease patients are arguably at high-risk of CAA despite IVIG, and could therefore potentially benefit from adjunctive corticosteroids as primary treatment for Kawasaki Disease. Therefore there remains significant equipoise regarding the use of corticosteroids as primary treatment combined with IVIG for all patients, i.e. not just the most severe cases.

Where can I find out more about KD-CAAP?

Access

You can find out more about the KD-CAAP clinical trial by visiting the UCL KD-CAAP website here

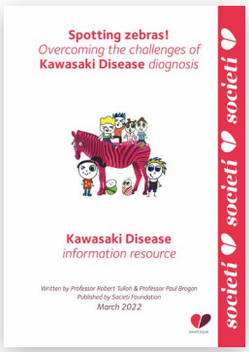
Access

You can also visit the KD-CAAP web pages here

KD-CAAP | MRC Medical Research Council | Smarter Studies Global Impact Better Health | UCL | conect 4children COLLABORATIVE NETWORK FOR EUROPEAN CLINICAL TRIALS FOR CHILDREN | societi.co.uk

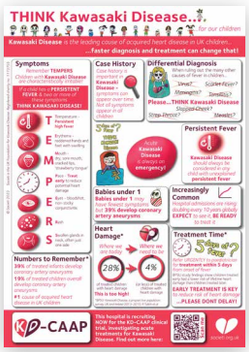
The following resources for the KD-CAAP Clinical Trial are available:

Spotting Zebras! Overcoming the challenges of Kawasaki Disease Diagnosis - available within this pack.



Kawasaki Disease - available within this pack.

Clinician information poster- available within this pack.



Time to 'Think Kawasaki Disease' RCPCH-BPSU webinar

Access

RCGP e-learning course

Access

KD-CAAP | MRC Medical Research Council | Smarter Studies Global Impact Better Health | UCL | conect 4children COLLABORATIVE NETWORK FOR EUROPEAN CLINICAL TRIALS FOR CHILDREN | societi.co.uk

The following patient/parent resources for the KD-CAAP Clinical Trial are available:

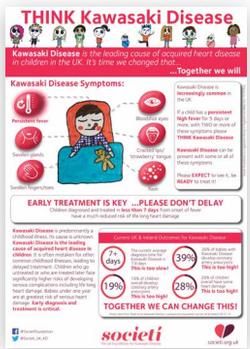
RCPCH endorsed TEMPERS mnemonic awareness leaflet - available to download

Access

Long term issues leaflet for parents and carers - available to download

Access

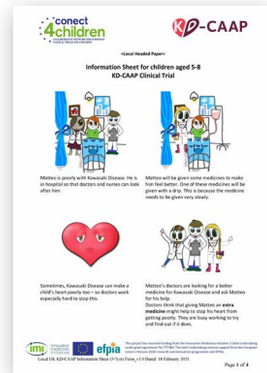
General awareness poster- available within this pack.



Family information portal

Access

Assent/consent forms - available at participating KD-CAAP centres



My Societi Youth Portal

Access

KD-CAAP | MRC Medical Research Council | Smarter Studies Global Impact Better Health | UCL | conect 4children COLLABORATIVE NETWORK FOR EUROPEAN CLINICAL TRIALS FOR CHILDREN | societi.co.uk

Spotting zebras!
Overcoming the challenges of **Kawasaki Disease** *diagnosis*

Kawasaki Disease
clinician information guide

Written by Professor Robert Tulloh, Professor Paul Brogan & Dr Filip Kucera

Published by Societi Foundation

November 2022

If a child has a **PERSISTENT FEVER** *and two or more of these symptoms*

THINK KAWASAKI DISEASE

Persistent fever

Cracked lips/ ‘strawberry’ tongue

Rash

Swollen or red fingers/toes

Bloodshot eyes

Swollen glands

This is an information pack prepared to support a workshop session at RCPCH conference. It has been produced based on a RCPCH training webinar given by Professor Robert Tulloh and Professor Paul Brogan. We’d actively encourage you to watch the webinar which provides an excellent training session for staff teams.
To watch the webinar, please visit here or click the access button

Access

Spotting Zebras contents

Time to 'THINK Kawasaki Disease'

Thank you for your interest in Kawasaki Disease!

Kawasaki Disease is the leading cause of acquired heart disease in children in the western world – outcomes have not improved in 3 decades. It's time we changed that!

By the end of this booklet and workshop session, you will:

- **Understand diagnosis** considerations – including differences of presentation and when to **THINK Kawasaki Disease**
- Have **knowledge of differential diagnosis** issues and red flags for Kawasaki Disease
- Have **knowledge of the urgency** with which the disease needs to be treated – and the confidence to consider Kawasaki Disease
- Have **awareness of disease severity** and the criticality of EARLY treatment
- **Abandon prevailing 'myths'** around this disease which are hampering treatment / adversely impacting children affected

Persistent fever

Cracked lips/ 'strawberry' tongue

Rash

Swollen or red fingers/toes

Bloodshot eyes

Swollen glands

Kawasaki Disease Epidemiology

Epidemiology

- Medium vessel vasculitis
- Predilection for coronary arteries
- World wide distribution
- Male preponderance 2:1
- Commoner in children of Black African descent in the UK
- Some seasonality and occasional epidemics – UK winter/spring peak

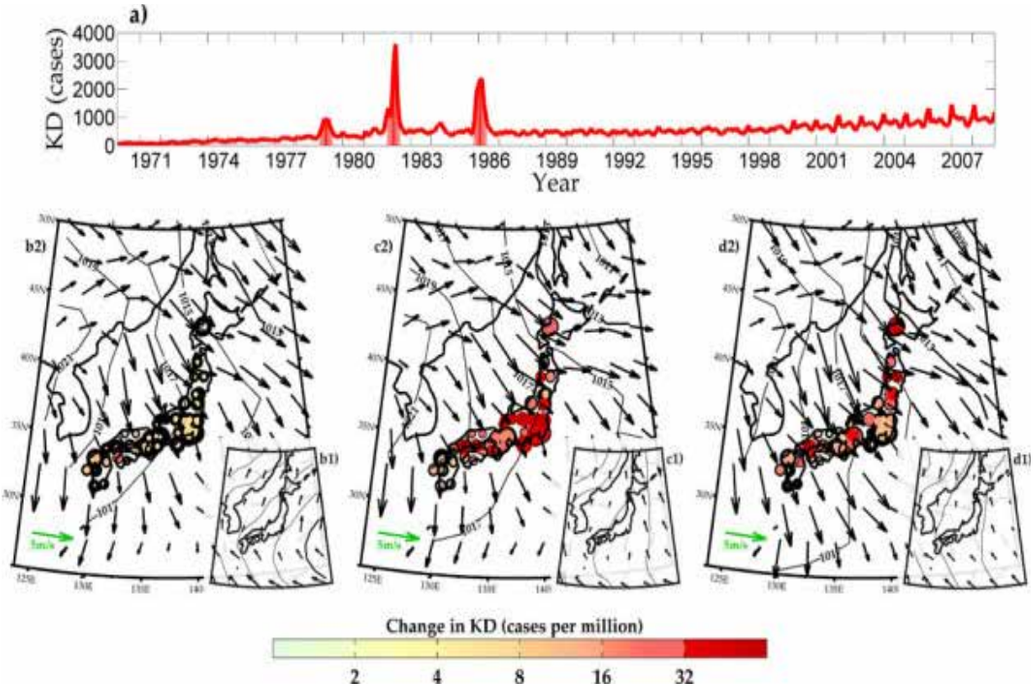
- Japan[1] 20141: 322/100,000 (<5 years)
- South Korea: 134.4/100,000
- USA: 19-25/100,000
- Skane, Sweden: 5.5/100,000
- **UK 4.55 (BPSU) - 9.1 (THIN) /100,000[2]**
- **Fourfold increase in hospital admissions (England) 2006-2018[3]**

1. 23rd National survey; Makino et al 2018 2. BPSU - Tulloh RM et al Arch Dis Child 2019;104:640-646 / THIN – BJGP 2016;66:e271-6
3. Societi Foundation FOI 2019

Infection or toxin?

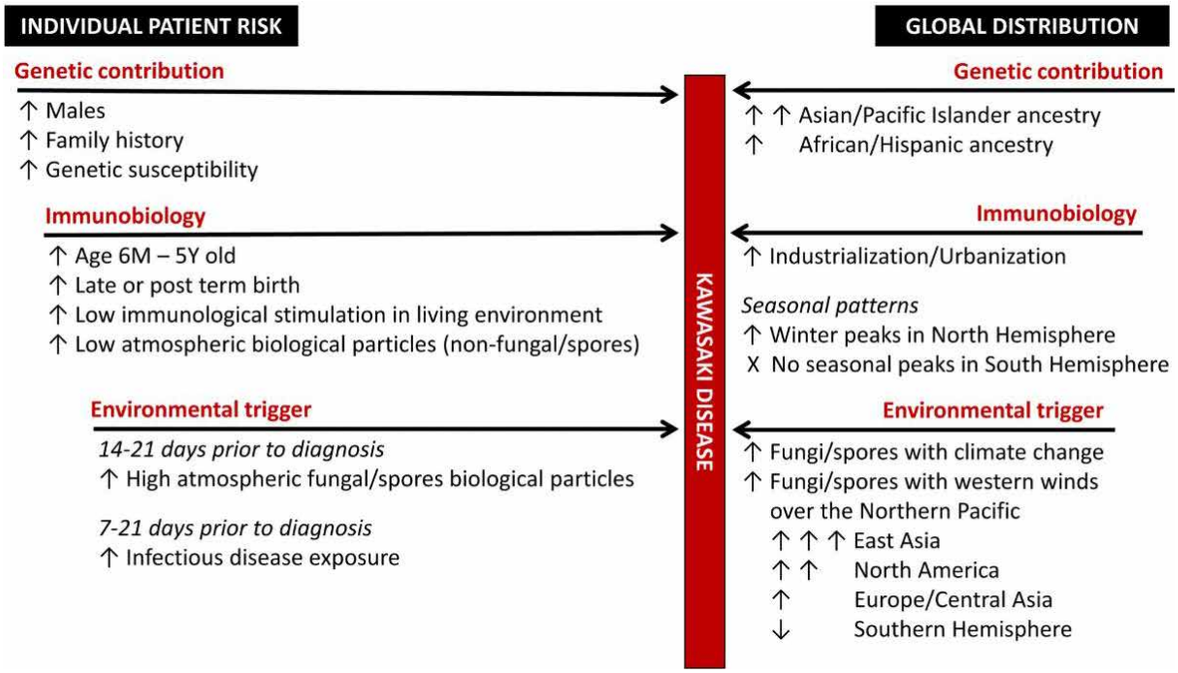
Infection or toxin?

- **Blowing in the wind?** A theory
- **Seasonality** - Kawasaki Disease is somewhat seasonal
- **Age of onset** - 0-5 years but 25% patients are more than 5 years old
- **No single infectious cause found** - research is ongoing
- Wind patterns confirm wind correlates with season variation I
- GWAS Variants - TGFB2 SMAD3
- Polymorphism in FCGR2A receptor - immune activation



Rodo X PNAS 2014;111:795 Khor CC Nature Genetics 2011 13;43:1241-6

Environmental epidemiology



Environmental epidemiology of Kawasaki disease: Linking disease etiology, pathogenesis and global distribution

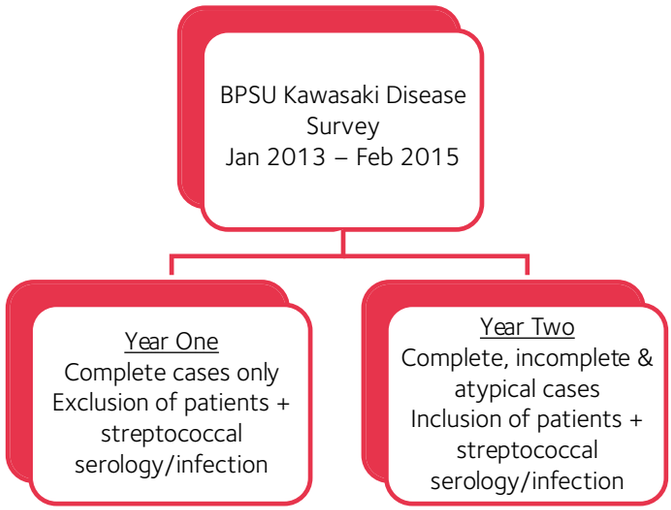
Cedric Manlhiot, Brigitte Mueller, Sunita O'Shea, Haris Majeed, Bailey Bernknopf, Michael Labelle, Katherine V. Westcott, Heming Bai, Nita Chahal, Catherine S. Birken, Rae S. M. Yeung, Brian W. McCrindle

Approach – UK & Ireland BPSU Survey

UK BPSU Survey 2013 - 2015:

Approach taken

- Incidence: demographics (sex, age, ethnicity)
- Clinical Presentation: Link between symptoms and presentation
- Clinical Management: What acute treatment is being given?
- Outcome: What are the complications at 30 days?



BPSU - Tulloh RM et al Arch Dis Child 2019;104:640-646

Results - demographics

Demographics:

- 601 children notified
  - 10 not KD
  - 37 duplicates
- 553 included in study
  - 215 girls, 323 boys
  - F:M 1:1.5
  - 2m-15yrs age range

Age (yrs)	No. Children
Less than 5	422
Older than 5	131
Total	553

Type	No. Children
Complete	389
Incomplete	162
Post mortem	2

Results - Ethnicity

Ethnicity:

The number of Black and mixed White & Black, and other is higher than expected (only 7% of UK population is in these ethnic groups).

Ethnic group	No. Children	% of reported
White	356	68%
Black (African+Caribbean)	47	9%
Indian Subcontinent	41	8%
Chinese	16	3%
Japanese	4	1%
Mixed	38	7%
Other	22	4%
TOTAL	553	

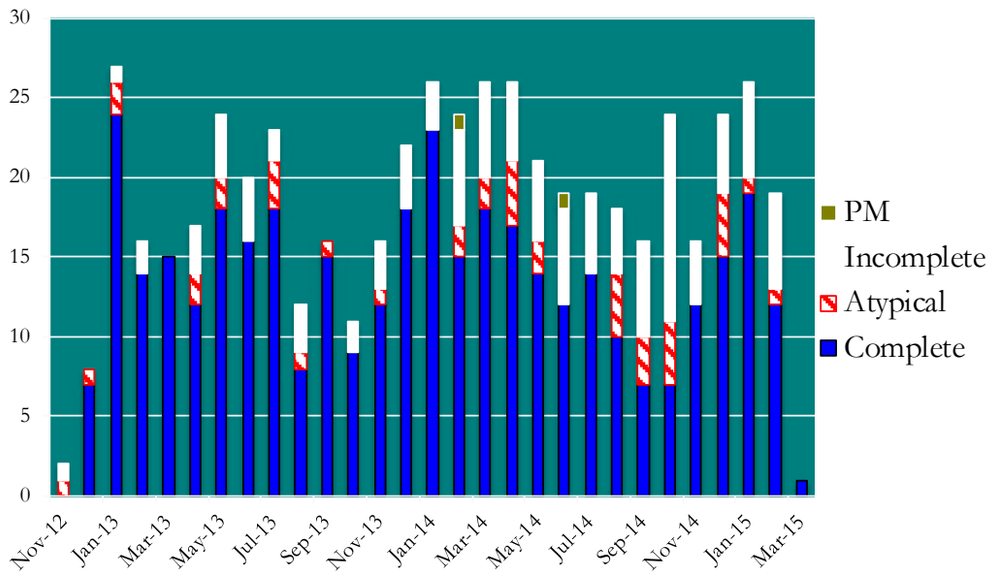
It is noted that we found an excess representation of Black Africans or mixed Black and White ethnicity in our population. If you look at the seasonality of presentation, the cases were more likely to present in January and in the summer months each year, possibly associated the incidence with prevailing weather patterns.

BPSU - Tulloh RM et al Arch Dis Child 2019;104:640-646

Results - CAA and seasonality

Cardiac sequelae:

	CAA+	CAA-	Total
Dec - May	78	239	321
June - Nov	49	160	215
Total	127	399	553



BPSU - Tulloh RM et al Arch Dis Child 2019;104:640-646

Results - regionality

Regionality:

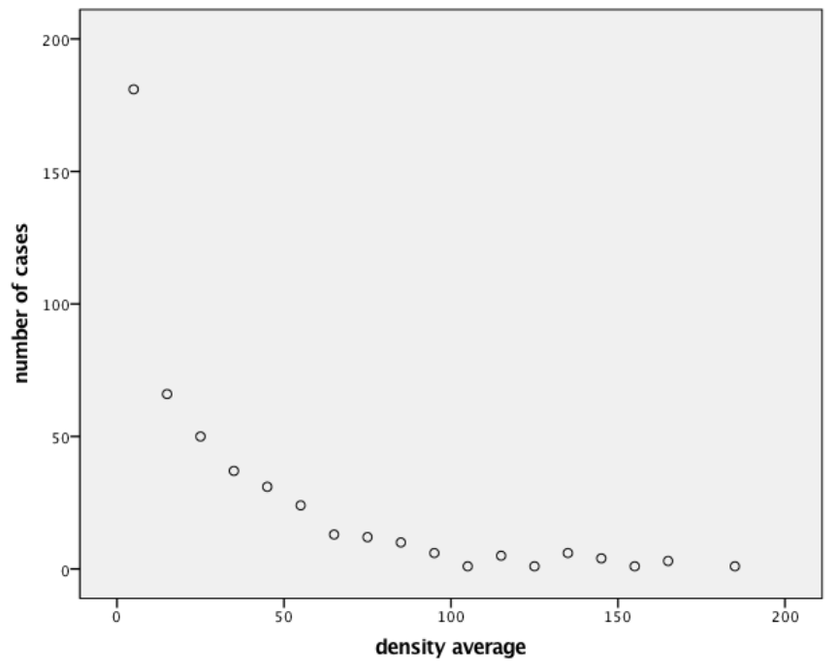
Country/Region	No. cases	Region	No. cases
Scotland	33	West Midlands	41
Eire	31	East Midlands	27
Wales	37	East of England	51
Northern Ireland	12	London	84
North East Region	16	South East	78
Yorkshire and Humberside	34	South West, Inc. C.I.	53
North West/IoM	53	**Total**	**553**

Kawasaki Disease is seen in all areas

BPSU - Tulloh RM et al Arch Dis Child 2019;104:640-646

Inverse relationship to urbanicity

Inversely related to urbanicity per sq Km:



Very strong relationship with rurality - higher incidence in children from rural areas

BPSU - Tulloh RM et al Arch Dis Child 2019;104:640-646

Diagnosis

Diagnosis:

- 441 (80%) saw a GP between the onset and admission
- Median time from first symptom to GP was 2 dy (0-27)
- Median time from GP to admission was 1 dy (0–32)
- Median time from onset to diagnosis was 7 dy (0-36)
- Median time admission to diagnosis was 1 dy (0-25)

Diagnosis	CAA+	CAA-	Total
< 8 days	62 (48%)	231 (58%)	298
8-14 days	45 (36%)	105 (26%)	151
15+days	16 (13%)	49 (12%)	66
Total	127	399	553

BPSU - Tulloh RM et al Arch Dis Child 2019;104:640-646

Results - key findings

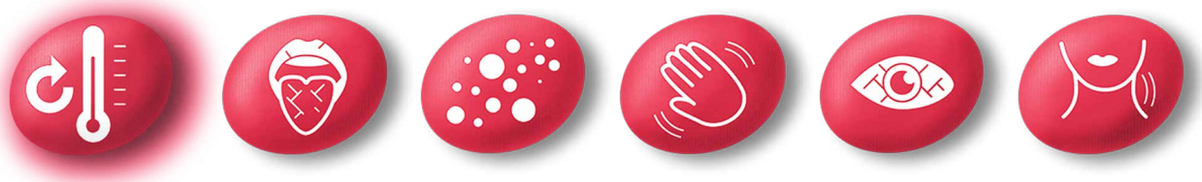
UK BPSU Survey 2013 - 2015:

- 47% cases were incomplete Kawasaki Disease in infants
- 28% all cases were incomplete Kawasaki Disease

BE ALERT to incomplete Kawasaki Disease - If you see a child with persistent fever plus 2 or more symptoms **- THINK Kawasaki Disease!**

EARLY treatment is critical - DON'T DELAY

- 39 % infants develop coronary artery aneurysms
- 28% all children have some heart complications
- 19% of all children develop coronary artery aneurysms
- More common in rural areas
- Higher incidence in black and minority ethnic groups
- Seen more often in winter / spring
- Increasing delay in treatment = increasing risk of cardiac complications

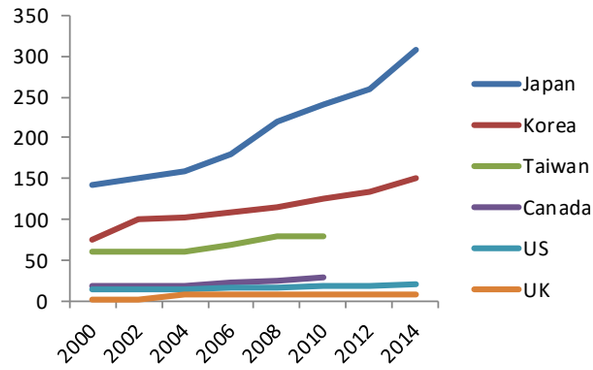


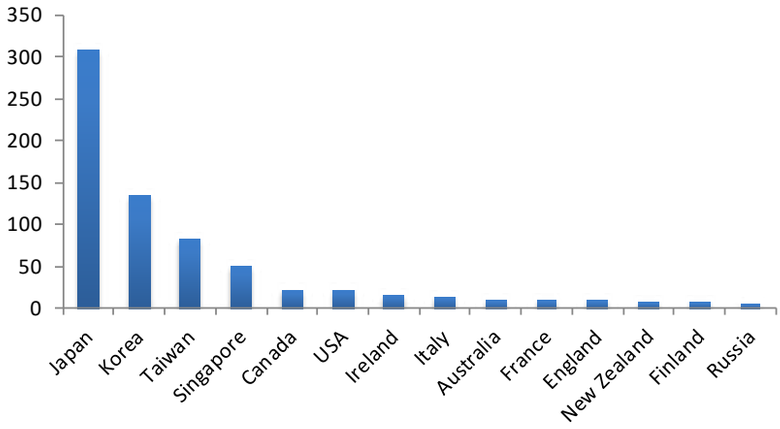
Persistent fever | **Cracked lips/ 'strawberry' tongue** | **Rash** | **Swollen or red fingers/ toes** | **Bloodshot eyes** | **Swollen glands**

Incidence doubling every 10 years

Incidence:

- Increasing worldwide – graphs show incidence per 100,000 children <5 years
- Commonest cause of acquired heart disease in children - more common than rheumatic fever acquired heart disease
- Up to 47% cases in UK/Ireland infants under 1yr are incomplete
- 28% of all cases in UK/Ireland are incomplete

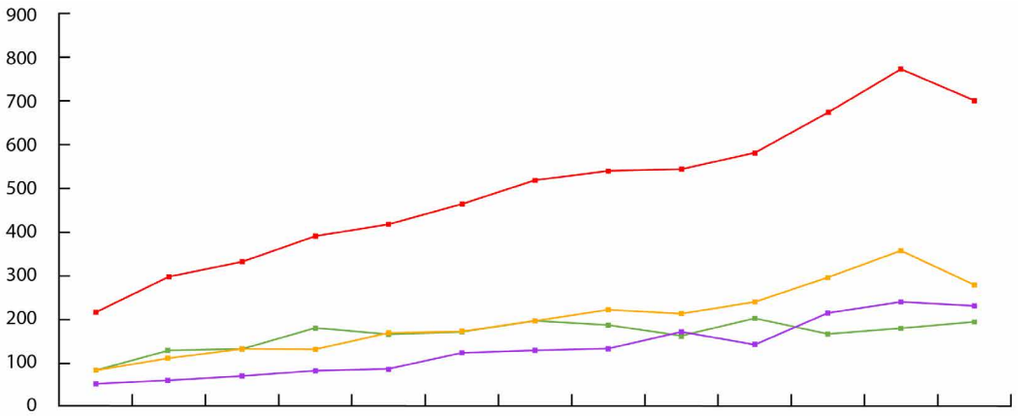




Makino N Pediatrics 2018 epub Hall E, Tulloh RM Br J Gp 2016;66:271

Increasing admissions – England (2006–2018)

Societi data shows rapidly rising number of hospital admissions in England



	2006	2007	2008	2009	2010	2011	2012	2013	2014	2015	2016	2017	2018
Female	51	59	69	81	85	122	128	132	170	141	213	239	230
Male	82	110	131	130	168	171	195	221	212	239	295	356	278
Unknown	82	128	131	179	164	170	195	186	161	201	165	178	193
Total	215	297	331	390	417	463	518	539	543	581	673	773	701

McCormack R Societi Foundation, Freedom of information request July 2018

Clinical features

"Classical" Kawasaki Disease is currently diagnosed with fever plus any 4 of these symptoms

BUT! Fever of >5 days duration PLUS 2 or more features - THINK Kawasaki Disease:

Persistent fever:

Persistent high fever. Can be unremitting with anti-pyretics, may be spiking and can come and go. Parental/carer reports of very high fever should form part of the case history.

Polymorphous rash:

Rash can take may 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' - whilst often shown in images to be bright red, may 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. Area of pallor adjacent to the iris known as limbic sparing, typical of the conjuctival 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 - text books often refer to specific sizes (who measures these?!) If tender and prominent consider Kawasaki Disease.

Do not wait for 5 days of fever if you have suspicion of Kawasaki Disease. **TREAT!**

Symptoms may appear in series and not all at the same time.

BE ALERT to incomplete Kawasaki Disease - If you see a child with persistent fever plus 2 or more symptoms -

THINK Kawasaki Disease!

More clues to **Kawasaki Disease**

More clues:

- Perineal rash
- BCG scar inflammation

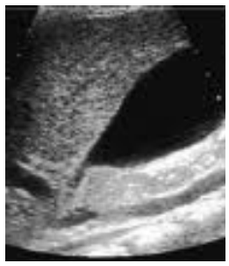
Cardiac clues:

Echo Findings
N.B. Do not delay treatment pending echo findings!

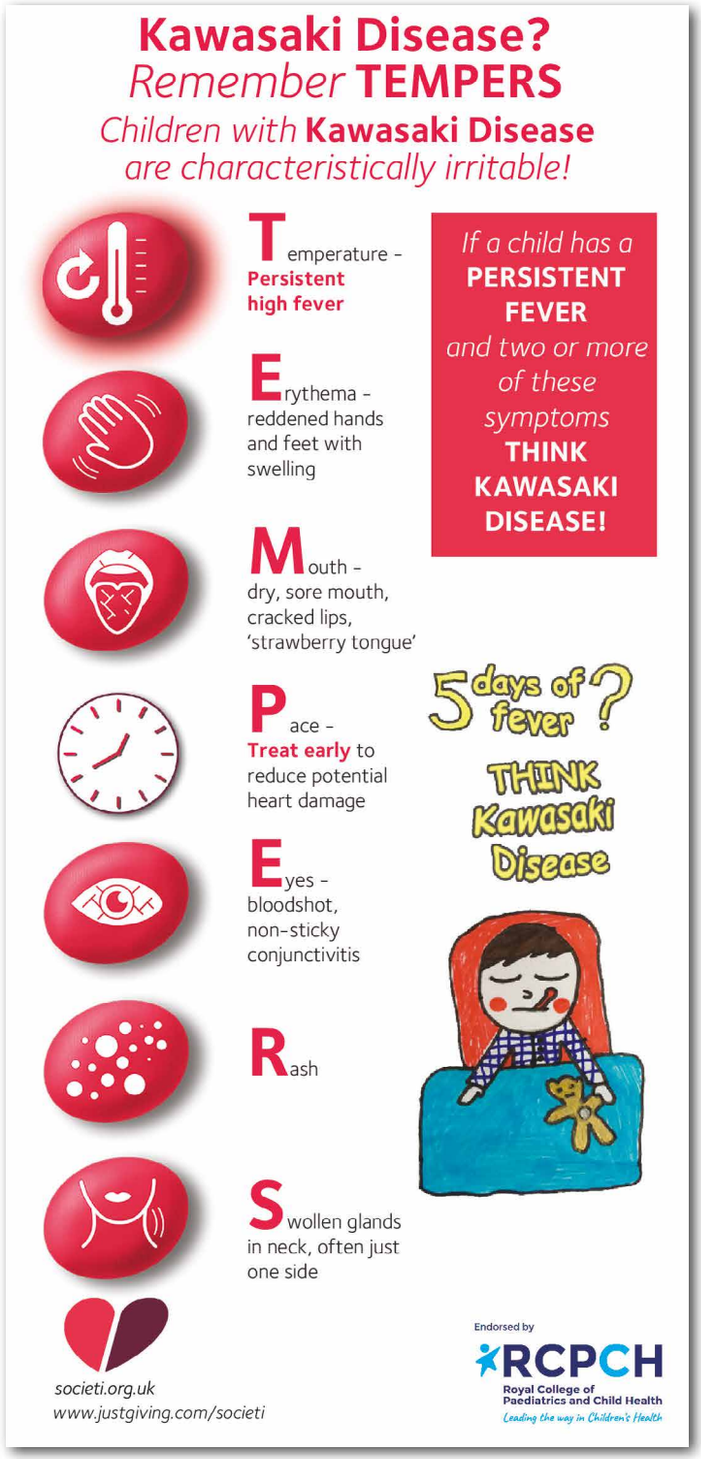
- Inflammation of coronary arteries and coronary artery aneurysms
- Pericarditis
- Valvulitis
- Myocarditis

Other clues:

- Irritability – irritability – irritability! Remember TEMPERS! Children with Kawasaki Disease are characteristically and disproportionately irritable
- Diarrhoea / abdominal pain
- Aseptic meningitis
- Urethritis
- Uveitis
- Hydrops of gallbladder



Hydrops of gallbladder



Later clues to diagnosis

Later clues:

Skin peeling – sub acute feature: 10 – 25 days after fever onset

N.B. Absence of skin peeling is NEVER a basis on which to dismiss a diagnosis of Kawasaki Disease!

Skin peeling is a late sign, part of the healing process of Kawasaki Disease.

Presentation considerations

Presentation considerations:

- Infant – may present with persistent fever and rash – and few other features. Features may be mild or unapparent. Early diagnosis of Kawasaki Disease in this age group is essential as 39% develop CAA
- Young child – remember sequential presentation of features – full and detailed clinical history is critical
- Older child – this group tends to experience delays in diagnosis. Clinical presentation may also include vomiting, diarrhoea, sore throat
- 47% of UK & Ireland infant cases present as incomplete Kawasaki Disease; 28% of cases overall are incomplete – high index of suspicion is needed!

BPSU - Tulloh RM et al Arch Dis Child 2019;104:640-646

Investigations

Investigations:

- Clinical features
- CRP / ESR raised
- WBC raised
- Albumin low
- Sodium low
- Viral titres/ ASOT/ Throat swab negative
- Platelets lower early/ raised later (>10/7)

Risk factors – cardiac sequelae

Risk factors – cardiac sequelae:

- Age under 1 year : 39% have coronary artery aneurysms despite treatment
- Few clinical features (contributes to late diagnosis)
- Low albumin, low platelets, high CRP, male
- Late treatment:
- In BPSU Study those without coronary artery aneurysms were treated at 6.8 days
- Those with coronary artery aneurysms were treated at 10.2 days
- 1.6% had giant coronary artery aneurysms

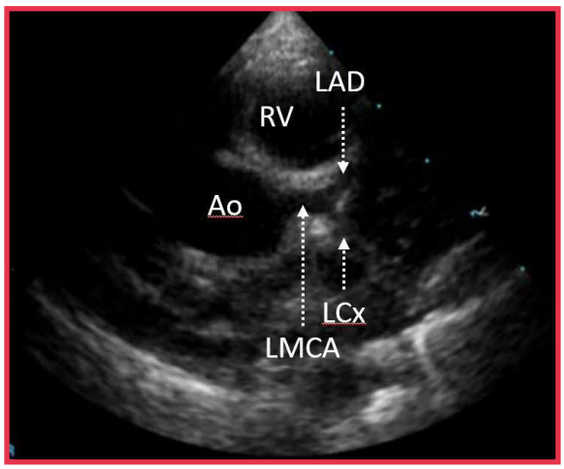
EARLY treatment is critical – DON'T DELAY

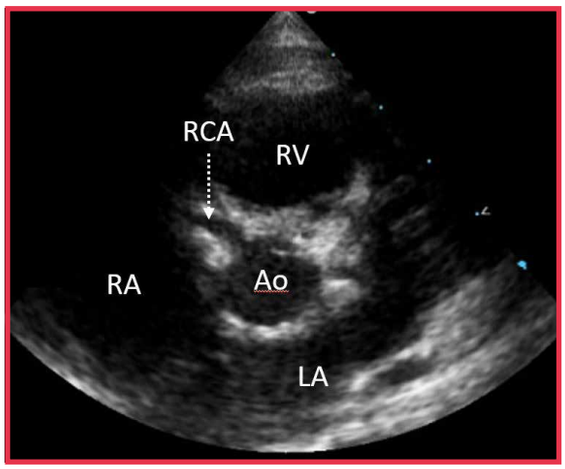
SO: Any infant with prolonged fever, **THINK Kawasaki Disease** and treat if you suspect the diagnosis: EARLY ECHOCARDIOGRAM; but **don't delay** treatment awaiting an echo!

Investigations - echocardiography

Investigations:

- Routine technique
- Full study - Don't just think coronary
- Myocarditis
- Pericardial effusion
- Valve regurgitation





LMCA left main coronary artery, LCx left circumflex coronary artery, LAD left anterior descending coronary artery, RCA right coronary artery, Ao aortic valve, RV right ventricle, RA right atrium, LA left atrium

Left CA views:

LMCA (left main coronary artery)

- Parasternal short axis view at level of aortic valve; precordial parasternal long axis view of left ventricle (superior tangential)
- Subcostal (ventricular) long axis

LAD (left anterior descending coronary artery)

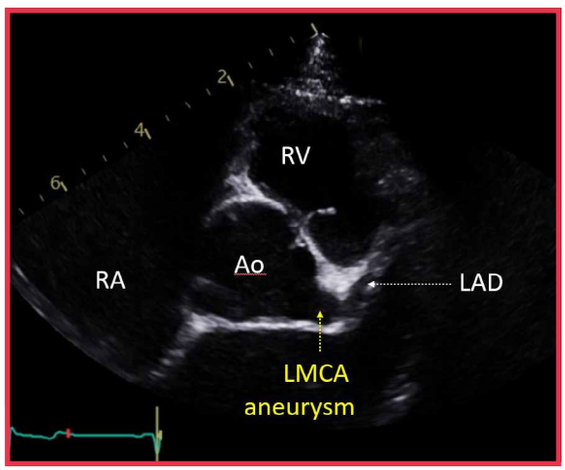
- Parasternal short axis view at level of aortic valve
- Parasternal superior tangential long axis view of left ventricle
- Parasternal short axis view

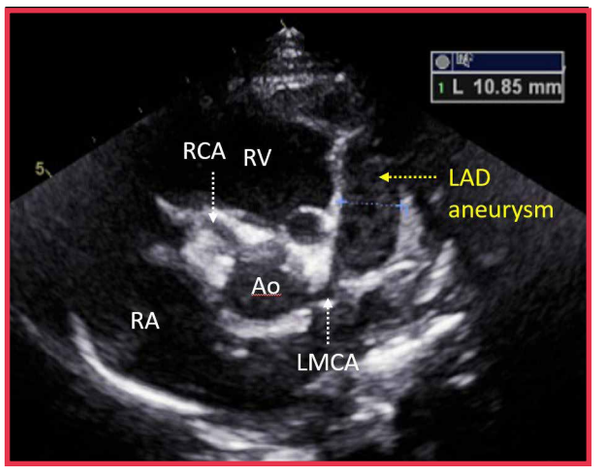
LCx (left circumflex coronary artery)

- Parasternal short axis view at level of aortic valve; apical 4-ch

McCrindle BW Circulation 2017;135:927-999

Images LMCA/LAD:





LMCA left main coronary artery, LAD left anterior descending coronary artery, RCA right coronary artery, Ao aortic valve, RV right ventricle, RA right atrium

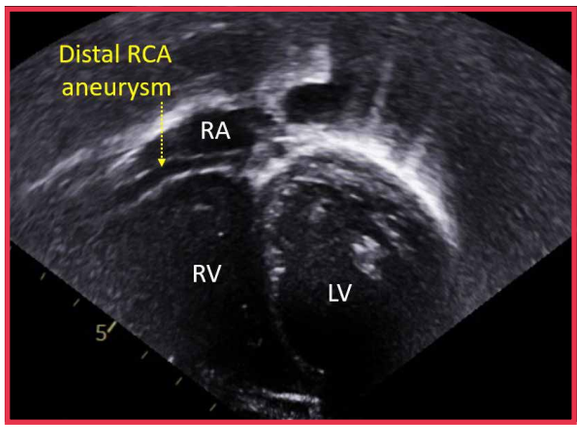
Kucera F Personal Library

The parasternal short axis 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. It would be easy to miss a large aneurysm, because the coronary may be so big that it does have the normal shape or structure of a normal coronary artery.

Investigations - echocardiography

Giant CAA – cardiac anatomy:

Sometimes the coronary arteries are unusually well visible in places where they are usually difficult to visualize, such as the right atrioventricular groove (first picture) or interventricular sulcus (second picture). THINK - are they dilated?



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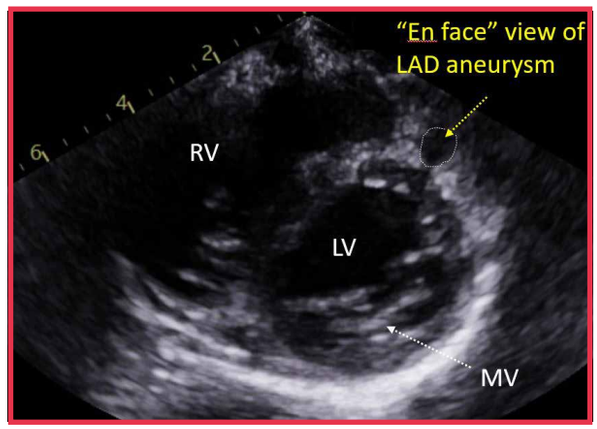


Kucera F Personal Library

Right CA views:

RCA, proximal segment

- Parasternal short axis view at level of aortic valve
- Parasternal long axis view (inferior tangential) of left ventricle
- Subcostal coronal projection of right ventricular outflow tract
- Subcostal short axis view at level of atrioventricular groove

RCA, middle segment

- Parasternal long axis view of left ventricle (inferior tangential); apical 4-chamber view
- Subcostal (left ventricular) long axis view; subcostal short axis view at level of atrioventricular groove
- RCA proximal (#1) and mid (#2) are observed in the atrioventricular groove from the third intercostal space at the left and right sternal border

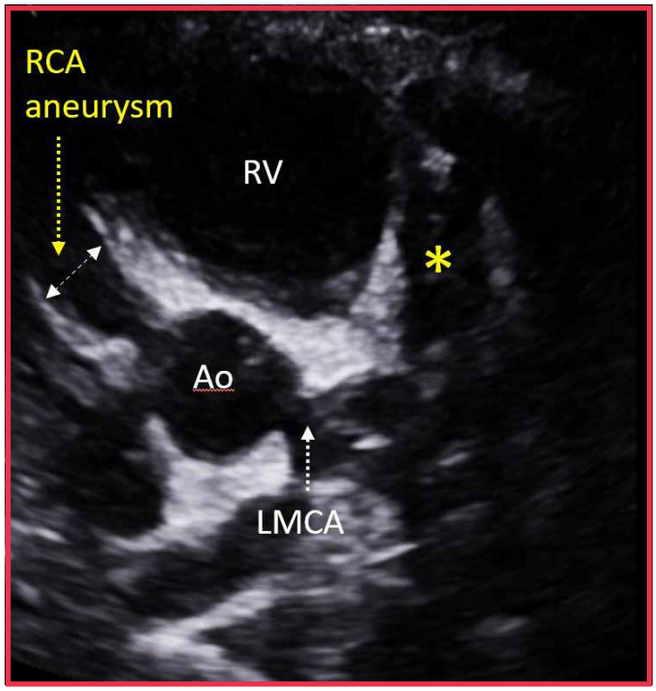
RCA, distal segment

- Apical 4-chamber view (inferior); subcostal atrial long axis (inferior)

McCrindle BW Circulation 2017;135:927-999

RCA (right coronary artery):

It is important to measure the internal diameter of the coronary artery and to relate to normal by means of a z score. Here the measurement of the dilated proximal right coronary gave a z score of +22. There is also dilatation of the left coronary artery and in particular of the left anterior descending coronary artery (star).

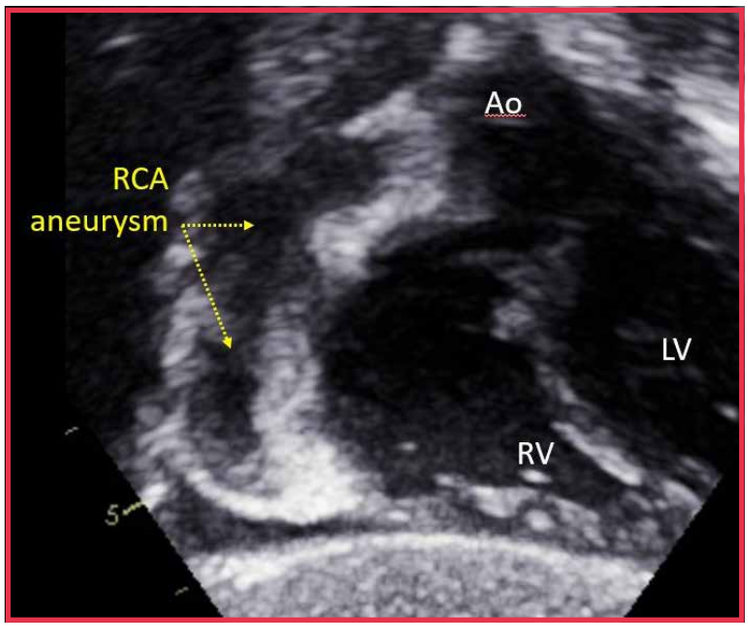


RCA right coronary artery, LMCA left main coronary artery, Ao aortic valve, RV right ventricle

Kucera F Personal Library

Images RCA:

Severely aneurysmal right coronary artery seen from subcostal long axis view.



Ao aortic valve, LV left ventricle, RV right ventricle

Kucera F Personal Library

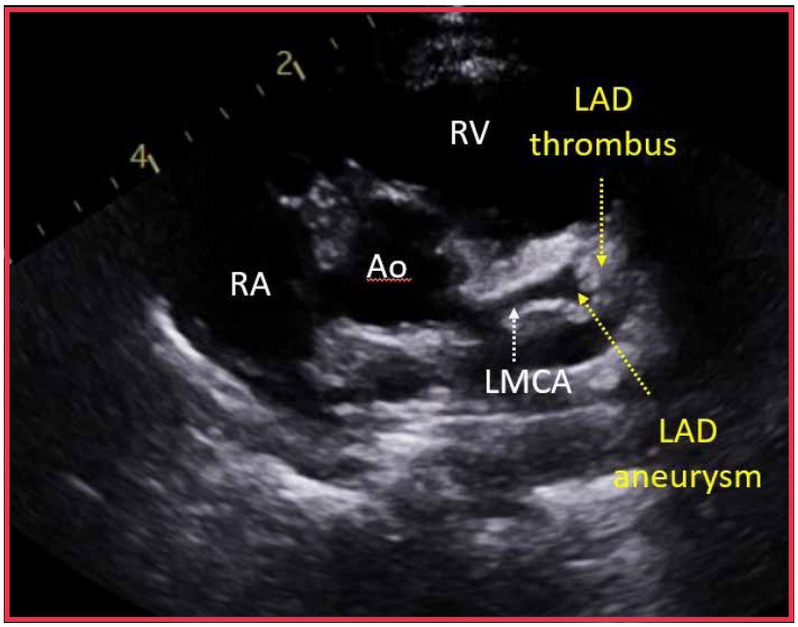
Posterior descending coronary artery:

- Apical 4-chamber (inferior)
- Subcostal atrial long axis (inferior)
- Precordial long axis (inferior tangential) imaging
- Posterior interventricular groove

McCrindle BW Circulation 2017;135:927-999

Coronary thrombosis

It is also important to look for the possible presence of coronary thrombi. This example demonstrates a thrombus in a fusiform LAD aneurysm.



Ao aortic valve, RA right atrium, RV right ventricle, LMCA left main coronary artery, LAD left anterior descending coronary artery

Kucera F Personal Library

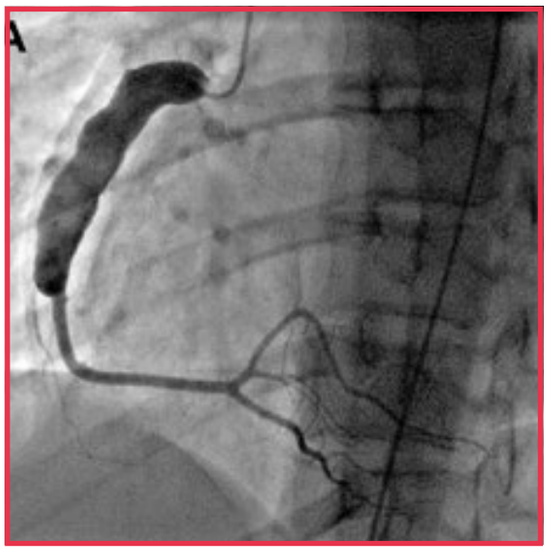
Coronary aneurysm

Acute Kawasaki Disease mortality:

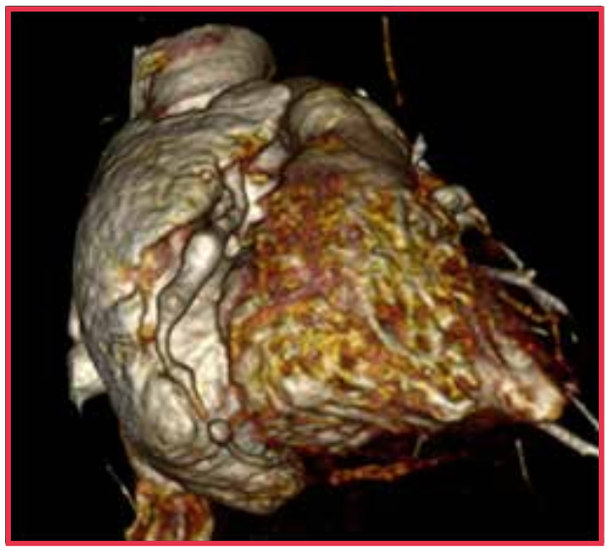
If the child is not treated, then the mortality of the condition is much higher.

- Lowered with treatment
- 0.36% - treated
- 2-3 % - untreated

Giant CAA



Tulloh RM Personal Library



Courtesy to Dr O Tann

Conventional invasive angiogram (first picture) and CT angiogram in different patients demonstrating fusiform right coronary artery aneurysm.

A post mortem case is seen of an aneurysmal coronary artery - not recognised as part of Kawasaki disease during life.

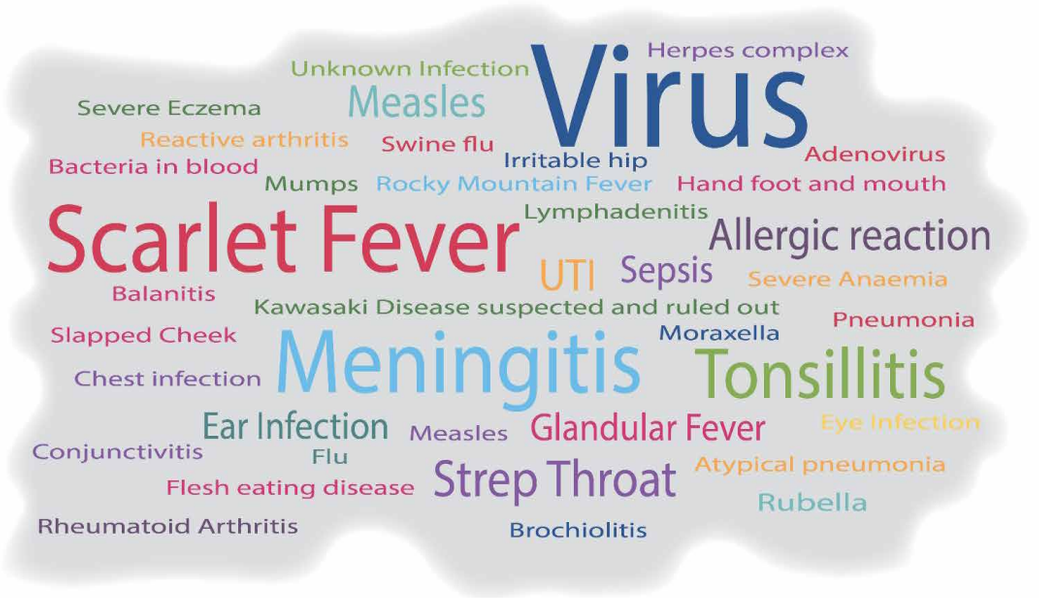
Tulloh RM Personal Library

Differential diagnosis:

Significant consequences arise from this disease – yet it remains under-recognised and frequently misdiagnosed. Consider differential diagnosis:

- Scarlet fever (does not cause red eyes)
- Viral infection
- - adenovirus, enterovirus, measles, parvovirus, Epstein–Barr virus, cytomegalovirus
- Meningitis – if you're considering Meningitis – **THINK Kawasaki Disease**
- Systemic juvenile idiopathic arthritis (sJIA)
- Other vasculitides
- Lymphoma

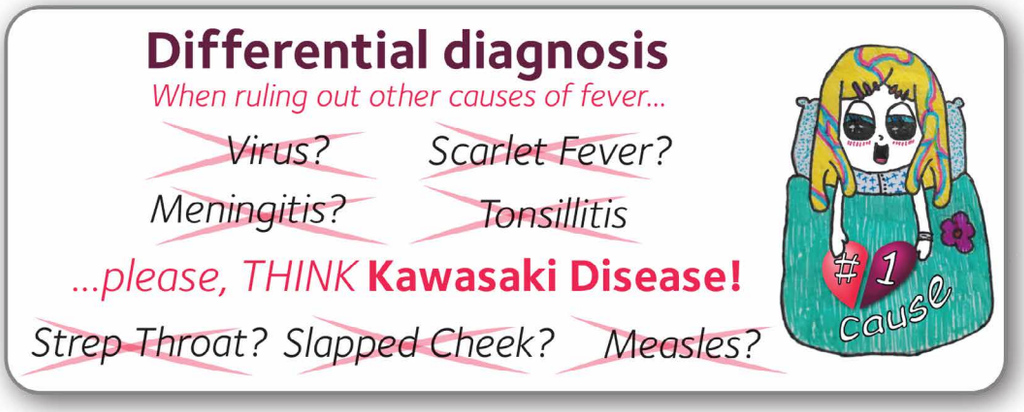
Societi Foundation review of the diagnoses given to UK children prior to eventual diagnosis with Kawasaki Disease indicates these prior incorrect diagnoses – by proportion



McCormack R Societi Foundation, Diagnosis Day experience June 2018

Persistent Fever PLUS 2 or more features –

THINK Kawasaki Disease



Diagnosis delay - consequences

Diagnosis delay - consequences:

- **DELAY!** Children being diagnosed on average at 7.8 days – TOO LATE!
- Children treated after 7 days = 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

EARLY treatment is critical - DON'T DELAY

- 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

BPSU - Tulloh RM et al Arch Dis Child 2019;104:640-646

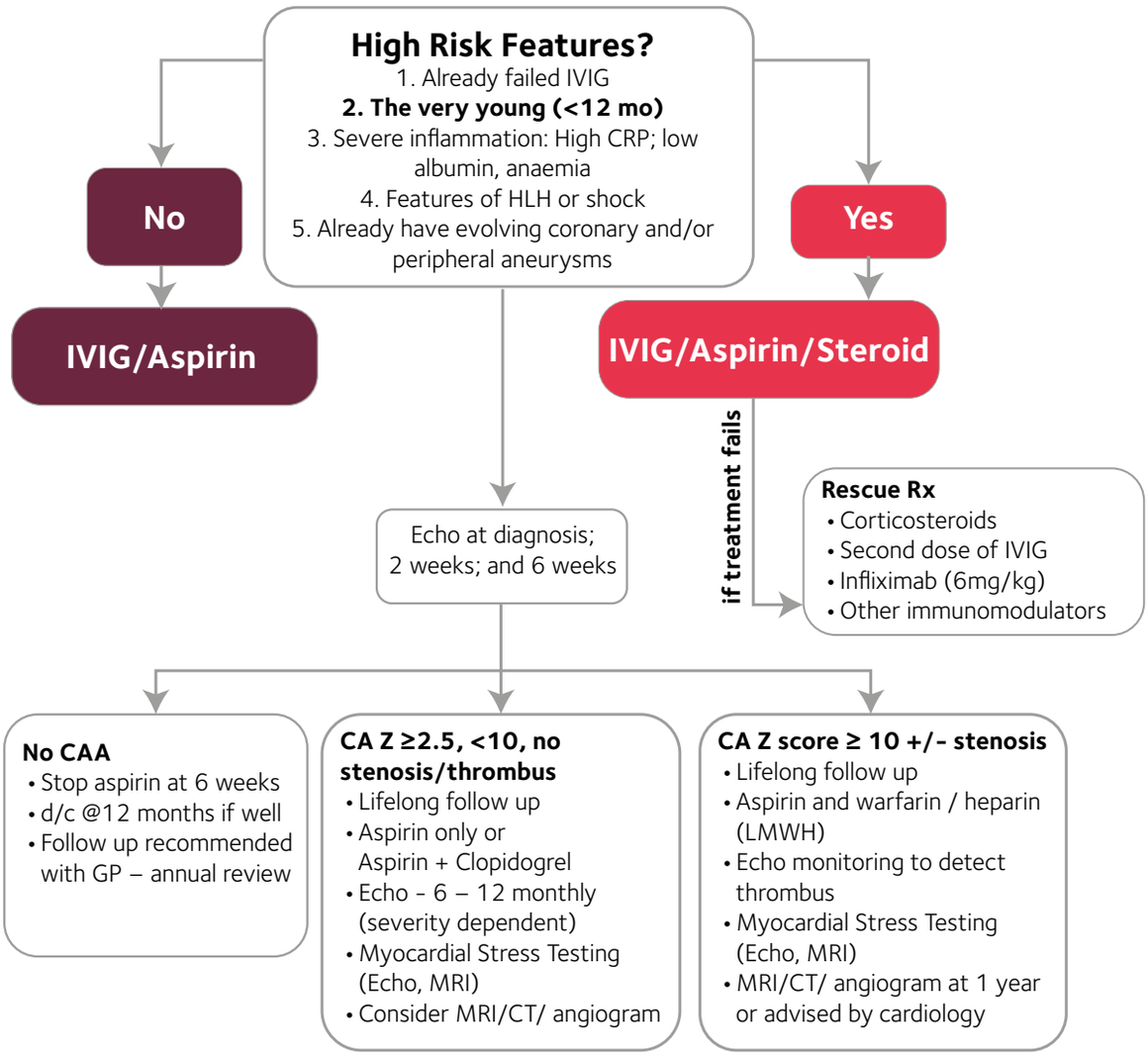
Tackling diagnosis delay

Tackling diagnosis delay:

- Recognise that Kawasaki Disease is increasingly common – **seen more than some bacterial meningitis**
- Remember sequential presentation of signs – ensure a detailed clinical history
- Incomplete Kawasaki Disease – 47% of cases in infants and 28% of cases overall
- Reluctance to diagnose because worried about ruling out infection e.g. scarlet fever
- Essential to have an increased index of suspicion – **THINK Kawasaki Disease**
- With increasing incidence – outcomes have not improved in 3 decades - time for change!
- **EXPECT to see Kawasaki Disease – and be READY to treat it!**

BPSU - Tulloh RM et al Arch Dis Child 2019;104:640-646

High risk features:



Brogan P 2019

Management

As soon as diagnosis is made:

- Immunoglobulin 2g per kilogram IV - single dose over 12hrs
- Aspirin 10mg per kilogram 4 times a day
- Supportive management, cream to fingers etc
- Perform an ECG alternate days
- Echocardiography – at diagnosis at 2 weeks and at 6 weeks
- Reduce to low dose aspirin as fever/markers resolve - 5mg per kilogram per day
- Do not repeat blood tests unless required
- Difficult cases require re-treatment with immunoglobulin + corticosteroids

N.B. IVIG resistance – 15 – 20%

- IVIG resistant patients have poorer prognosis - Risk of CAA: 20 – 30%

- Other treatments include:
  - Anti-TNF (infliximab)
  - Anti IL-1 (anakinra)
  - Ciclosporin

Other treatments

Corticosteroids:

Corticosteroids have been shown as beneficial in the prevention of coronary artery aneurysms in Kawasaki Disease.

- RAISE study: Kobayashi et al. Lancet 2012
  - N=253: IVIG/aspirin Vs IVIG/prednisolone/aspirin
  - **23% CAA in standard Rx group, Vs 3% in steroid group (NNT 5)**
- **Two meta analyses in 2012: both unequivocally show benefit of corticosteroids for the prevention of CAA**
  - Chen et al Heart Aug 2012
  - Zhu et al EJ Paeds Mar 2012
- Tulloh RMR, Mayon-White R, Harnden A, et al
  Kawasaki disease: a prospective population survey in the UK and Ireland from 2013 to 2015
  Archives of Disease in Childhood 2019;104:640-646
- Green J, Wardle A, Tulloh RMR. corticosteroids for the treatment of Kawasaki disease in Children. Cochrane database of systematic reviews 2022;5:1465-1858 - https://doi.org//10.1002/14651858.CD011188.pub3

Other treatments:

- 2,746 Kawasaki Disease patients
- Early addition of corticosteroids to conventional IVIG therapy was associated with reduced risk of CAA compared with IVIG therapy alone: odds ratio 0.424 (95%CI, 0.270-0.665)
- Corticosteroids were more effective when started earlier in the disease course

JAMA Pediatrics | Original Investigation

Coronary Artery Complication in Kawasaki Disease and the Importance of Early Intervention
A Systematic Review and Meta-analysis

Shaojie Chen, MD, MM, PhD; Ying Dong, MD, MM, PhD; Marcio Galindo Kiuchi, MD, MS, PhD; Jiazhi Wang, MD; Ruotian Li, MD, PhD; Zhiyu Ling, MD, PhD; Tingquan Zhou, MD, PhD; Zhenglong Wang, MD, PhD; Martin Martinek, MD; Helmut Pürerfellner, MD; Shaowen Liu, MD, PhD; Mitchell W. Krucoff, MD

CONCLUSIONS AND RELEVANCE This study highlights the importance of timing to prevent coronary artery complication in treating KD. High-risk patients with KD benefit greatly from a timely and potent adjunctive corticosteroid therapy strategy.

JAMA Pediatr. 2016;170(12):1156-1163. doi:10.1001/jamapediatrics.2016.2055
Published online October 17, 2016.

Longer term management

Some children will present with severe coronary artery dilation and are at high risk of thrombosis, or this may already be present.

For those with thrombosis present, multi-department discussion should take place to define the optimum treatment for that child, but it is likely to consist of heparinisation and possible thrombolysis. This needs to take place where acute paediatric haematology support is available.

For longer term management, more information is available in the publication:

Brogan P, et al: Lifetime cardiovascular management of patients with previous Kawasaki disease. Heart 2020 Mar;106(6):411-420.doi: 10.1136/heartjnl-2019-315925.Epub 2019 Dec 16

It is beyond the scope of this publication to give specific details, but the authors can be contacted for further advice. Most notably, those children with giant coronary artery aneurysms are at high risk of acute thrombosis within the first 2 years of presentation. They should be managed with anticoagulation plus additional aspirin, in order to reduce the risk of acute myocardial ischaemia.

Table 1: Classification of coronary artery dilation or aneurysms (after AHA guidance with modification) - *(Brogan P, et al: Lifetime cardiovascular management of patients with previous Kawasaki disease. Heart 2020 Mar;106(6):411-420.doi: 10.1136/heartjnl-2019-315925.Epub 2019 Dec 16)*

Classification of 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 6 weeks 6 months 12 months Discharge if normal at 12 months.	None	No	No—annual cardiac and general health review with GP recommended*
2	Dilation only (2<Z score≤2.5): resolves within 1 year	2 weeks 6 weeks 6 months 12 months 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): (a) current or persistent, (b) decreased to normal or Z score <2.5	2 weeks 6 weeks 6 months 12 months Annual review	Coronary angiography (preferably CT) at 12 months as baseline. Consider stress imaging for inducible myocardial ischaemia every 2 years. Imaging (echo) for coronary surveillance annually	Yes	Yes
4	Medium aneurysm (5≤Z score<10): (a) persistent aneurysm, (b) decreased to normal or Z score<2.5	2 weeks 6 weeks 6 months 12 months Annual review	Coronary angiography (preferably CT) at 12 months as baseline. Consider stress imaging for inducible myocardial ischaemia annually. 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 6 weeks 3 months 6 months 9 months 12 months Then every 6 months	Coronary angiography (preferably CT) at 6–12 months as baseline. Consider stress imaging for inducible myocardial ischaemia annually. 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 Practioner; PSP, person-specific protocol.

Kawasaki Disease – therapeutic pitfalls

Therapeutic pitfalls:

- **Delay in treatment**
- Failure to recognise high risk cases
- Over-reliance on resolution of fever as metric of therapeutic success: **must aim for zero fever, zero CRP**
- "No point in treating beyond day 10" – this is a myth! If inflammation is active – treat!
- Not treating incomplete cases – these are high risk cases – **must not delay treatment**

EARLY treatment is critical – DON'T DELAY

Management & follow-up

As soon as diagnosis is made:

- Echocardiogram
  - at 10 days, 6 weeks (stop aspirin if normal)
  - at 6 months
- Long term follow up by GP (no CAA persisting @ 6 wks)
- Lifetime follow up by cardiologist (CAA persists @ 6 wks)
- Recurrence 1 in 50
- "Reactivation" and re-peeling common

PLUS

- Societi – UK Foundation for Kawasaki Disease – detailed parent & family information at www.societi.org.uk – includes details of UK parent support group
- Societi "Longer Term Issues" parent & carer information leaflet www.societi.org.uk

Cardiac sequelae – long term

Cardiac sequelae:

- 500 patients with coronary artery aneurysms
- 35-year period
- Regression of CAA in 75%
- 24 patients had Major Adverse Cardiac Events (3x death, 1x heart transplant, 6x coronary artery bypass graft, 1x percutaneous coronary intervention, 2x symptomatic myocardial infarction, 8x asymptomatic myocardial infarction or coronary artery occlusion)

Friedman J Am Heart Assoc 2016

Giant CAA patients:

- 245 patients with giant CAA
- Median observational period 20 years
- 30-year cardiac event free rate was 36% and the survival rate was 90% (87% for bilateral and 96% for unilateral giant aneurysms).
- During follow up, death, acute myocardial infarction and coronary artery bypass graft occurred in 6%, 23% and 37%, respectively.

Tsuda Am Heart J. 2014

Cardiac sequelae – long term

Patient safety alert:

- Lifetime specialist cardiac management for all patients with CAA persisting after 6 weeks
- **Risk of death and serious harm**
- Long term clinical guidance for cardiac management published 2019

This patient safety alert can be downloaded by clicking the access button below or visit the Societi website here.

Access

NHS Improvement

Patient Safety Alert

Stage One: Warning

Risk of death and serious harm from failure to recognise acute coronary syndromes in Kawasaki disease patients

11 May 2016

Alert reference number: NHS/PSA/W/2016/004

Alert stage: One - Warning

Around 10 to 20% of all children with Kawasaki disease (KD) develop aneurysms and are at long-term risk of thrombosis and/or stenosis of the coronary artery, which may result in coronary thrombosis and myocardial ischaemia or infarction in patients with KD related aneurysms. [1, 2]

Actions

Who:
All providers of NHS-funded care

Transition to adult care

Transition to adult care:

- Seamless transfer from paediatric to adult care is essential for this patient group
- BMI, blood pressure, lipids and HbA1c, hs-CRP
- ECG and echocardiography
- Consider stress echocardiography or stress MRI
- Consider Coronary CT angio (including calcium scoring)
- Review of Patient Specific Protocol
- Advice on lifestyle factors, smoking, diet and family planning (as applicable)
- Lifetime cardiovascular management of patients with previous Kawasaki Disease available in this pack

Recap

Recap on our aims:

- Understand the diagnosis considerations for Kawasaki Disease – including differences of presentation across ages, and when to THINK Kawasaki Disease
- Have knowledge of differential diagnosis considerations and red flags for Kawasaki Disease
- Have knowledge of the urgency with which the disease needs to be treated – confidence to consider Kawasaki Disease
- Have awareness of disease severity and the criticality of EARLY treatment
- Abandon prevailing 'myths' around this disease which are hampering treatment / adversely impacting children affected

Thank you!

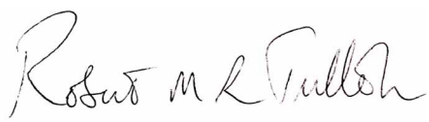
Thank you:

Thank you for your interest in Kawasaki Disease. We hope the information in this resource has been helpful to you.

Incidence is on the rise, which means it is even more important to know Kawasaki Disease and ensure you can recognise it and treat it as early as possible.

There are lots of clinician resources and Kawasaki Disease information available to download from the Societi Foundation website. Please visit www.societi.org.uk to find out more and keep an eye out for updates as and when they occur.

With my very best wishes,



Professor Robert Tulloh
for Societi Foundation

NICE
National Institute for
Health and Care Excellence

Current NICE guidance on Fever in Under 5's and Kawasaki Disease

Updated NICE guidance published in November 2019 states:

Kawasaki Disease

1.2.26 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. [2019]

1.2.27 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. [2019]

1.2.28 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. [2019]

For a link to the above guidance online, please **click the access button:**

Access

Clinician Q & A

Following many of the discussions we have had with clinicians during events, conferences and webinars, we have put together some frequently asked questions which we hope you find helpful. If you are a clinician and have a question about Kawasaki Disease which isn't answered here, please get in touch. We will be happy to try and answer your questions with the help of the experts on our Scientific Advisory Board.

Diagnosis

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. Around 25% of cases occur in children over the age of 5, 75% are under 5. 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 experienced diagnosis delay and poorer outcomes as a result. Consider Kawasaki Disease in ANY child with persistent fever for 5 days.

What other diagnoses have been ruled out when Kawasaki Disease is considered? Are there any treatments that were administered prior to that diagnosis? (e.g. antibiotics)

Causes of fever in children are numerous and varied. 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 will in Kawasaki Disease.

Virus – runny nose typically associated with viral infection is not a feature of Kawasaki Disease. Remember Kawasaki 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 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.

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? (In view of the fact that fever and rash is a very common presentation)

Access

Please refer to the flow diagram provided in **European recommendations** (**click access button** for the link or visit **https://doi.org/10.1093/rheumatology/key344**). 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 more often 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.

Key points:

- Continue to consider a potential Kawasaki Disease diagnosis even if commencing treatment for another diagnosis.
- If your patient does not respond as expected to treatment and maintains a high fever at 5 days – consider Kawasaki Disease and treat urgently.
- Remember that Kawasaki Disease can be present alongside other illnesses e.g. Strep throat – do not discount because of presence of another illness
- Recent history is key – obtain a detailed history of symptoms, however fleeting, as these will inform you
- Although there is no diagnostic test for Kawasaki Disease, a C-reactive protein blood test can be incredibly useful for raising suspicions because the vast majority of viral infections are not associated with an elevated c-reactive protein, but in Kawasaki Disease it is high.

Differentiating between Kawasaki Disease and PIMS-TS?

The presenting signs and symptoms of PIMS-TS are sometimes like those of bad cases of Kawasaki Disease and sometimes like other severe diseases. PIMS-TS is a distinct entity that creates inflammation within the body and can cause many organs to be under stress or maybe to fail and require intensive care - including the heart. But the nature of the heart involvement in PIMS-TS is rather distinct from Kawasaki Disease and does not appear to target the coronary arteries the way Kawasaki Disease does.

Treatment

Given the current concerns around availability of IVIG, and how often we give steroids for other indications, would it now be appropriate to consider steroids early in the course?

IVIG and aspirin are the essential first line treatments for Kawasaki Disease. A rapid, systemic approach to the early reduction of fever and "switching off" of inflammatory processes is the aim. Corticosteroids have been shown to be very helpful as an additional therapy, in children who are in high risk groups or who fail to respond to IVIG.

Access

Children in Japan, where Kawasaki Disease is of increased frequency, have benefited from steroid use upfront. **The KDCAAP clinical trial** (**click the access button** for more information or visit **https://www.societi.org.uk/kd-caap/**) - the single greatest opportunity for transformation in outcomes in Kawasaki Disease in a generation - is trying to establish whether its safe and its effective to use corticosteroids, in addition to standard care, to try and prevent coronary complications in children with Kawasaki Disease in the U.K. and in Europe.

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 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 risks associated with the administration of IVIG as a blood product and clinicians should always balance the risk of treatment versus non-treatment.

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

Can I ask about the dose of steroids you use for high risk cases? Also you mentioned that you aim for CRP of zero, how long do you wait for this before escalating treatment, as presumably due to the half-life of CRP, it'll take a bit of time for this to fall, even if you've turned off inflammation? Would you give more treatment just for a CRP result, if child clinically improving otherwise?

There are no data to guide you. Please refer to the range of dosing provided in a **European guidance paper** (**click the access button** for a link or visit **https://doi.org/10.1093/rheumatology/key344**). The KDCAAP trial will use oral prednisolone at 2 mg per kilogram per day, tapering when the C-reactive protein (CRP) is less than 10 and fever has settled. Some advise 3 days of 30mg per kilogram methylprednisolone intravenously (to a maximum of 1gm/day) once per day. Then a dose of 2mg/kg oral prednisolone per day until day 7 or until CRP normalizes; then wean over next 2-3 weeks. The key point is to make sure the CRP AND fever is settling: aim for "0 fever 0 CRP".

Coronary artery aneurysms

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 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. See **Societi's Long Term Issues leaflet** (**click the access button** for a link or visit **https://www.societi.org.uk/resource/understanding-some-of-the-possible-longer-term-issues/**) for information on non cardiac issues which may arise.

If the coronaries appear normal on echo, and the patient is not discharged, what follow-up protocol is recommended?

Undertake an echo at 6 weeks (following acute illness) and if coronaries are normal, aspirin can be stopped. Care should be continued to 12 months (see above) if there are no ongoing cardiac issues. At 12 months, the patient should be discharged to Primary care.

What do you say in clinic to a family with coronary artery aneurysms with respect to the short and longer term?

Kawasaki Disease with lasting cardiac damage is a life changing diagnosis. With increasing damage severity, the impact on the patient also increases. Care is needed when sharing insight about future care needs and risks ahead.

The patient group with giant aneurysms is at increased lifetime risk of major cardiac events, Myocardial infarction, stenosis and sudden death – with risk level increasing with severity of cardiac damage during the acute phase. Patients with persisting aneurysms and giant coronary artery aneurysms have highest levels of risk but those with small or moderate aneurysms also need to be followed up carefully.

Lifetime care must be undertaken by a clinician with active interest and expertise in Kawasaki Disease. Long term medication will be essential for these patients and a clinical regime for active review, annual tests (more frequent for the most severely affected) and regular imaging (at intervals determined by cardiac damage severity) will need to be put in place.

Patients with life changing and life threatening outcomes may require psychological support and counselling. This should be provided where needed and offered where considered helpful.

Access

Lifetime cardiac management guidance for the U.K. (available as a hard copy in this pack and online at **https://www.societi.org.uk/research/lifetime-cardiovascular-management-of-patients-with-previous-kawasaki-disease/** - **click the access button** for a link) has been developed and was published in 2019.

Access

Societi have prepared a **Long Term Issues leaflet** (**click the access button** for a link or visit **https://www.societi.org.uk/resource/understanding-some-of-the-possible-longer-term-issues/**) for parents and carers of children which provides additional information and is helpful as patients adjust and resume pre-illness routines.

How can you reassure families of children with Kawasaki Disease and no coronary artery aneurysms in terms of their long term health; some families are asking about angiograms/MRIs etc?

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 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 for 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.

Access

See **Societi's Long Term Issues leaflet** (**click the access button** for a link or visit **https://www.societi.org.uk/resource/understanding-some-of-the-possible-longer-term-issues/**) for information on non-cardiac issues which may arise.

Age and incidence

Youngest infant reported to have Kawasaki Disease?

Access

Case reports exist (internationally) of infants as young as 12 days being diagnosed with Kawasaki Disease. (**click the access button** for a link or visit **https://fn.bmj.com/content/86/2/f135**). In the UK, infants as young as 6 weeks of age have been diagnosed and treated for Kawasaki Disease.

Access

Research by the BPSU (**click the access button** for a link or visit **https://research-information.bris.ac.uk/en/publications/kawasaki-disease-a-prospective-population-survey-in-the-uk-and-ir**) shows that babies under one year old tend to show the fewest symptoms but are more likely to develop coronary artery aneurysms - 39% of infants in the U.K. and Ireland who are affected by Kawasaki Disease develop coronary artery aneurysms.

Incidence is rising across the world. Is this because recognition is better?

Incidence is rising – because of increased disease NOT increased awareness. In Japan, for example, where Kawasaki Disease is very common and awareness is very high, there is a continued and rapid rate of increase in cases. In the UK, awareness is very low presently yet incidence is rising sharply. With increased awareness we'd expect to see subsequent increased correct diagnosis. Currently diagnosis is often delayed, demonstrating poor awareness – Kawasaki Disease is arrived at as a diagnosis after on average 2 or 3 prior misdiagnoses (Societi Foundation diagnosis day research 2018). This does not correlate with increased awareness – but increased disease burden. Expect to see Kawasaki Disease. Be ready to treat it.

Think you know **Kawasaki Disease?** *Here are some common clinical* **myths** *and the* **facts** *behind them!*

This "Myths and Facts" summary has been prepared for clinicians with input from Professor Robert Tulloh, internationally recognised expert in Kawasaki Disease. These myths hamper care and delay diagnosis - and so adversely affect outcomes for children. Please contact us if you know of other myths and we'll help debunk those too!

Symptoms & treatment

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

Fact: 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

Myth: There is a treatment window for IVIG of 10 days

Fact: 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!

Myth: Kawasaki Disease has no characteristic symptoms

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

Myth: IVIG reduces heart damage from 25% to 5%

Fact: 19% of all children develop permanent damage and 39% infants develop coronary artery aneurysms despite IVIG - linked to delayed treatment. Early treatment is critical!

Heart damage

Myth: Kawasaki Disease rarely causes heart damage

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

Who & how many?

Myth: Child is too young / too old for Kawasaki Disease

Fact: 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.

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

Fact: Kawasaki Disease is increasingly common. Cases are doubling globally every 10 years. In England, hospital admissions for Kawasaki Disease increased fourfold in the last decade. It's more common than bacterial meningitis and measles. Please EXPECT to see it and be READY to treat it

Diagnosis

Myth: Echocardiograms are a useful way to confirm a Kawasaki Disease diagnosis

Fact: 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

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

Fact: 47% 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

Impacts

Myth: The only lasting damage from Kawasaki Disease is to the heart

Fact: 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.

Long term care

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

Fact: 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

Myth: There are no known future health risks for patients

Fact: 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

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

Fact: 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

Kawasaki Disease?
Remember TEMPERS
Children with **Kawasaki Disease** *are characteristically irritable!*

Temperature - **Persistent high fever**

Erythema - reddened hands and feet with swelling

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

Pace - **Treat early** to reduce potential heart damage

Eyes - bloodshot, non-sticky conjunctivitis

Rash

Swollen glands in neck, often just one side

If a child has a **PERSISTENT FEVER** *and two or more of these symptoms* **THINK KAWASAKI DISEASE!**

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REVIEW

Lifetime cardiovascular management of patients with previous Kawasaki disease

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ABSTRACT

Kawasaki disease (KD) is an inflammatory disorder of young children, associated with vasculitis of the coronary arteries with subsequent aneurysm formation in up to one-third of untreated patients. Those who develop aneurysms are at life-long risk of coronary thrombosis or the development of stenotic lesions, which may lead to myocardial ischaemia, infarction or death. The incidence of KD is increasing worldwide, and in more economically developed countries, KD is now the most common cause of acquired heart disease in children. However, many clinicians in the UK are unaware of the disorder and its long-term cardiac complications, potentially leading to late diagnosis, delayed treatment and poorer outcomes. Increasing numbers of patients who suffered KD in childhood are transitioning to the care of adult services where there is significantly less awareness and experience of the condition than in paediatric services. The aim of this document is to provide guidance on the long-term management of patients who have vascular complications of KD and guidance on the emergency management of acute coronary complications. Guidance on the management of acute KD is published elsewhere.

BACKGROUND

Kawasaki disease (KD) was first described in Japan in 1967, predominantly affects young children and has potential life-long consequences.[1–4] Its incidence in children under 5 years ranges from 322/100 000 in Japan and South East Asian countries, to 4.5–25/100 000 in Europe and USA[3–5] and the disease has become increasingly common in the UK.[6 7] Its cause is unknown, but epidemiological observations suggest an environmental agent causing an inflammatory process in genetically predisposed individuals.[8] Although the acute febrile and exanthematous illness resolves spontaneously, 30% of untreated patients develop coronary artery aneurysms (CAA).[9]

Treatment of the acute illness with intravenous immunoglobulin (IVIG) reduces the risk of CAA,[10] and is now the standard recommended treatment.[2 11] The 10%–15% of patients who are unresponsive to IVIG may be treated with corticosteroids, infliximab or other immunosuppressive agents[2] and are at increased risk of CAA, as are those in whom treatment is delayed.[12 13] Following an acute episode of KD, British Paediatric Surveillance Unit data suggest that 19% of children overall and 39% of those aged under 1 year, still develop coronary involvement[6] 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.[13–15] Comparably high rates of CAA have also recently been reported from Sweden, Russia, Germany and North America.[16–18]

Although paediatricians are familiar with acute KD, there is less awareness of its long-term consequences and management of any subsequent acute coronary syndrome, in both paediatric and adult services. To help raise awareness a guidance document was produced by NHS England London Cardiac Strategic Clinical Network in 2015[19] and a national NHS Patient Safety Alert in 2016.[20]

Methodology

A writing group was convened to obtain consensus from experts in the UK and USA, concerning the long-term management of patients who had coronary artery complications from KD. A literature search was performed and data reviewed by convened experts resulting in wide ranging consensus across the UK and USA. Clinical and other specialists were in the areas of Paediatric Cardiology (RMT/OM/JCB), Adult Cardiology (TWJ/VD/HG/JG/PM/IM), Paediatric Rheumatology (PG/DE), Paediatric infectious disease (ML), NHS England (JC/HG), Societi patient charity (RM). Face to face meetings were held to derive consensus and external expert advice sought from individuals including emergency medicine, ambulance services, patient charities and pharmacy. In addition, endorsement and/or support was obtained from the organisations of the Royal College of Paediatrics and Child Health, Royal College of Physicians, British Cardiovascular society and the Royal College of Emergency Medicine.

CARDIOVASCULAR CONSEQUENCES OF KAWASAKI DISEASE

All cardiac tissues are involved in the acute inflammatory phase of the disease.[9] Vasculitis causes destruction of the normal arterial architecture and is followed by aneurysmal dilatation, particularly

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affecting the proximal coronary arteries.[21 22] Pathological studies in patients with previous KD reveal widespread changes[23] 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.[23] 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 KD show that CA dilation may be visible early in the illness, but maximal development is usually in the second and third week of the acute illness.[2] Those with persistent CA 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 SD units normalised for body surface area) are considered to have suffered long-term arterial damage.[11]

The risk of thrombotic and stenotic complications is related to aneurysm size.[24] 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.[25] 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.[11]

ASSESSMENT OF CARDIOVASCULAR RISK

As most episodes of acute KD occur in young children, assessment for coronary artery involvement is by serial transthoracic echocardiography, at diagnosis, 2 weeks and 6 weeks following onset of the disease, as a minimum. If abnormal, more frequent echocardiography will be required (up to twice weekly) to identify rapidly progressive coronary involvement and/or coronary thromboses. Echocardiography should be undertaken by someone appropriately trained and designated as such by the congenital cardiac network. Echocardiographic imaging is less definitive in older children or adults, for whom CT angiography or MRI may be needed.

On the basis of echocardiography, patients are classified into defined risk groups according to the 2017 American Heart Association classification,[11] each requiring different follow-up (table 1). It is recognised that echocardiography of coronary arteries can be demanding particularly in very young children. However, the most common locations of aneurysms are at the bifurcation of the left main coronary artery and in the proximal right coronary artery. These areas should be clearly imaged (as an absolute minimum). If technical issues limit the examination and it is not possible to obtain adequate views of the coronary arteries or calculate Z scores, the child should be referred for a repeat examination under sedation,

Table 1 Classification of coronary artery dilation or aneurysms (after AHA guidance with modification)[11]

Classification of 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 6 weeks 6 months 12 months Discharge if normal at 12 months.	None	No	No—annual cardiac and general health review with GP recommended*
2	Dilation only (2<Z score≤2.5): resolves within 1 year	2 weeks 6 weeks 6 months 12 months 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): (a) current or persistent, (b) decreased to normal or Z score <2.5	2 weeks 6 weeks 6 months 12 months Annual review	Coronary angiography (preferably CT) at 12 months as baseline. Consider stress imaging for inducible myocardial ischaemia every 2 years. Imaging (echo) for coronary surveillance annually	Yes	Yes
4	Medium aneurysm (5≤Z score<10): (a) persistent aneurysm, (b) decreased to normal or Z score<2.5	2 weeks 6 weeks 6 months 12 months Annual review	Coronary angiography (preferably CT) at 12 months as baseline. Consider stress imaging for inducible myocardial ischaemia annually. 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 6 weeks 3 months 6 months 9 months 12 months Then every 6 months	Coronary angiography (preferably CT) at 6–12 months as baseline. Consider stress imaging for inducible myocardial ischaemia annually. 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 Practioner; PSP, person-specific protocol.

performed by an expert echocardiographer. It should also be noted that the measurement of infant length must be carefully executed as the Z score calculation is extremely sensitive to variation in body surface area that incorporates both height and weight. Aneurysms of peripheral arteries may occur in patients with severe coronary involvement, so imaging of other vascular territories will also be required in these cases.

DEFINING PATIENT GROUPS

Acute KD in children results in varying levels of future risk following recovery from the acute phase. This guidance has been prepared focussing on patients of risk level 3 and above (see table 1) who require lifetime specialist management within cardiology services. Patients who have had KD but are at risk levels 1 or 2 should have follow-up through their General Practitioner. See also notes in table 1.

Patients who have had KD with subsequent coronary or other arterial involvement require continued input of a clinician with expertise in KD, complementing routine postintervention care and taking account of guidance given in table 1. KD presents lifelong risks for patients irrespective of intervention on localised aneurysms. Given the low prevalence of children with CAA following KD, specific studies in this population are difficult, and posology is generally based on adult cardiology principles and some mainly retrospective studies of these drugs used in children. The drugs and doses proposed are clinically reasonable suggestions for consideration by clinicians, based on available literature evidence, and in the absence of trial data (noting that some trial data may become available in future for direct oral anticoagulants (DOACs) in KD). Many of the indications are not licensed in the paediatric population, but it is acknowledged that are no licensed alternatives and children with CAA are at risk of cardiovascular events. Thrombolysis of a coronary event in a child is rare but medically critical and it is preferable to have an indication of agents that might be considered in this situation, acknowledging that it is clear there is a lack of evidence surrounding paediatric use.

LONG-TERM MANAGEMENT

The major long-term risks for patients with CAA are thrombosis within the aneurysm or coronary stenosis, either of which can result in myocardial ischaemia.[11] The risk of aneurysm thrombosis is greatest in the first 2 years after the acute episode of KD but persists life-long.[26] Long-term management is based on prevention of thrombosis, early detection of thrombosis or stenosis when they occur, general measures to lower cardiovascular risk (such as lipid lowering, control of hypertension, smoking cessation) and support for patients and their families to pursue a healthy lifestyle. Evidence levels vary considerably, and it is explicit that there is the need for clinicians to consider evidence levels and individual benefit risk, including discussions with patients and/or their guardian.

Antithrombotic therapy

Antiplatelet agents

All patients with KD receive aspirin during the acute illness, along with gastric protection if needed. Those who have CAA (persisting after 6 weeks) should remain on long-term aspirin (see online supplementary drug appendix for all doses), including those in whom there is later remodelling of the CAA. It needs to be remembered that the switch from high-dose to low-dose aspirin is to minimise the risk of thrombosis in situ, following evidence from those who have had myocardial infarction.[27] Those with giant CAA should remain on low dose aspirin (or clopidogrel) and have an anticoagulant added. Other antiplatelet medications (such as ticagrelor) have been used but on the basis of evidence derived from non-KD populations. The alternative of an antagonist of ADP mediated activation of platelet aggregation such as clopidogrel may be considered in individuals where the use of aspirin is problematic, for example, in patients requiring non-steroidal anti-inflammatory drugs (NSAIDs) for other comorbidities such as arthritis, since NSAIDs interfere with the antiplatelet effect of aspirin.[11] In addition, clopidogrel (or other thienopyridine) may be added to aspirin therapy for those with large but not giant aneurysms, based on the inference from adult trials that this would be a more effective antiplatelet strategy.[11]

Anticoagulants

There are no randomised controlled trials of anticoagulation therapy in KD but there is a lower rate of CAA thrombosis and better outcome for patients with giant aneurysms maintained on long-term warfarin.[11] Although warfarin is the most widely used anticoagulant, it is difficult to use in very young children, and a subcutaneous low molecular weight heparin (such as Enoxaparin) is preferable converting to warfarin in older children.[28 29] Although clinical trials are underway, direct oral antithrombins (or DOACs) are increasingly used in adults, under expert supervision, when warfarin is felt to be inappropriate or insufficiently effective (for instance, due to failure to achieve an INR consistently in the therapeutic range or thrombus formation while on warfarin). These may become a future alternative to heparin or warfarin in children and young adults, but trials regarding safety and efficacy are currently lacking and therefore this cannot be routinely recommended at the time of writing.

Data from Japan show that the risk of thrombosis in children with giant CAA is greatest in the first 2 years after disease onset, but persists throughout life[26] and a US study showed that aneurysm size was the strongest predictor of major cardiac events.[18] Combined anticoagulation and antiplatelet therapy are therefore recommended for all patients with KD with a coronary artery Z score ≥10.[11]

Other drug therapies

Beta-blockers

Not routinely prescribed but may be appropriate for some cases of CAA when associated with myocardial ischaemia or if antiarrhythmic therapy is indicated. The current advice is for beta blockers to be used lifelong in patients with prior infarction and depressed (<40%) ejection fraction.

Statins

Although the pathology of KD differs from that of atherosclerotic heart disease, and despite a lack of definitive evidence, statins should be considered for patients with persisting CAA due to the potential benefit of their anti-inflammatory effect.[30]

For all the drug therapies, physicians should consult the SmPC, consider BNFc posology where available and also check for any relevant Direct Healthcare Professional Communications.

Avoidance of cardiovascular risk factors

Patients who have ever had CAA should be counselled to lower their cardiovascular risk from an early age, by measures such as eating a diet low in animal fat, taking regular and appropriate exercise, maintenance of ideal weight (reducing the risk of diabetes), avoidance of smoking and monitoring for hypertension and hyperlipidaemia.

Table 2 Follow-up assessments

Assessment	Each visit	Additionally at transition
Clinical	History Examination Medication review	
ECG	12 lead	
Imaging (see also table 1)	Echocardiography	CT calcium scoring and angiography with ischaemia testing (stress MRI, stress echo, CTFFR) if indicated prior to transition to adult services
Blood tests	Lipid profile every 5 years HbA1c	
Psychological	Family and patient dialogue	During transition process from 13 to 18 years—patient focused dialogue
Advice	Smoking Exercise Diet Family planning PSP review	

ADP, Adenine di-Phosphate; AHA, American Heart Association; CTFFR, CT fractional flow reserve; PSP, person-specific protocol.

Exercise

After the acute illness, patients with previous KD should be encouraged to undertake regular aerobic exercise which is tailored to their disease severity. Competitive sports may need to be restricted in those with giant aneurysms, and body contact sports should be avoided in patients on anticoagulants.

Psychological support

Children may suffer psychological stress adjusting to teenage and young adult life with the constant threat of an acute coronary ischaemic event. Care teams have to balance providing honest advice on the risks, and the 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 patients with KD.

Regular clinical assessment and investigations

Table 1 suggests the frequency of cardiovascular follow-up and recommends imaging/stress testing, by level of patient risk. Patients with small or remodelled aneurysms may be seen less frequently, but those with giant aneurysms need regular imaging and assessment to detect developing thrombi within aneurysms, particularly in the early years after the acute KD illness, when the risk of thrombosis is greatest. Table 2 suggests additional tests to be undertaken during a visit, and in the transition period from paediatric to adult care, before the decision is made on the appropriate long-term follow-up regime. Each assessment should focus on evaluating the size of persisting aneurysms, the detection of thrombi within aneurysms and whether there is evidence of impaired myocardial perfusion suggesting the development of coronary stenoses.

Imaging considerations

Patients with CAA require repeated assessment throughout life and imaging should minimise cumulative radiation exposure, using modalities such as echocardiography and MRI. While modern multidetector CT can achieve high-resolution coronary imaging at much lower radiation doses than in the past, CT (or even invasive) coronary angiography should be undertaken only when other modalities cannot be used to define stenotic lesions or plan interventions. Cardiac MRI has no known risk unless gadolinium enhancement is used[31] and in addition to providing detailed information on aneurysm size and presence of thrombi, it can detect small myocardial scars and fibrosis that cannot be detected by other modalities.[32] Adenosine or exercise stress MRI should be used in older children and adults for the investigation of myocardial ischaemia. In addition, there may be a role for positron emission tomography or nuclear stress imaging in order to determine the haemodynamic and perfusion defects in KD, but large trials have not yet been performed (only isolated studies), so the role of these techniques is not fully established.[32–34]

If CT angiography at transition demonstrates evidence of coronary artery stenosis or if there is admission with chest pain, then ischaemia testing (Stress MRI, Stress echo, CT fractional flow reserve) could be considered to determine if there is evidence of functional tissue hypoperfusion.[35] If this is abnormal, then progression to stress imaging with MRI or echocardiography should be undertaken. In addition, MRI/MRA should be used to screen for non-cardiac aneurysms in cases of severe disease.[11]

Person-specific protocol

All patients with a history of KD at risk level 3 and above (see table 1) require a person-specific protocol (PSP). The PSP (see online supplementary file 2) 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) so they have prior knowledge of the patients' KD history and can act quickly in the event of a suspected cardiac emergency. The PSP includes the patient's KD history and 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. A suggested template for the KD PSP is given as an online supplementary file 2. 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 the emergency situation.

The PSP should be agreed with the patient (if adult) or carers (if child) and should include direct phone contact numbers (24 hours) for the specialist KD 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.

Engagement with primary care

Good communication between the specialist cardiac centre and the patient's Primary Care team is essential. All health, care and school services should be aware of plans for the emergency management of complications, as documented in the PSP.

TRANSITION FROM PAEDIATRIC TO ADULT SERVICES

All patients with a history of KD and who are in risk level 3 and above (table 1) require planned transition to adult cardiac follow-up at age 16–18 years. The timing of such transition should reflect the developmental needs of the individual concerned. During transition, joint paediatric and adult clinical supervision is recommended, until such time as safe transfer of care can occur. Transition should be to a specialist KD clinic,

led by staff with a specific interest in KD, with access to interventional cardiology, assessment of anticoagulation and 24 hours availability of cardiac CT or MRI.

Many children with CAA during the acute illness or persisting during early follow-up may have undergone resolution of their CAA at the time of transition or their cardiac status may be unknown. A rational approach to transition includes making a cardiovascular assessment (table 1) together with specific testing to detect subclinical ischaemia, valve dysfunction and myocardial fibrosis. Because arterial calcification is a feature of KD vascular lesions, the CT calcium score is particularly useful for risk stratification of young adults (table 2).[36]

Myocardial ischaemia may develop in patients with CAA at any age, either due to thrombosis within the aneurysm or slow development of a coronary stenosis during vascular remodelling. As clinical features cannot reliably determine the underlying aetiology, urgent imaging should be undertaken to rule out coronary thrombosis in all patients with new onset suspected myocardial ischaemia (10) (figures 1 and 2). It is important to stress that:

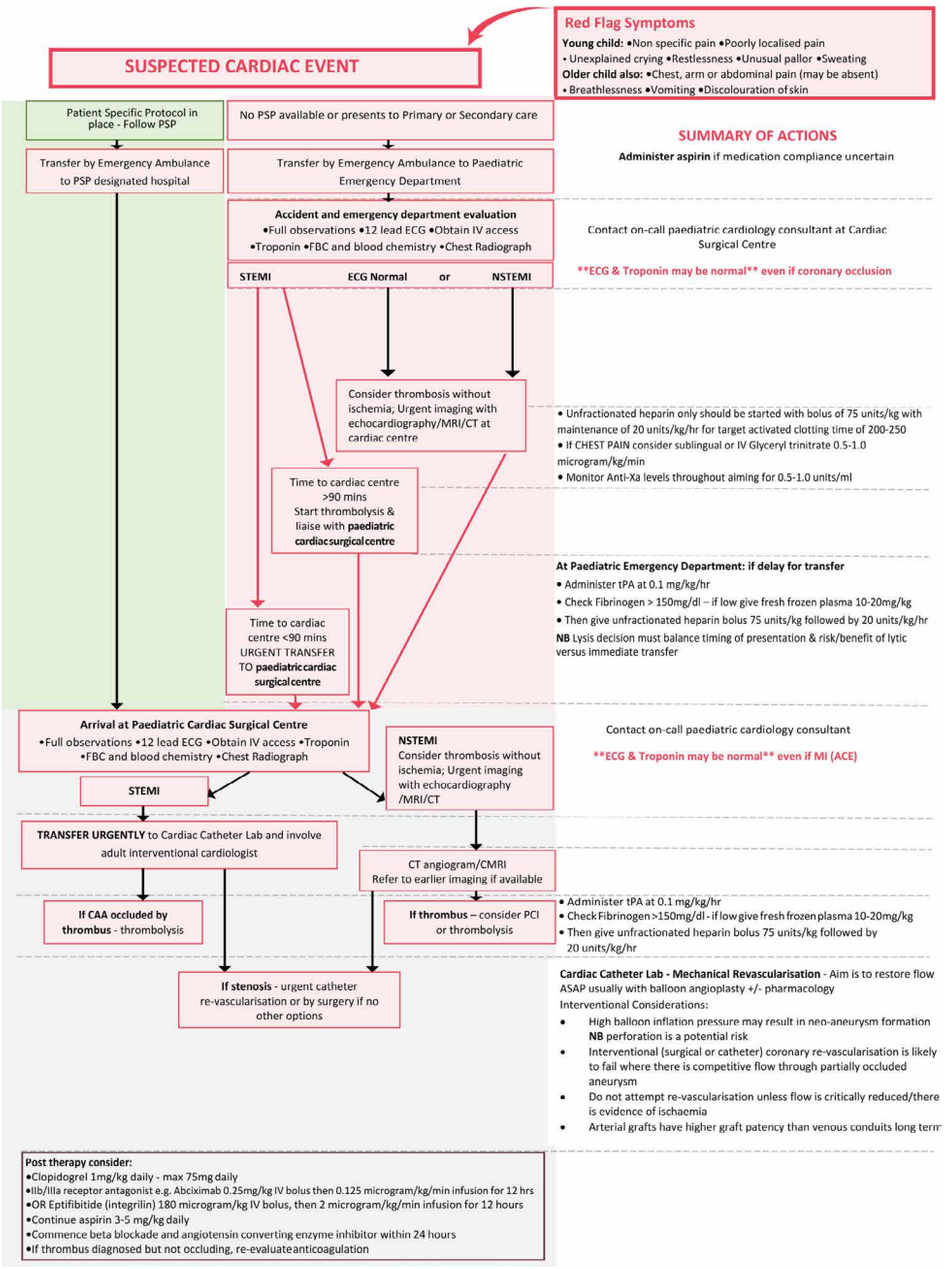

Figure 1 Kawasaki disease emergency management of suspected myocardial ischaemia in children with previous Kawasaki disease and possible coronary artery aneurysms. CAA, coronary artery aneurysms; nSTEMI, non-STEMI; PSP, person-specific protocol; STEMI, ST-elevation myocardial infarction.

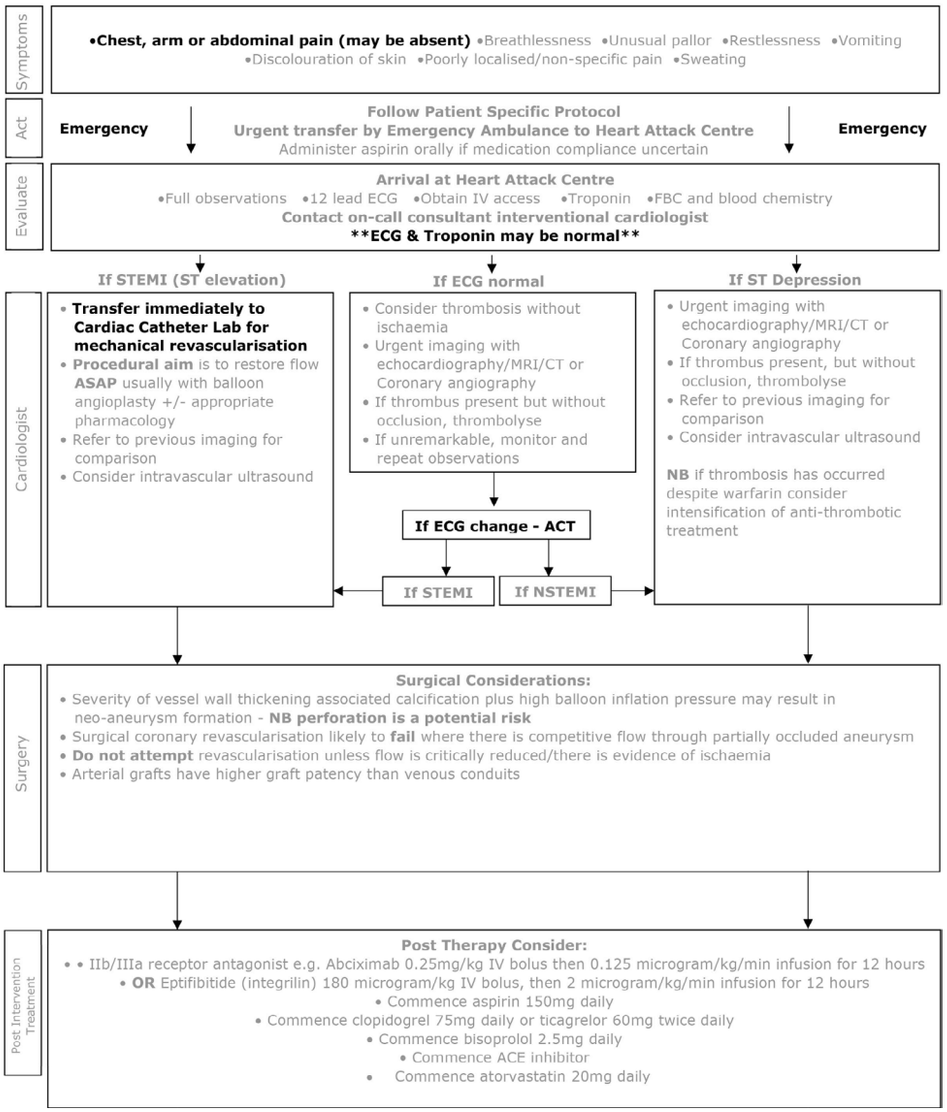

Figure 2 Kawasaki disease emergency management of suspected myocardial ischaemia in adults with previous Kawasaki disease and possible coronary artery aneurysms. nSTEMI, non-STEMI; STEMI, ST-elevation myocardial infarction.

1. 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.
2. 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.[11]
3. In all patients with a previous history of KD CAA, an initial ECG and troponin may be unremarkable, even with significant myocardial ischaemia.
4. 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 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.

An unusual feature of children with persistent significant coronary involvement as a consequence of KD is that they can develop significant coronary collaterals over time, such that even complete thrombotic occlusion of a coronary artery may not result in myocardial ischaemia. Coronary thrombosis per se is therefore not necessarily a call to action if there is no myocardial territory at risk but always requires rapid review of antithrombotic strategy and of the overall management plan. The presence of myocardial ischaemia is the most important factor that should prompt consideration of coronary intervention.

Existing care pathways—gaps in paediatric provision

In the UK, adults with suspected acute coronary syndrome (ST-elevation myocardial infarction (STEMI) or high-risk non-ST elevation myocardial infarction (nSTEMI)) are usually taken by the Ambulance Service to a designated Heart Attack Centre. Patients presenting to general hospitals undergo emergency triage and are usually then transported to a Heart Attack Centre if appropriate. There is no similar arrangement for coordinated management of suspected acute coronary syndromes in children. Paediatric services are largely unfamiliar with the detection and management of myocardial ischaemia due to its rarity in children, and many hospital emergency departments for children have no on-site paediatric cardiology. Children's specialist cardiac centres are often located away from accident and emergency services or adult interventional cardiology centres.

Addressing gaps

It is therefore essential that, together with general raised awareness of the risk of acute coronary syndrome in people who have had a past episode of acute KD, a PSP and local pathway are in place for every patient with persistent or remodelled CAA so that they can reach the required cardiac expertise rapidly in the event of a suspected acute coronary syndrome. These should form and inform part of the PSP (see above).

Myocardial ischaemia—presentation to primary or secondary care

It is inevitable that some patients, both adults and children, will present to a primary or secondary care service where the required cardiac expertise is not available. We summarise below the potential complications and actions required to ensure patients reach appropriate care rapidly.

- If the patient does not have a PSP or the deterioration occurs at work or school, the patient is likely to be transported by ambulance services to the nearest Heart Attack Centre (adult patient) if paramedics diagnose STEMI or high risk nSTEMI or the nearest children's accident and emergency centre, where the required cardiac expertise may not be available.
- 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 on 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.

Acute investigations—paediatric

A pre-existing paediatric KD acute coronary syndrome pathway should be in place at the designated centre and the child comanaged by the paediatric cardiology team and coronary intervention service. Urgent assessment should include clinical examination, an ECG, serial high sensitivity troponins and an echocardiogram, with awareness and acknowledgement of their PSP, and an understanding that absence of ECG changes or rise in troponin does not exclude a KD-related cardiac event. If ST elevation is present on the ECG, urgent contact with the appropriate interventional cardiologist should be made, with likely triage direct to the cardiac catheter laboratory (see below). If obvious STEMI is not present, but acute myocardial ischaemia is suspected, imaging by CT angiography or cardiac MRI should be undertaken to establish whether thrombus formation within a CAA has occurred or if coronary stenosis is the cause of symptoms, as the therapeutic options differ. Those with thrombus present in the coronary aneurysm, but without complete vessel occlusion, should be considered for intravenous thrombolysis and intensification of antithrombotic measures. Successful thrombolysis can be achieved in over 50% of patients with aneurysms using repeated daily infusion of tissue plasminogen activator (tPA) (alteplase).[37 38] If thrombosis has occurred despite anticoagulation with warfarin, intensification of antithrombotic treatment by transfer to unfractionated heparin, switching to a DOAC and addition of other antiplatelet agents should be considered in adults and might be a possibility in children and young adults if their safety and efficacy is confirmed in the future.

Emergency management of paediatric acute coronary syndrome

Experience from the management of acute coronary syndrome in adults has demonstrated the importance of time to coronary reperfusion. Broadly, the longer the time to restoration of normal coronary blood flow, the greater the extent of myocardial damage and the worse are outcomes. Most paediatric cardiologists have little experience in managing acute myocardial ischaemia, so close collaboration with adult interventional cardiology services is essential. With the advent of smaller guide catheters and devices, patients with coronary artery internal dimensions of at least 1.5 mm are suitable candidates for percutaneous coronary intervention (PCI) in the setting of STEMI. Technical considerations and the size of the child will determine which patients are candidates for PCI or when thrombolysis is the preferred initial treatment. A carefully mapped pathway, set out and agreed in advance of any emergency event and taking account of local context, should be made and documented within the PSP in order to ensure a timely and smoothly orchestrated response by the paediatric cardiology and supporting adult interventional cardiology teams.

Paediatric protocol

Although clear guidelines for adult STEMI have been issued, guidance for the paediatric population is limited; box 1 suggests a protocol for STEMI or other coronary ischaemic events in children

Interventional cardiology—all ages

Management of suspected myocardial ischaemia in patients with KD aneurysms differs from standard management of adult chest pain because of the high risk of large thrombi within coronary aneurysms, and the different anatomy of the artery damaged by inflammation, calcification and fibrosis as a consequence of KD. The procedural aim in the emergency setting should be to restore flow as quickly as possible. In the presence of acute occlusion with a large thrombus burden, angioplasty without stenting may be the preferred option. Routine thrombus aspiration is not supported but may be required to achieve recanalisation, acknowledging the associated risk of thromboembolisation.[39] Intravascular ultrasound (IVUS) is essential to assess true vessel size and guide management. If the thrombus is not occlusive, medical therapy with aspirin, clopidogrel, tPA and IIb/IIIa platelet inhibitor should be considered. Other oral antiplatelets (such as ticagrelor) have been used but on the basis of evidence derived from non-KD populations.[40]

Box 1 Suggested protocol for ST-elevation myocardial infarction or other coronary ischaemic events in children

- As most children with known coronary artery aneurysms will already be on aspirin, additional oral aspirin should only be administered if there is uncertainty about compliance or the child is not already on aspirin.
- If there is ST elevation on the initial ECG, cardiovascular collapse or clinical suspicion of myocardial ischaemia and expected transport time to a congenital cardiac surgical centre with colocated interventional cardiology or Heart Attack Centre is more than 90 min, then tissue plasminogen activator (tPA) should be administered prior to transport. For tPA to be effective, fibrinogen must be >1500 mg/L. If low, then intravenous fresh frozen plasma (10–20 mL/kg) should be given and a further check performed. While giving tPA, unfractionated heparin (UFH) should be commenced through a separate line.
- If there is ST depression on the ECG, UFH should be started. There should be an initial intravenous bolus of 75 units/kg, with maintenance of 20 units/kg/hour for target activated clotting time 200–250 or an activated partial thromboplastin time ratio in the range 1.5–2.5. If there is chest pain, sublingual or intravenous glyceryl trinitrate should be started.
- Patients too ill to transfer, or in whom delay in transfer to a paediatric cardiac surgical centre is likely, should be discussed with an interventional cardiologist and thrombolysis considered prior to transfer.[47]

Patients with angina due to stenotic lesions (ie, thrombus within the aneurysm is not the cause of ischaemic symptoms) may require PCIs. However, a number of issues specific to KD pathology need to be considered before any procedure is undertaken. The intense luminal myofibroblastic proliferation and calcification in KD can pose particular challenges to interventionists; debulking or modification of calcification with rotational atherectomy or cutting balloon technology may be required. Due to the severity of vessel wall thickening and associated calcification, high balloon inflation pressures may lead to neo-aneurysm formation. Moreover, the frequency of a heavy thrombus load and the large calibre of the aneurysms themselves present additional challenges for coronary stent deployment.

There is limited experience with the use of covered or drug-eluting stents in this patient population.[41] Intravascular imaging, either by IVUS or optical coherence tomography, plays an important role in guiding treatment, as inadequate appreciation of the diameter of vessels due to thrombus may lead to undersizing and/or inappropriate stent placement.[14 15 23 42 43]

Clopidogrel should be given orally, in addition to aspirin, prior to intervention. For additional or postprocedure therapy, consider:

- Abciximab (currently in short supply): or
- Eptifibatide (Integrilin).
- Aspirin continued at low dose along with Clopidogrel.
- For patients at increased risk of thrombosis (such as those with large or giant aneurysms and recent coronary thrombosis) 'triple therapy' with aspirin, a second antiplatelet agent and anticoagulation with warfarin, low molecular weight heparin or a direct oral anticoagulant (DOAC) should be considered. Trials of DOACs for this clinical indication are underway; in adults, many already prefer a DOAC to warfarin.
- Atorvastatin for possible additional anti-inflammatory effect.
- In order to reduce the risk of postprocedural heart failure and arrhythmia, then beta blockade and ACE inhibitor within 24 hours of procedure.

Cardiac surgery

Revascularisation is likely to fail when flow through a partially occluded aneurysm competes with graft flow and so bypass grafting should not be considered unless flow through the aneurysm is critically reduced. When surgery has been undertaken in this patient population both saphenous vein and arterial grafts have been used[44] but arterial grafts have a much higher rate of graft patency over time compared with venous conduits.[45 46] A saphenous graft might supply adequate flow acutely, but the conduit may degenerate while the patient is young.

'Excluding' an aneurysm (by surgically occluding the native coronary artery) at the time of bypass grafting has been undertaken in some past cases in an attempt to reduce the potential for bypass graft occlusion due to competitive flow. This approach is not recommended as it has significant associated risks; if the aneurysm is excluded, an immature internal mammary LIMA graft may not supply adequate blood flow to the left ventricular anterior wall at the time of surgery, resulting in continuing ischaemia.

Elective coronary interventions should be planned after careful discussion with a broad multidisciplinary team. Cardiac transplantation has been successfully performed for the patient with rare KD with end-stage cardiomyopathy and inoperable multivessel coronary artery disease.

NON-CARDIAC COMPLICATIONS

Thrombosis within extracardiac aneurysms

Patients with aneurysms of extracardiac arteries (most commonly axillary and iliac/femoral) are at risk of luminal thrombosis. This may present with features of peripheral ischaemia such as claudication, pallor, pain, loss of pulses or discolouration 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.

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.

SUMMARY

Patients with CAA as a result of KD in childhood are at lifelong risk of cardiac complications and require lifetime follow-up at specialist regional KD clinics. Those with established CAA have a continuing increased risk at all ages; in Japan, it has been reported that major adverse cardiovascular events occur in 64% of patients within 30 years of diagnosis.[26]The management of suspected myocardial ischaemic events in these patients differs from that of adults, who have acute coronary syndromes due to atherosclerotic heart disease. Each patient at risk requires a PSP to ensure that

Box 2 Key elements for management of previous Kawasaki disease (KD) in children and adults

- Those who have coronary aneurysms following acute KD, whether persisting or remodelled, are at lifelong risk of coronary thrombosis, coronary stenoses and acute coronary syndromes.
- An individual's lifetime risk is related to the severity of residual cardiac pathology (particularly coronary aneurysms) after the initial illness.
- Every child or adult who has had coronary artery aneurysms (CAA) following KD, whether persisting or remodelled, requires lifelong uninterrupted follow-up by a cardiology team within a specialist KD clinic with services agreed by the relevant Congenital Cardiac Network and adult interventional cardiology service.
- A child with a past history of KD aneurysms, who presents with any symptoms or signs which could be due to aneurysm thrombosis or acute coronary syndrome, should be managed using a pathway of care predefined by the local specialist children's congenital cardiac network in accordance with this guidance.
- An adult with a past history of KD and CAA, who presents with any symptoms or signs which could be due to aneurysm thrombosis or acute coronary syndrome, should be taken directly to a Heart Attack Centre (HAC). Those who present to a local hospital should be transferred urgently to a HAC to rule out CAA thrombosis, progressive coronary stenoses or acute coronary syndrome. Delay is likely to have an adverse effect on outcome.
- Every child or adult followed-up for CAA should have a person-specific protocol (PSP) written, detailing the pathway of care to be followed if a suspected acute coronary syndrome should occur.
- Aneurysm thrombosis and acute coronary syndromes in patients with previous KD may present with atypical symptoms and initial absence of typical changes on the ECG or changes in cardiac enzymes. All patients with chest pain or suspected acute coronary syndrome should be imaged urgently to rule out thrombus.
- Emergency access to interventional cardiology services will be required to manage suspected acute coronary syndromes in children and should be part of the care pathway defined. The congenital cardiac centre and the HAC should ideally be colocated, but where not, arrangements for emergency access should be clear, agreed in advance of any need and documented in a PSP.
- Congenital Cardiac Networks should take the lead on disseminating learning and best practice in line with this guidance, to all those who may be involved in the care of patients who have had KD. Where these do not exist, they should be established with adult and paediatric cardiology input and ensure access to specialist cardiac imaging, interventional cardiology and cardiac surgery.
- Centralising the follow-up of affected patients will help concentrate and build expertise, enable the development of care pathways for the emergency management of acute complications and facilitate research.
- Transition of care from a paediatric to adult service should be planned in advance and be well-coordinated.

they reach an appropriately equipped centre with specialist expertise and that they do so without delay (Box 2).

Person-specific protocol

See online supplementary file 2.

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Clinician poster

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THINK Kawasaki Disease...

...for our children

Kawasaki Disease *is the leading cause of acquired heart disease in UK children...*
...faster diagnosis and treatment can change that!

Symptoms

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

Case History

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

Differential Diagnosis

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

~~*Virus?*~~ ~~*Scarlet Fever?*~~ ~~*Meningitis?*~~ ~~*Tonsillitis?*~~

Please...THINK Kawasaki Disease

~~*Slapped Cheek?*~~ ~~*Strep Throat?*~~ ~~*Measles?*~~

5 days of fever?

THINK Kawasaki Disease

Acute **Kawasaki Disease** *is always an* **emergency!**

Persistent Fever

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

Babies under 1

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

Increasingly Common

Hospital admissions are rising: doubling every 10 years globally

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

Heart Damage*

28% *Where we are today* of treated children with heart damage

This is too high!

4% *Where we need to be* (or less) of treated children with heart damage

Treatment Time*

5 days of fever?

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

BPSU 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 DONT DELAY!

Numbers to Remember*

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*

**BPSU: Kawasaki Disease, a propsective population survey, UK and Ireland 2013-2015; R Tulloh et al*

societi.org.uk

General awareness raising poster

Access

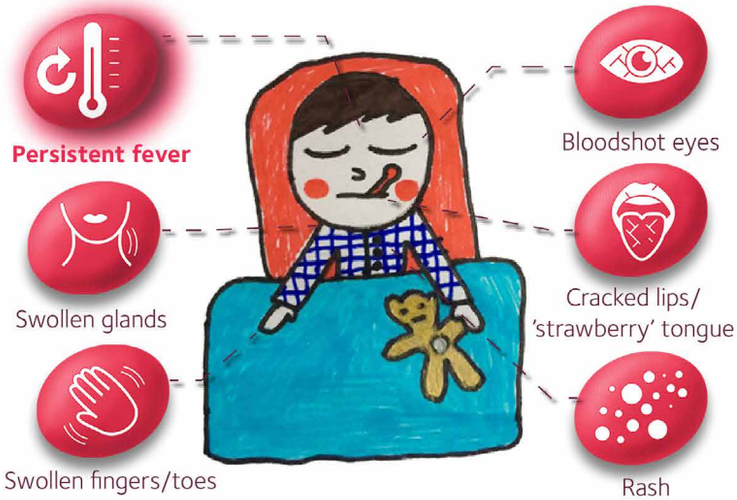
This general awareness rasing poster is intended as a waiting room resource for patients. **Click the access button** to download a printable copy or contact **info@societi.co.uk** and we'll be happy send you some copies free of charge.

THINK Kawasaki Disease!

Kawasaki Disease *is the leading cause of acquired heart disease in children in the UK. It's time we changed that...*

...Together we will

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**

Kawasaki Disease can be present with **some or all** these symptoms

Kawasaki Disease is **increasingly common** in the UK

Please **EXPECT** to see it, be **READY** to treat it!

EARLY TREATMENT IS KEY

PLEASE DON'T DELAY! Children diagnosed and treated in **less than 5 days** from onset of fever have a **much reduced risk** of life long heart damage

BABIES UNDER 1 YEAR

can show **fewest symptoms** but have the **highest risk** of serious heart damage

Kawasaki Disease is mostly a childhood illness and there's no known cause. It's **the leading cause of acquired heart disease in UK children**.

It's **often mistaken** for other common childhood illnesses, leading to delayed treatment. Children who are untreated or who are treated later face a much higher risk of developing serious complications, including life-long heart damage.

Babies under one year are at greatest risk of serious heart damage. **Early diagnosis and treatment is critical.**

Current UK & Ireland Outcomes for Kawasaki Disease

7+ days — The current average diagnosis time for Kawasaki Disease is 7.8 days **This is too slow!**

39% — 39% of babies with Kawasaki Disease develop coronary artery aneurysms **This is too high!**

19% — 19% of children overall develop coronary artery aneurysms **This is too high!**

28% — 28% of children overall have some heart damage **This is too high!**

TOGETHER WE CAN CHANGE THIS!

Data from Tulloh et al, Kawasaki Disease: a prospective population survey UK & Ireland 2013-15

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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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