

## Joint Trust Guideline for the Diagnosis and Management of Kawasaki Disease in Children

### A Clinical Guideline

<b>For Use in:</b>	Children's Assessment Unit, Buxton Ward
<b>By:</b>	Medical and nursing staff in Paediatrics
<b>For:</b>	Children with Kawasaki disease
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This guideline has been approved by the Trust's Clinical Guidelines Assessment Panel as an aid to the diagnosis and management of relevant patients and clinical circumstances. Not every patient or situation fits neatly into a standard guideline scenario and the guideline must be interpreted and applied in practice in the light of prevailing clinical circumstances, the diagnostic and treatment options available and the professional judgement, knowledge and expertise of relevant clinicians. It is advised that the rationale for any departure from relevant guidance should be documented in the patient's case notes.

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6.1	19/04/2022	No clinical changes	Hannah Massey
6.2	09/11/2022	Small amendment to Investigations- Echocardiogram. 6-8 weeks from onset changed to 2 weeks and 6 weeks from onset. 2 appendices added to end of guideline.	Dr Rao Kollipara (Paediatric Consultant, JPUH), Dr Shastri

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## 1. Glossary

CRP	C- reactive protein
ESR	Erythrocyte sedimentation rate
UE	Urea and electrolytes
FBC	Full blood count
LFT	Liver function test
WCC	White cell count
Echo	Echocardiogram
ECG	Electrocardiogram
ASOT	Antistreptolysin O titre
ALT	Alanine transaminase
ANA	Antinuclear antibodies
IVIG	Intravenous immunoglobulin
EBV	Epstein Barr virus
CMV	Cytomegalovirus
NSAID	Non-steroidal anti-inflammatory drugs
HLH	Hemophagocytic Lymphohistiocytosis

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## 2. Quick reference guideline/s

### 2.1 Diagnosis and management of Complete Kawasaki Disease in Children

#### Algorithm A

#### FEATURES OF KAWASAKI DISEASE

Fever > 5 days duration and  
 Polymorphous rash  
 Changes in extremities  
 Bilateral non exudative bulbar conjunctivitis  
 Changes in lips and oral cavity  
 Cervical lymphadenopathy  
 See text for further details

≥4 CRITERIA

Perform Lab tests

- FBC, UE, LFT
- CRP ESR
- Urine microscopy
- Troponin-I

Echo – positive  
 Consult Cardiologist

- Echo
- ECG

#### Consider if the Patient has High Risk Features. This includes

- Already failed IVIG?
  - Severe disease: Those under 12 months, those with persistently elevated CRP despite IVIG treatment, liver dysfunction, hypoalbuminaemia and anaemia
  - Features of HLH of shock
  - Already evolving coronary aneurysms with ongoing inflammation, if known
- If in doubt seek expert advice

#### No High Risk Features

- Start IVIG 2g/kg over 12 hours
- Start aspirin 30-50mg/kg/day in four divided doses

#### High Risk Features Present

- Start IVIG 2g/kg over 12 hours
  - Start aspirin 30-50mg/kg/day in four divided doses
- And**
- Consider methylprednisolone 10-30mg/kg over 2-3 hours once daily for 3 days then oral prednisolone 2mg/Kg daily to 7 days and wean over 2-3 weeks.
  - Consider discussion with rheumatology and cardiology

#### Disease Defervescence

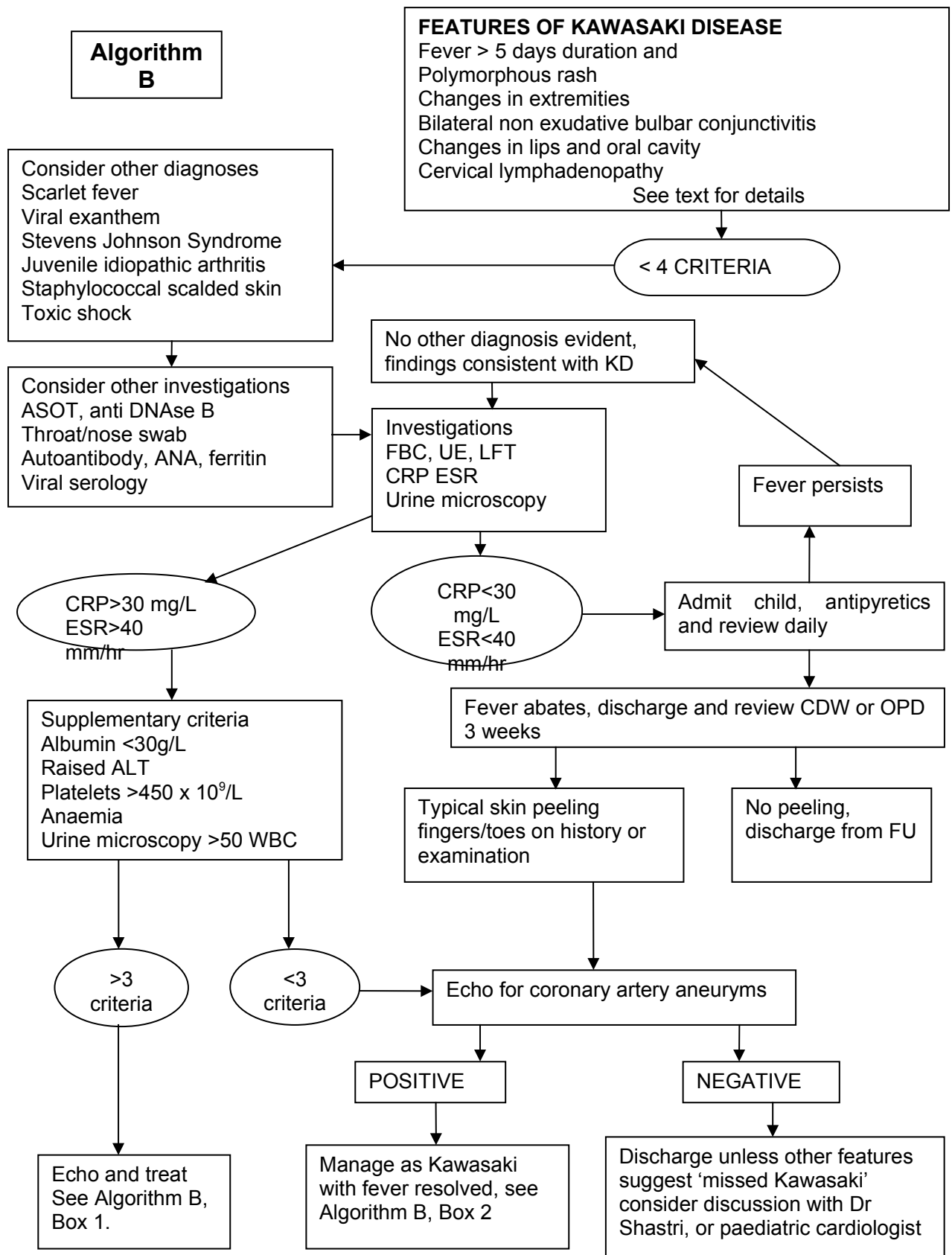
- No fever for 48 hours, falling crp, child improving clinically
- Reduce aspirin to 3-5mg/kg/day
  - Patients need a repeat echo at 2 weeks booked on ice by the physiology department and at 6 weeks In Dr Shastri's cardiac clinic

#### No Disease Defervescence or Disease recrudescence

- Give second dose of IVIG 2g/kg over 12 hours
- Consider giving methylprednisalone if not already given
- Consider discussion with rheumatology and cardiology team
- Consider other immunosuppressant such as infliximab.

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## Evaluation of Suspected Incomplete Kawasaki Disease



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## 3. Rationale

Kawasaki disease is an uncommon disease of childhood that is difficult to diagnose, having many features that overlap with other commoner diseases in childhood. The early diagnosis and prompt treatment of this condition is essential to reduce mortality and morbidity associated with cardiovascular complications.

## 4. Broad recommendations

1. Kawasaki disease requires a high degree of clinical vigilance as

- It is rare.
- It is diagnosed on clinical criteria rather than diagnostic interventions.
- It has potentially life-threatening complications, including coronary artery vasculitis with aneurysm formation.
- Treatment is available but must be given early if it is to be effective.

2. A Consultant should assess the child before commencing treatment with IVIG and aspirin.

## 5. Definition

Kawasaki disease is an acute self-limiting vasculitis of unknown aetiology that occurs predominantly in infants and young children.

It affects large-medium vessels and is characterised as an acute febrile illness associated with features of systemic vasculitis.

## 6. Epidemiology

- a) Incidence: varies considerably worldwide from 3.4 -100 per 100,000 children.
- b) Peak age of onset: 1-3 years but can occur in infancy or in later childhood/adolescence
- c) Risk factors:
  - M>F 1.5:1
  - Race, East Asian > Asian > Black > Caucasian
  - Later winter/ early spring peak
- d) Pathogenesis: remains unknown although clinical and epidemiological features strongly suggest an infectious cause
- e) Prognosis: In the absence of therapy 15-25% will develop coronary artery aneurysms which may lead to ischaemic heart disease and sudden death. This risk is reduced to < 5% with timely use of IVIG (within 10 days of onset of fever)

## 7. Making a diagnosis

In the absence of a diagnostic test, making a diagnosis depends on recognition of key clinical features and the exclusion of alternative diagnoses with similar presentations.

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## 8. History and Examination

### 8.1 Typical or complete cases

**Fever of at least five days duration** (defined as recorded temperature of 38 degrees or above or tactile temperature by parent) and 4 of 5 classical features from the following list

#### I. Changes in extremities

- Acute: Erythema of palms, soles; oedema of hands, feet
- Subacute: Periungual peeling of fingers and toes in weeks 2 and 3.
- Chronic: Deep transverse grooves (Beau's lines) may appear across the nails after 1-2 months of onset of fever.

#### II. Polymorphous rash - the rash may take various forms:

- Nonspecific diffuse maculopapular eruption
- Urticarial exanthem
- Scarletiform rash
- Erythroderma
- Erythema multiforme-like rash
- Micropustular eruption (rare)
- It is always non- bullous and non-vesicular
- The rash is usually extensive with the involvement of the trunk and extremities and accentuation in the perineal region, where early desquamation may occur

#### III. Bilateral bulbar conjunctivitis without exudate

- Spares the limbus (pale ring immediately surrounding pupil)
- Painless
- Mild iridocyclitis or anterior uveitis may be noted by slit lamp; it resolves rapidly and rarely associated with photophobia or eye pain

#### IV. Changes in lips and oral cavity

- Erythema, dryness, fissuring, peeling, cracking and bleeding of lips
- Strawberry tongue with erythema and prominent fungiform papillae
- Diffuse erythema of the oropharyngeal mucosa

#### V. Cervical lymphadenopathy

- Least common, usually unilateral

Even in the presence of the above, it remains important to exclude other conditions with similar findings which include:

- Viral exanthems (e.g. measles, adenovirus, enterovirus, EBV)
- Scarlet fever



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- Staphylococcal scalded skin syndrome
- Stevens-Johnson syndrome
- Juvenile idiopathic arthritis (systemic onset)
- Toxic shock syndrome
- Drug hypersensitivity reactions

### 8.2 Atypical Or “Incomplete Cases”

These have fewer diagnostic features. They can however still develop complications, so making the diagnosis remains very important. Where fewer than 4 features are present, a high degree of clinical vigilance is required. The following less common clinical findings involving other systems should be looked for.

System	Finding
Neurological	Extreme irritability
	Aseptic meningitis
	Sensorineural hearing loss – transient during acute phase
Musculoskeletal	Arthritis and arthralgia, myositis
Gastrointestinal tract	Diarrhoea, vomiting and abdominal pain
	Hepatitis
	Acute acalculous distension of gallbladder (hydrops) - during first 2 weeks of illness may be identified by ultrasound scan
Genitourinary	Urethritis, meatitis
	Sterile pyuria
Other	Erythema, induration of BCG inoculation site
	Mild anterior uveitis (slit lamp examination required)

It is also important to remember common diagnostic pitfalls, including

- Rash and mucosal changes may be mistaken for drug reactions
- Sterile pyuria may be mistaken for a partially treated UTI
- CSF pleocytosis may be mistaken for viral meningitis

Supportive evidence should be sought through investigations (see section below).

In addition to incomplete case the diagnostic criterion of a fever for 5 days can also lead to a delay in treatment. Clinicians should not delay in making a diagnosis of Kawasaki disease and instituting treatment if:

- 5/6 diagnostic criteria of Kawasaki are present before day 5 of fever.
- CAA or coronary dilatation are present.
- There is evidence of persistent elevation of inflammatory markers with no other explanation in patients where there remains clinical suspicion of Kawasaki's

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## 9. Complications

Serious complications are rare but include

Acute phase (<10 days from onset)

- Myocarditis +/- endocarditis
- Pericarditis +/- effusion/tamponade
- Valvular incompetence

Subacute phase

- Coronary artery vasculitis – dilatation +/- aneurysms
  - First detectable 10 days
  - Peak onset 3-4 weeks
- Coronary artery thrombosis and stenosis
- Systemic large vessel vasculitis (1-2%)
  - Cerebral
  - Subclavian, axillary, brachial aneurysms
  - Peripheral ischaemia/gangrene

## 10. Investigations

In the presence of less than 4 features of Kawasaki Syndrome, these are useful to aid the decision to treat 'incomplete' disease (see Algorithm A).

### i. Bloods

Full blood count

- Mild anaemia
- Leukocytosis with neutrophilia and immature forms
- Thrombocytosis after week 1, peaks in the third week, normalises by 4-8 weeks

Urea and electrolytes, liver function, plasma lipid profile

- Hyponatremia
- Hypoalbuminaemia
- Elevated serum transaminases
- Elevated gamma glutamyl transpeptidase
- Abnormal plasma lipids
- Raised Troponin-I

### ii. Urine microscopy and culture

- Sterile pyuria

### iii. Others – Pleocytosis of cerebrospinal fluid

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- iv. Echocardiogram - should be arranged as soon as possible ideally by Dr Shastri, however, treatment should not be deferred.
  - In acute phase – if positive for coronary artery aneurysm, repeat echo after 2-3 days to monitor progression
  - 2 weeks and 6 weeks from onset
  - 12 months from onset
- v. ECG – should be done at presentation
  - Prolonged PR interval
  - Non specific ST and T wave changes
  - Arrhythmias

Investigations to exclude/ confirm alternative diagnosis may be considered (discuss with consultant)

- ASOT and anti-DNAase B
- Blood culture, urine culture
- Nose/throat/skin swab
- Lumbar puncture
- Coagulation screen
- ANA, Rheumatoid factor, ferritin
- Serology for EBV, mycoplasma, CMV, parvovirus, measles etc.

### 11. Management

#### 11.1 Definitive treatment

Children should be reviewed by a consultant before starting definitive treatment. Treatment should be started for.

- All children meeting criteria for complete or typical Kawasaki disease without alternative diagnosis
- All children with sufficient clinical criteria to suspect Kawasaki disease and where laboratory data is supportive in absence of a definitive alternative diagnosis. (See Algorithm B)

Treatment should be started **within 10 days** of the onset of symptoms and if possible, **within 7 days** to be most effective, but can be started beyond 10 days in the presence of ongoing signs (and/or laboratory evidence) of inflammation.

##### i. First line treatment

- Intravenous immunoglobulin (IVIG) 2 gram/kg IV as single infusion over 12 hours. IVIG request form to be completed and emailed as an attachment to Colin Green, D & T Pharmacy Advisor.

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- Aspirin – 30-50mg/kg/day in 4 divided doses. All other NSAIDs should be stopped. This dose should be continued until the child has been afebrile for >48-72 hours or for a maximum of 14 days

Thereafter aspirin to continue at 3-5mg/kg/day once daily until review of echocardiogram 6-8 weeks after onset of illness.

NOTE: Corticosteroids have been used as initial therapy or in conjunction with IVIG in the treatment of Kawasaki disease. However, there is little evidence to support steroids first line use in most children with Kawasaki disease. It may be appropriate to consider it along side IVIG for children who have high risk features as shown in algorithm B. This should be discussed with a specialist.

### ii. Second line treatment

Approximately 10% of patients with Kawasaki disease fail to respond with initial IVIG therapy. Failure to respond usually is defined as persistent or recrudescence fever > 36 hours after completion of initial IVIG infusion.

- Repeat IVIG 2gram/kg as a single infusion over 10-12 hours
- Consider Methylprednisolone 10 (up to maximum 30) mg/kg over 2-3 hours once daily for 3 days, followed by 2mg/Kg prednisolone for 4 days, weaning over 2-3 weeks
- Discuss with paediatric rheumatology team. The local link is Dr Shastri, if he is unavailable, discuss with Dr Bale or Dr Armon (paediatric rheumatology team at Addenbrookes Hospital). If they are unavailable the case can be discussed with the Great Ormond Street hospital infectious disease team.
- Discuss with Cardiologist at Great Ormond Street Hospital (#6111)

## 11.2 Supportive management

- Fluid balance to be maintained and monitored closely
- Regular antipyretics/analgesics, all NSAIDs to be stopped when aspirin is commenced
- Consider need for lansoprazole / omeprazole with aspirin treatment, and definitely treat with PPI if aspirin and steroids given

## 11.3 Management of coronary artery aneurysms

- If echocardiogram shows coronary artery aneurysms, the Cardiologist should be contacted. These children will need long term aspirin therapy
- Children taking long term salicylates should receive annual influenza vaccine
- Patients who require long term aspirin due to CCA should be considered for varicella zoster virus vaccine. In view of the association between VZV, aspirin and Reye's syndrome.

## 11.4 Long term follow up of uncomplicated cases

- If echocardiogram is normal at 6-8 weeks, then aspirin can be stopped. Repeat echocardiogram in 12 months

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- Children who have received IVIG should not receive live vaccines for at least three months.

### 12. Clinical audit standards

All children with suspected Kawasaki disease should be treated with IVIG within 24 hours of a consultant confirmed diagnosis.

### 13. Summary of development and consultation process undertaken before registration and dissemination

The guideline was drafted by the authors listed above and circulated among the Paediatric Consultants and other medical staff, who have agreed the final content.

The document was reviewed in 2022 and not clinical changes were required but a short review date given because a new appendix for nurses is being developed.

This version has been endorsed by the Clinical Guidelines Assessment Panel.

### 14. Distribution list / dissemination method

Childrens Assessment Unit, Buxton ward

### 15. References/ source documents

1. Newburger JW et al: Diagnosis, Treatment, and Long-Term Management of Kawasaki Disease: A Statement for Health Professionals from the Committee on Rheumatic Fever, Endocarditis and Kawasaki Disease, Council on Cardiovascular Disease in the Young, American Heart Association *Pediatrics* 2004;114;1708-1733
2. Baumer JH:Kawasaki Disease: what to do with incomplete cases? *Arch Dis Child Pract Ed* 2005; 90:ep102-ep 104
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4. Furukawa et al Effects of steroid pulse therapy on immunoglobulin-resistant Kawasaki disease. *Arch Dis Child* 2008 Feb;93(2):142-6.
5. Eleftheriou D, Levin M, Shingadia D, etal. Management of Kawasake disease. *Archives of Disease in Childhood* 2014;99:74-83.

Also see the Patient Information leaflet (Appendix one)

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## Appendix 1 - Kawasaki Disease - Information for Parents

### What is Kawasaki disease?

Kawasaki disease is an illness which affects children's blood vessels, causing them to be inflamed (red, hot, swollen) It affects young children the most (80% of children are under 5 years of age). It is very rare in this country, affecting 150-200 children per year in the UK. Boys are more likely to have this illness than girls.

### What causes Kawasaki disease?

Although the cause is not yet fully understood, it is thought to result from an infection.

### What are the symptoms of Kawasaki Disease?

The main symptom is fever that is higher than 38 degrees centigrade, lasting for at least 5 days. The other symptoms are:

- Soreness of the mouth and lips.
- Reddening of the tongue with raised bumps (strawberry tongue).
- Rashes on the body, hands and feet.
- Swelling of the hands and feet.
- Reddening of the eyes.
- Swollen glands in the neck.
- Significant discomfort and irritability in young children.

Once the fever improves, the red eyes and swollen glands will disappear. However, during the third week of illness the skin around the hands and feet may peel.

### Are there any complications of Kawasaki disease?

Most children make a full recovery without any problems but for some children there is a risk of developing swelling or 'ballooning' of the blood vessels of the heart (termed coronary aneurysms). This may cause other heart problems. The risk of aneurysms is reduced if children are treated within 10 days of the start of the illness.

### What tests will your child undergo in hospital?

There is no single test for Kawasaki disease; however, some tests are carried out to help to confirm the diagnosis. These are:

- Blood tests - to look for signs of anaemia, raised markers of inflammation and increased platelet count (cell which helps in blood clot formation in blood vessels)
- ECG (electrocardiogram) - to look for any abnormalities of heart rhythm.
- Echocardiogram (heart scan or echo) - To look for how well the heart is functioning and for changes in the blood vessels in the heart (coronary artery aneurysms)

### What is the treatment for Kawasaki disease?

As soon as this illness is suspected, your child will begin a course of treatment including:

- An intravenous dose of immunoglobulin (a purified human blood plasma product) given in a drip over 12 hours. This will reduce the inflammation and if started within 10 days of the onset of illness, helps to prevent coronary artery damage.
- Aspirin given every 6-8 hours (to prevent clot formation in the coronary arteries) Most children will respond to this treatment and their fever should improve within 48 hours.

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### What happens after the first two days of treatment?

If your child does not have any further fever, then the following will change:

- The aspirin dose will be reduced to once daily.
- Your child will be discharged when their general condition improves.
- An echocardiogram will be repeated after 6-8 weeks, if this is normal then the aspirin will be stopped.
- A further echocardiogram will be done after 1 year.

### What happens if the treatment does not work?

If your child has persistent fever within the first 48 hours of treatment, then your medical team will:

- Give another dose of intravenous immunoglobulin.
- They may add steroid medication (IV and / or oral).
- Consider consulting a cardiologist (Heart Specialist) for further advice.

### What happens if there are problems seen on the echocardiogram?

If there are any signs of swelling of the coronary arteries or any signs that the heart is not functioning as well as it should, your medical team will consult a paediatric cardiologist (children's heart specialist) for further advice. Your child may need further tests to look at heart function and may have to have long term treatment with aspirin.

### What happens after discharge from hospital?

Following discharge, you may notice that your child is tired and does not eat well for nearly 2 weeks. This is quite normal, and most children make a full recovery. However, if your child has any of the following symptoms please contact the number below:

- Shallow, rapid breathing.
- Stomach pains.
- Vomiting (with or without blood).
- Return of fever or other symptoms of Kawasaki disease.

It is recommended that your child has the flu vaccine if they are on long term aspirin treatment, this can be arranged with your GP. Please contact them directly to discuss this. Your child will also receive a follow up appointment in the children's outpatient clinic in approximately 6-8 weeks. This will be to discuss your child's progress with a consultant paediatrician or senior paediatric trainee (doctors who are expert in the care of children).

### How to contact the Jenny Lind Children's Department

- There is a doctor and nurse available in the department 24 hours a day 7 days a week in the Children's Assessment Unit on: **01603 289774**.
- For outpatient appointment enquiries please contact: **01603 287055**.
- For questions about your child's medication please contact: **01603 286286** and ask for the **Pharmacy Helpline**
- The main number for the hospital is: **01603 286286**

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Appendix 2 – [Management of Kawasaki Disease - ADC Document](#)

Appendix 3 – [Fifteen-Minute Consultation: Kawasaki Disease: How to Distinguish from other Febrile Illnesses: Tricks and Tips – ADC Document](#)