BMJ Best Practice

Kawasaki disease

The right clinical information, right where it's needed

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Summary

- Acute febrile illness lasting 5 or more days.
- Typical signs include fever, polymorphic rash, injected eyes, and mucosal erythema with strawberry tongue.
- Swelling and erythema of the hands and feet occur in the acute stage, followed by desquamation in the second week.
- Unilateral non-purulent cervical lymphadenopathy is present in about 40% of cases.
- Coronary aneurysms develop in 20% to 25% of untreated patients.
- Standard treatment includes intravenous immunoglobulin and/or aspirin. In resistant cases, corticosteroids or a tumour necrosis factor (TNF)-alpha inhibitor may be necessary.

Definition

Kawasaki disease (KD) is an acute, febrile, self-limiting, systemic vasculitis of unknown origin that almost exclusively affects young children. In an immunogenetically pre-disposed host, one or more infectious agents may play a role in triggering the clinical manifestations of the disease. Clinically, it is characterised by fever, polymorphic rash, conjunctivitis, mucosal erythema with strawberry tongue, induration of the hands and feet, and unilateral cervical lymphadenopathy. Morbidity and mortality depend on coronary aneurysms that develop in 20% to 25% of untreated patients. KD is the leading cause of acquired heart disease in children under 5 years of age in the US and other developed countries.

Epidemiology

Kawasaki disease (KD) almost exclusively affects young children, with peak incidence between 13 and 24 months of age.[2] It is rare in the first 6 months of life, and 80% of all cases occur before age 5 years.[3] Although an HLA association has not yet been identified, the incidence of KD is significantly increased in Japan and Korea, as well as among Asian-American children in the US. It affects approximately 5000 US children annually.[4] Published hospitalisation data in the US showed a rate of 24.7 per 100,000 children less than 5 years of age in 2010. Children of Asian/Pacific origin had the highest rate (50.4 per 100,000), followed by children of black (29.8) and white (22.5) origins.[4] An earlier report from 1997 to 2000 showed an annual incidence of 16.9, 11.1, and 9.1 per 100,000 in the US for black, Hispanic, and white children <5 years of age, respectively.[5] However, the annual incidence of KD among Native Americans and Alaskan native children <5 years in 1999 was found to be only 4.3 per 100,000, despite the Asian ancestral origin of these children.[6] The figures for children of Asian-American and Pacific Island origin are reported to be higher, at 32.5 per 100,000.[5]

The annual incidence in Japan was estimated in 1999 as between 75 and 125 cases per 100,000 in children <5 years of age.[7] However, a more recent study showed that children of Japanese ancestry have a much higher incidence of 240 per 100,000 children <5 years of age.[4] The recurrence rate in Japanese children is 3%.[4] The high incidence among Asian ethnicities suggests that host genetic factors may play a significant role in the pathogenesis of KD.

Aetiology

The cause of Kawasaki disease (KD) remains unknown. However, the following observations suggest that this disease is triggered by an unknown infectious agent.

- Clinical picture: KD overlaps with infectious diseases such as scarlet fever and adenoviral infection.
- Seasonal occurrence: in the US and other geographic areas, the peak occurrence of KD is in the winter/spring, similar to that seen in numerous viral diseases.
- Epidemics with clear epicentre: temporal clusters have been reported in the US, Japan, and worldwide.[3]Moreover, in Japan, outbreaks have been observed to start in one area and spread throughout the country over a period of 3 months.[8]
- Age at onset: peak incidence is in the toddler age group; 80% of the cases are in infants under 5 years old, and the rarity of cases under 3 months of age suggests protective transplacental antibodies.[3] [7]

Studies have failed to identify viruses such as parvovirus B19, retrovirus, EBV, herpes, measles, or human corona (NL-63) viruses as causative agents for KD.[9] 1[B]Evidence So far, no evidence has been found to prove causality to any particular virus.

Similarly to viral illnesses, bacterial diseases may be linked to KD. The fever and other clinical manifestations of KD, such as mucous membrane lesions and desquamating skin rash, overlap with other well-defined infectious toxin-mediated diseases such as staphylococcal and streptococcal toxic shock syndrome (TSS), and scarlet fever. TSS toxin-secreting *Staphylococcus aureus* isolated from a patient with KD, manifested with coronary aneurysm, has been reported.[10] It is speculated that infection produces an immune-mediated reaction, causing the signs and symptoms of the disease in an immunogenetically susceptible host. It has been proposed that, in both KD and TSS, the disease is caused by viral or bacterial toxins acting as superantigens.[11] [12] A superantigen theory for KD continues to be investigated; however, significant supportive data are currently lacking.[13]

In the largest KD genomic-wide association study, involving five different independent sample collections in Japan, the most significantly associated genetic susceptibilities were variants with high affinity to FC receptor for immunoglobulin G (FCGR2A) and variants related to the T-cell receptor region regulator known as ITPKC (inositol 1,4,5-triphosphate 3-kinase C).[14] [15]

Although similarities exist between KD and acrodynia (mercury hypersensitivity), studies to link KD to drugs, toxins, chemicals, and heavy metals have shown negative results.[16]

Pathophysiology

Kawasaki disease (KD) is a systemic vasculitis manifested by relatively prolonged fever, rash, conjunctivitis, mucous membrane changes, cervical lymphadenopathy, and changes in hands and feet. The most serious complication of this unique illness is the development of an acute coronary artery vasculitis with dilatation or aneurysm formation. Initially, KD was considered just to be a self-limiting, benign condition. However, subsequent reports suggest that up to 2% of patients die from coronary abnormalities, and 20% to 25% of untreated patients develop coronary artery aneurysms (CAAs) or ectasia. In addition, KD may lead to myocardial infarction, sudden death, and ischaemic heart disease.[17]

In the early phase of the disease, there is development of oedema and neutrophil infiltration in the coronary arterial wall, with a rapid transition to mononuclear cells.[18] This is followed by local production of matrix metalloproteinases that cause destruction of the internal elastic lamina and media, with progress to fibrous connective tissue replacement of the intima and media, leading to aneurysm formation, scarring, and stenosis.[19]The standard treatment for KD, intravenous immunoglobulin, neutralises circulating antibodies through anti-idiotypic antibodies and downregulates these inflammatory events.[20]

Reports are available from children with KD who did not develop coronary abnormalities during the acute phase of the disease and died years later due to unrelated causes. Autopsies performed on these children demonstrated coronary artery intimal thickening and medial fibrosis.[21]

Classification

Clinical stages[1]

Clinically, the course of untreated Kawasaki disease (KD) is divided into the following stages:

- Acute febrile stage (lasting weeks 1 to 2)

- Fever, irritability, cervical adenitis, conjunctivitis, rash, mucosal erythema, painful erythema of the hands and feet, arthralgia or arthritis, possible myocarditis, and pericarditis.

- Subacute stage (lasting weeks 2 to 4)
  - Fever, rash, and lymphadenopathy have resolved; if fever persists there is an increased risk of cardiac complications; persistent irritability, poor appetite, and conjunctival injection; desquamation of extremities begins at this stage.
  - The patient may be completely asymptomatic if given IVIG. Periungual desquamation may be the only apparent clinical manifestation.
  - Cardiac abnormalities (coronary artery ectasia [Fig-1]

    or aneurysms) may develop during this stage, and rarely, later in patients treated with IVIG.
- Convalescent (lasting weeks 4 to 8)
  - All signs of inflammation have receded and acute phase markers normalise.
  - If present, coronary artery ectasia or aneurysms may persist and enlarge.
- Chronic stage (variable)
  - If present, coronary artery dilation may resolve.
  - However, coronary artery aneurysms may persist through to adulthood. Such patients are at risk of subsequent coronary artery thrombosis, rupture, and myocardial infarction.

Secondary prevention

In guidelines published by the American Heart Association (AHA), a stratification system to categorise patients by their risk level for development of myocardial ischaemia has been proposed.[1]

- Low-risk level: patients without detectable coronary artery aneurysm (CAA). Data from long-term follow-up (10 to 20 years after onset) have shown that their morbidity and mortality are similar to those in the normal paediatric population. Angiography is not necessary in these patients, and they do not need antiplatelet therapy (low-dose aspirin) beyond the recommended 8 weeks after onset. Careful assessment with counselling every 5 years is recommended to determine the future risk of ischaemic heart disease. No restriction of physical activity beyond 8 weeks is necessary.
- Moderate-risk level: patients with regressed CAAs. In this group of patients with Kawasaki disease (KD), individuals have 50% regression of their CAAs to the level of normal lumen diameter, as shown by angiography. The rate of CAA resolution is inversely related to its size. Studies have revealed that, although regression had occurred, it was through intimal thickening and endothelial dysfunction. These patients need to be treated with low-dose aspirin, at least until aneurysm regression is demonstrated. Cardiology follow-up should be performed annually, with ECG and echocardiogram. Stress test and myocardial perfusion studies twice a year are highly recommended. Angiography is needed if evidence of ischaemia is present. High-impact physical activity should be limited and guided. If regression of aneurysms occurred by 8 weeks from onset, no restrictions beyond the first 8 weeks are needed. Careful assessment with counselling every 3 to 5 years is recommended to determine the future risk of ischaemic heart disease.
- High-risk level: patients with angiographic evidence of large or giant aneurysms, or coronary obstruction. These patients with KD need long-term antiplatelet therapy and warfarin (to keep INR at 2 to 3), or low molecular weight heparin (to keep anti-factor Xa level at 0.5 to 1 units/mL). Beta-blockers may be considered in patients with large or giant aneurysms that can potentially develop myocardial ischaemia.[1] For atherosclerotic disease, beta-blockers are a critical part of management; the same applies to the pathophysiology of KD coronary disease, and they are recommended for patients with myocardial ischaemia or MI.[1] Contact or high-impact sport should be avoided to reduce the risk of bleeding. Cardiology follow-up with ECG and echocardiogram, and stress test with myocardial perfusion scan performed twice a year, are highly recommended, and would be followed by angiography if ischaemia is present.

Case history

Case history #1

A previously healthy 1-year-old girl was admitted to a children's hospital with a 7-day history of spiking fever up to 39.5°C (103°F). Three days after the onset of fever she developed left-sided neck swelling and nappy rash, and became progressively fussy and irritable. She was seen in an emergency department, diagnosed with cervical adenitis, and sent home on oral antibiotics. The mother noted continued irritability, high fever, and decreased oral intake. On subsequent admission she was extremely irritable, with a temperature of 38.9°C (102°F), heart rate of 140 beats per minute, respiratory rate of 40 breaths per minute, and blood pressure 110/54 mmHg. There were no signs of nuchal rigidity. Both palpebral and bulbar conjunctivae were deep red and injected, lips were dry and crusted, the oropharynx hyperaemic with some areas of ulcerated mucosa, and the tongue papillae were enlarged and red (strawberry appearance). Examination of the neck revealed a mildly tender left unilateral mass, measuring 4 cm. The skin showed a generalised polymorphous, erythematous, macular, blanching rash, in addition to severely red and desquamated perineal region. Her extremities, especially palms and soles, were swollen, red, and mildly tender.

Other presentations

Some cases do not fulfil well-accepted criteria and are called incomplete/atypical Kawasaki disease (KD). This presentation is more common among children <1 year of age, who are at higher risk for the development of coronary artery aneurysms (CAAs) if untreated. In these cases of insufficient clinical criteria, presence of coronary abnormalities or CAAs must be shown on echocardiogram. A patient can present with prolonged fever (>5 days) and 2 or 3 of the classic criteria such as generalised polymorphous skin rash and red injected eyes. Infantile periarteritis nodosa is part of the spectrum of KD. The coronary artery aneurysmal lesions are clinically and pathologically indistinguishable from those seen in KD. Acute febrile mucocutaneous lymph node syndrome was initially described before KD was recognised. It is now part of the spectrum of KD.

DIAGNOSIS

Step-by-step diagnostic approach

Diagnosis is based on clinical signs and symptoms. There are no unique laboratory diagnostic tests for the disease. The principal signs were recognised and reported in 1974, and these criteria have been updated by the American Heart Association and endorsed by the American Academy of Pediatrics.[1] [24]

Acute stage

The acute stage generally lasts 7 to 11 days. Patients with classic Kawasaki disease (KD) must have 5 days of fever that is refractory to antibiotic therapy. The fever must be high; usually greater than 39°C (102°F), but is often over 39.9°C (104°F). Patients are often irritable beyond that expected for the extent of fever. In addition, patients must have 4 more of the following 5 signs and symptoms:

- Polymorphous erythematous rash
- Non-purulent bilateral conjunctival injection (occurs in 90%)

- Oropharyngeal changes, including diffuse hyperaemia, strawberry tongue, and lip changes (e.g., swelling, fissuring, erythema, and bleeding)
- Peripheral extremity changes, including erythema, oedema, induration, and desquamation, which may cause difficulty walking
- Non-purulent cervical lymphadenopathy. This occurs in 40% of cases (although other reports are 50% to 75%) and is generally a single, enlarged, non-suppurative cervical node measuring approximately 1.5 cm or more.

These criteria are only guidelines in order to prevent misdiagnosis or overdiagnosis. According to these guidelines, a diagnosis can be made on day 4 of the fever if 4 principal criteria are met, especially when redness and swelling of the hands and feet are present. Experienced clinicians who have treated many KD patients, in rare instances, may establish diagnosis on day 3 of the fever in the presence of a classic clinical presentation.[1]

However, clinicians should be aware that there are cases of KD with incomplete signs and symptoms that do not fulfil these criteria; this refers to incomplete (atypical) KD. In these cases of insufficient clinical criteria, evidence of the presence of coronary artery abnormalities or aneurysms must be shown on echocardiogram. Incomplete KD occurs most commonly in infants who are at risk of developing coronary artery abnormalities and who may have prolonged fever as the only clinical finding. In these patients, positive echocardiogram for coronary abnormalities has a very high specificity for the diagnosis. In addition, the presence of 3 or more of the following laboratory features may increase the index of suspicion for KD: 1) anaemia; 2) platelet count of >450,000 after day 7 of fever; 3) albumin <3.0 g/dL; 4) elevated alanine aminotransferase (ALT); 5) WBC count >15,000; 6) urine with >10 white blood cells per high power field (WBC/hpf).[1]

In the absence of a diagnostic test, these criteria become pivotal in diagnosing a patient with KD. Some laboratory tests may be supportive, such as acute phase reactants including erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP). These are significantly raised (to a greater degree than that found in common viral infections).[25]

Uncommon findings on physical examination in acute stage

Less common findings may include: stiff neck secondary to aseptic meningitis, facial palsy, anterior uveitis (70%), pleural effusion, pulmonary infiltrates, pericardial effusion with or without myocarditis, and congestive heart failure (CHF).

Others include: abdominal pain, diarrhoea, hepatitis, obstructive jaundice, gall bladder distension or hydrops of the gall bladder, pancreatitis, joint involvement (arthralgias or arthritis), meatitis, vulvitis, urethritis with sterile pyuria, proteinuria, nephritis, and acute renal failure. In addition, peripheral extremity gangrene, pustules, erythema multiforme-like lesions, perianal erythema (50% to 70%), macules, papules, measles-like rash, and scarlet fever-like erythema may be found.

Subacute stage

This stage lasts between 2 to 3 weeks, whereby the presenting signs and symptoms are in the process of resolution, including persistent irritability, anorexia, and other acute signs and symptoms. It may still be possible to see conjunctival injection and some degree of fissured lips.

However, typical for this phase are decreased fever, acral desquamation, coronary aneurysm formation, decline in the acute phase markers, and development of thrombocytosis.

Convalescent/chronic stage

This stage lasts between 4 and 6 weeks. This is the recovery phase when all signs of illness have disappeared, and it continues until the levels of acute phase reactants (ESR and C-reactive protein) have returned to normal in all those KD patients who eventually develop full recovery.

However, for those patients who develop cardiac sequelae, the most significant clinical finding that persists through this phase is the presence of coronary artery aneurysms. Many will improve and few will get worse. There is a tendency for smaller aneurysms to resolve on their own (60% of cases), but in a few patients the aneurysms will expand to large or giant size, and complications such as thrombosis or myocardial infarction may develop.

Initial investigations

Patients who present with the classic manifestations of KD, with fulfilment of the accepted criteria (namely, fever lasting 5 or more days and 4 of the 5 listed criteria), should have some basic investigations that will include FBC and acute phase markers (ESR and C-reactive protein). If these tests show findings that are consistent with KD, the diagnosis is established. The most helpful findings are raised ESR and C-reactive protein and, to a lesser extent, anaemia, raised WBC count and thrombocytosis.

During the acute stage, many acute-phase reactant markers such as ESR, C-reactive protein, serum ferritin, and alpha-1-antitrypsin are significantly raised. These tests tend to return to normal levels at the end of the subacute phase towards the convalescent phase. If ESR and C-reactive protein were normal or very mildly raised (ESR <40 mm/hour and/or C-reactive protein <190 nanomol/L [<20 mg/L or<2 mg/dL]) at the onset of the acute stage, then the diagnosis of KD would be in question. At this point, infectious-disease consultation is needed to rule out streptococcal infections (especially scarlet fever) and viral illnesses. Mild to moderate normochromic anaemia is observed in the acute stage, along with a moderate to alarmingly raised level of WBC count with a left shift. During the subacute stage, platelet count elevation is the outstanding marker. It begins to rise in the second week and continues to rise during the third, usually with levels of up to 1000 x 10^9/L (1 million/microlitre), but counts as high as 2000 x 10^9/L (2 million/microlitre) are occasionally observed.

Other investigations

Because coronary artery aneurysms are the hallmark of KD, echocardiography should be performed at diagnosis and repeated in the second or third week of illness and at 8 weeks after the initial onset of the disease. If the echocardiographic findings are abnormal at any stage in the course of the illness, the patient should be referred to a paediatric cardiologist for a complete cardiac work-up and follow-up care.

Additional tests are performed to exclude or identify other organ system involvement:

- Liver function tests: should be done routinely in all patients with suspected KD to assess for hepatitis. The patient may have abdominal pain, jaundice, and nausea and/or vomiting in addition to high fever.
- Urinalysis: should be done routinely in all patients with suspected KD; it will show a mild to moderate sterile pyuria of urethral origin in 50% of patients. If urinalysis is abnormal, a culture should be performed to rule out a urinary tract infection.
- Chest x-ray: performed if pericarditis or pneumonitis suspected.
- ECG: to exclude conduction abnormalities.
- Ultrasonography of the gall bladder: to exclude hydrops of the gall bladder (if suspected).

- Ultrasonography of the testes: to exclude epididymitis (if suspected).
- Lumbar puncture: performed if patients present with nuchal rigidity and high fever. This test is necessary to exclude meningitis.

Emerging tests

Magnetic resonance angiography and cardiac catheterisation with angiography are emerging investigations, both of which are superior to echocardiography in identifying coronary aneurysms and any other abnormalities. These tests are the responsibility of the cardiologist and would be ordered when the echocardiogram findings are not clear or when the echocardiogram shows giant aneurysms.

Risk factors

Strong

Asian ancestry

- Kawasaki disease (KD) is most common in Asian children, especially those of Japanese descent.
- Some cases of KD show familial susceptibility. Children in Japan who have parents with KD seem to have a more severe form of this disease and are more susceptible to recurrence.
- KD likely has a genetic susceptibility. Genome-wide multipoint linkage analysis of affected sibling pairs in Japan identified evidence of linkage at chromosome 12q24.[22] 2[B]Evidence

age 3 months to 4 years

- Most patients (80%) are affected when they are <5 years of age.[1] [3] However, KD is rare in infants younger than 3 months, and has been rarely described in adolescents and adults.
- In the US the peak age of onset is 13 to 24 months. In Japan, the peak age of onset is 6 to 11 months.[8]

Weak

male gender

- Disease occurs more often in males than in females (1.5:1).[3] [23]

History & examination factors

Key diagnostic factors

presence of risk factors (common)

- Key risk factors include Asian ancestry, age 3 months to 4 years, and male sex.

polymorphous rash (common)

- Non-specific polymorphic rash. This is usually a diffuse, maculopapular erythematous rash. Occasionally scarlatiniform- or erythema multiforme-type rash with target lesions on the arm and trunk.
- Groin erythema or desquamation and fine pustules over extensor surfaces of extremities can occur.

conjunctival injection (common)

- The patient has a history or presents with non-purulent non-exudative bilateral conjunctival injection (in 90% of cases).
- Less common are episcleritis or uveitis (anterior and/or posterior).

mucositis (common)

- History or physical findings of dry, erythematous, fissured lips that bleed easily, erythema of the oral and pharyngeal mucosa, and strawberry tongue with prominent papillae and erythema (alone or in combination in 90% of cases). No oral exudates, ulcerations, or Koplik's spots. Strawberry tongue may be present, but oropharyngeal/mucosal changes may be variable. Discrete oral lesions would be suggestive of a different disease.

skin changes in the peripheral extremities (common)

- Refusal to ambulate due to tender induration of the palms and soles, often with erythema and oedema. Usually the skin on wrists and ankles is unaffected. The changes to the peripheries may be acute (swelling and erythema) as well as subacute (desquamation).
- Periungual desquamation of fingers and toes about 2 weeks after onset may be seen, as may transverse grooves across the nails (Beau lines) 1 to 2 months after onset.

enlarged cervical lymph nodes (common)

- Unilateral lymphadenopathy is observed in approximately 40% of patients, with node diameter above 1.5 cm.
- Node is sometimes erythematous, but is not fluctuant or purulent and is unresponsive to antibiotics.

coronary artery aneurysms (common)

- Coronary artery abnormalities (mainly aneurysms) develop in approximately 20% to 25% of untreated patients.
- Presence is not a key feature in the classic presentation of Kawasaki disease (KD). However, it is a key feature in incomplete/atypical presentation.

fever and extreme irritability (common)

- Fever usually over 39°C (102°F). Most patients present because of prolonged fever of at least 5 days in duration with often abrupt onset. Fever is unresponsive to antibiotics, if given.
- There is an associated significant irritability that is much greater than would be expected for the magnitude of fever. During this acute phase, many patients will develop poor intake, abdominal pain, nausea, and diarrhoea.
- In addition to fever, patients must have 4 more of the following 5 signs and symptoms for diagnosis: polymorphous erythematous rash, non-purulent bilateral conjunctival injection, oropharyngeal changes (including diffuse hyperaemia, strawberry tongue, and lip changes, peripheral extremity changes (including erythema, oedema, induration, and desquamation), non-purulent cervical lymphadenopathy.

Other diagnostic factors

pericarditis with effusion (uncommon)

- Not part of the diagnostic criteria.

congestive heart failure (CHF) (uncommon)

- Not part of the diagnostic criteria.

joint pain or oedema (uncommon)

- Arthralgia and arthritis involving multiple joints (e.g., including hands, knees, ankles, and hips) are more common if intravenous immunoglobulin treatment is delayed.

neurological manifestations (uncommon)

- Headaches and stiff neck (secondary to aseptic meningitis), facial palsy, and cerebral infarction are rare, but can occur.

gastrointestinal manifestations (uncommon)

- Abdominal pain, diarrhoea, hepatitis, obstructive jaundice, gall bladder distension or hydrops of the gall bladder, and pancreatitis are rare clinical findings.

urological manifestations (uncommon)

- Sterile pyuria is the most common, but meatitis, urethritis and vulvitis (in females), proteinuria, nephritis, and acute renal failure can occur.

other dermatological manifestations (uncommon)

- Peripheral extremity gangrene, pustules, erythema multiforme-like lesions, perianal desquamation, macules, papules, measles-like rash, and scarlet fever-like erythema are rare clinical findings.

Diagnostic tests

1st test to order

Test	Result
FBC • In the acute stage, a mild to moderate normochromic anaemia is observed, along with a moderate to alarmingly raised WBC count with a left shift. • During the subacute stage, platelet count elevation is the outstanding marker. It begins to rise in the second week and continues to rise during the third, usually with levels up to 1000 x 10^9/L (1 million/microlitre), but counts as high as 2000 x 10^9/L (2 million/microlitre) are occasionally observed.	**anaemia, leukocytosis, and thrombocytosis**
serum erythrocyte sedimentation rate (ESR) • During the acute stage, many acute-phase reactant markers, such as the ESR, C-reactive protein (CRP), serum ferritin, and alpha-1-antitrypsin, are significantly raised. These tests tend to return to normal levels at the end of the subacute phase toward the convalescent phase.	**raised**
serum C-reactive protein (CRP) • During the acute stage, many acute-phase reactant markers, such as ESR, CRP, serum ferritin, and alpha-1-antitrypsin, are significantly raised. These tests tend to return to normal levels at the end of the subacute phase towards the convalescent phase.	**raised**

Test	Result
serum liver function tests • Icteric and anicteric hepatitis can develop, with mild elevations in aminotransferase values observed in 40% of patients. • Raised alanine aminotransferase (ALT) levels can indicate a more serious course. • Bilirubin levels are raised in 10% of patients.	**raised liver enzymes; low level of albumin**
urinalysis • Will show a mild to moderate sterile pyuria of urethral origin in 50% of patients. • If urinalysis is abnormal, a culture should be performed to rule out urinary tract infection.	**sterile pyuria**
chest x-ray • Looks for cardiomegaly in the case of pericarditis, myocarditis, or subclinical pneumonitis. • Should be performed to assess baseline findings and to confirm any clinical suspicion of congestive heart failure (CHF).	**cardiomegaly or, more rarely, pneumonitis**
echocardiogram • Echocardiography is the study of choice to evaluate for coronary artery aneurysms. During the acute stage, a baseline echocardiogram is important to rule these out and seek evidence of myocarditis, valvulitis, or pericardial effusion. Diffuse dilatation of coronary lumina can be observed in 50% of untreated patients by the tenth day of illness. • Echocardiography should be performed at diagnosis and repeated in the second or third week of illness and at 2 months after the initial onset of the disease. If the findings are abnormal at any point, the patient should be referred to a paediatric cardiologist for a complete cardiac work-up and follow-up care.[1]	**coronary dilatations or aneurysms**
ECG • Needs to be obtained to evaluate for various conduction abnormalities. Children with Kawasaki disease (KD) may also have acute infarction. • Tachycardia, a prolonged PR interval, ST-T wave changes, and a decreased voltage of R waves may indicate myocarditis. Q-wave or ST-T wave changes may indicate an MI.	**conduction abnormalities and/or myocardial infarction**

Other tests to consider

Test	Result
ultrasonography of the gall bladder • May be necessary if liver or gall bladder dysfunction is suspected.	**hydrops of the gall bladder in some patients**
ultrasonography of the testes • In case of testicular involvement in males, a scrotal sonogram to evaluate for epididymitis should be performed. Epididymitis is an inflammatory process that can occur in various vasculitides and affects boys aged 9 to 14 years. It can be observed in younger boys with Henoch-Schonlein purpura and KD.	**epididymitis in males with testicular involvement**

Test	Result
lumbar puncture • May be needed in patients who present with high fever and nuchal rigidity. • Some patients with KD may have aseptic meningitis. • Aseptic meningitis could be one of the adverse effects of intravenous immunoglobulin treatment.	**aseptic meningitis in some patients**

Emerging tests

Test	Result
magnetic resonance angiography • Free-breathing 3-dimensional coronary magnetic resonance angiography may accurately define coronary artery aneurysms in patients with KD. This technique is requested by the consultant cardiologist and provides a non-invasive alternative when the image quality of echocardiography is insufficient. It can reduce the need for serial radiographic coronary angiography in this patient group.	**coronary dilatations or aneurysms**
cardiac catheterisation and angiography • A subset of patients with KD, especially those with findings of large or giant coronary artery aneurysms (>8 mm in diameter), may require cardiac catheterisation and angiography to detail these abnormalities better.	**coronary artery aneurysms**

Differential diagnosis

Condition	Differentiating signs / symptoms	Differentiating tests
Systemic juvenile idiopathic arthritis (systemic JIA)	• A syndrome of fever, rash, lymphadenopathy, and arthritis. These patients often present with fever of unknown origin (FUO) and occasionally have organomegaly and serositis (pericarditis, pleuritis). • Iritis and subcutaneous nodules are rare. • The rash is a fine, evanescent salmon pink, usually appears on the trunk, proximal extremities and, less commonly, on the face. The rash accompanies the spikes of fever and tends to disappear when the fever is down. • These patients do not develop coronary artery aneurysms. • Unlike with other forms of JIA, patients with systemic JIA are usually anaemic and have extremely high acute-phase markers (ESR and C-reactive protein), as is found in Kawasaki disease (KD).	• Presence of a positive rheumatoid factor (RF) or antinuclear antibody (ANA) test is a rare occurrence.
Scarlet fever	• An acute febrile illness caused by group A streptococcus. • The patients usually have evidence of upper respiratory tract infection, mostly pharyngitis, accompanied by a diffuse, fine papular erythematous rash that appears on the trunk, extremities, and face, but with circumoral pallor. • Resolution of the rash is associated with desquamation that starts in the face and progresses downward. • Unlike in KD, in scarlet fever lips are spared and there is no conjunctivitis or conjunctival injection.	• Positive throat culture, or positive serological test for group A streptococcus (streptozyme and/or ASO), will confirm the diagnosis.

Condition	Differentiating signs / symptoms	Differentiating tests
Acute rheumatic fever	• An acute illness that occurs 3 to 4 weeks following the onset of group A streptococcal pharyngitis. • These patients develop migratory polyarthritis and more than 50% develop carditis.[26] • Less commonly, the course may be associated with chorea, subcutaneous nodules, and erythema marginatum. • There is no development of coronary artery aneurysms, but untreated patients will eventually develop chronic valvular disease.	• Positive throat culture or positive serological test for group A streptococcus (streptozyme and/or ASO) will confirm the diagnosis.
Toxic shock syndrome	• An acute febrile illness that is associated with vomiting, diarrhoea, myalgia, strawberry tongue, and erythematous rash with subsequent desquamation. • Many develop acute respiratory distress, hypotension, and shock. • The disease is caused by staphylococcal or group A streptococcal infections. • Unlike KD, most of these patients present at 15 to 25 years of age.	• There is no diagnostic test for toxic shock syndrome. The diagnosis is based on clinical grounds. • Isolation of staphylococcus or group A streptococcus serotypes that produce TSS-1 toxin will support the diagnosis.
Staphylococcal scalded skin syndrome	• Caused by the staphylococcal epidermolytic toxins A and B. • There is a generalised skin erythema, with development of diffuse, sterile blisters and erosions; prominent circumoral erythema; and radial crusting and fissuring around the eyes, mouth, and nose. • In addition, areas of epidermis may separate in response to gentle force (Nikolsky's sign). These changes may lead to secondary infection, sepsis, and electrolyte imbalance.	• Diagnosis is made on clinical grounds. • Identifications of strains 55 and/or 71 of staphylococci in cultures.

Condition	Differentiating signs / symptoms	Differentiating tests
Stevens-Johnson syndrome	• A severe bullous form of erythema multiforme, also known as erythema multiforme major. • It is characterised by high fever, pronounced constitutional symptoms, skin rash manifested by diffuse bullae, and mucosal membranes involvement. • The severe explosive mucosal erosions and the widespread bullous skin lesion may differentiate this condition from KD. • There is no development of coronary artery aneurysms, although these patients may benefit from high-dose intravenous immunoglobulin.	• There is no diagnostic test for Stevens-Johnson syndrome. The diagnosis is on clinical grounds.
Drug reaction	• History of exposure to the drug, presence of oral lesions or ulcers, periorbital oedema, and low acute-phase markers may help to distinguish it from KD.	• Diagnosis is made on clinical grounds, although acute-phase markers (such as ESR and C-reactive protein) in KD are significantly higher than in an acute drug reaction.
Rocky Mountain spotted fever	• A febrile illness caused by rickettsial infection (*Rickettsia rickettsii*). The disease is transmitted by a tick bite and characterised by fever, headaches, abdominal pain, vomiting, and diarrhoea, followed by severe myalgias. • The hallmark of the disease is the rose-red blanching macular rash that appears first on the extremities, but subsequently spreads to involve the entire body, including palms and soles. • After several days the rash becomes petechial or haemorrhagic, with evidence of a palpable purpura. • In fulminant cases, multiorgan failure may develop, including myocarditis and renal or liver failure.	• Diagnosis is made on clinical grounds, although confirmation would be achieved using indirect fluorescent antibody technique for *R rickettsii* .

Condition	Differentiating signs / symptoms	Differentiating tests
Measles	• Unlike with KD patients, measles manifestations include exudative conjunctivitis, Koplik's spots in mouth, rash that typically begins behind the ears; patients usually also appear more unwell.	• Diagnosis is made on clinical grounds, although acute-phase markers (such as ESR and C-reactive protein) in KD are significantly higher, and confirmation of the viral disease would be achieved using antibody titres.

Diagnostic criteria

American Heart Association (AHA) diagnostic criteria[1]

Diagnosis is based on clinical signs and symptoms. There are no unique laboratory diagnostic tests for the disease. The principal signs were recognised and reported in 1974,and these criteria have been updated by the AHA (Committee on Rheumatic Fever, Endocarditis, and Kawasaki Disease; the Council on Cardiovascular Disease in the Young) and endorsed by the American Academy of Pediatrics.[1] [24] However, clinicians should be aware that there are cases of Kawasaki disease (KD) with incomplete signs and symptoms that do not fulfil these criteria; this refers to incomplete (atypical) KD. In such cases of insufficient clinical criteria, evidence of presence of coronary abnormalities or coronary artery aneurysms (CAAs) must be shown on echocardiogram.

Patients with classic KD must have 5 days of fever that is refractory to antibiotic therapy (if given) and 4 of the following 5 signs and symptoms:

- Bilateral conjunctival injection
- Polymorphous rash
- At least one of the following mucous-membrane changes:
  - Injected lips (and/or dryness, fissuring, peeling, cracking, and bleeding of the lips)
  - Injected pharynx
  - Strawberry tongue (with erythema and prominent fungiform papillae).
- At least one of the following extremity changes:
  - Erythema of the palms or soles (painful induration is common)
  - Periungual desquamation of the fingers and toes (2-3 weeks following the onset of fever).
- Cervical lymphadenopathy (at least one lymph node >1.5 cm in diameter), usually unilateral.
- Risk stratification for relative risk of future myocardial ischaemia has also been proposed:[1]
  - Low-risk level: patients without detectable CAAs
  - Low-moderate-risk level: patients with regressed CAAs
  - High-risk level: patients with angiographical evidence of large or giant aneurysms, or coronary obstruction.

Step-by-step treatment approach

The main goal of treatment is to prevent cardiac complications, especially coronary artery aneurysms. Other goals are to reduce the frequency and intensity of the other manifestations as early as possible. This may lead to a reduction in hospital stay and faster recovery.

Risk factors for complications (coronary aneurysms) include persistent fever, or persistently raised erythrocyte sedimentation rate (ESR) or C-reactive protein (CRP).

Presentation within 10 days of onset or with risk factor for cardiac complications

The standard treatment includes the administration of a single infusion of intravenous immunoglobulin (IVIG), given early in the course of the disease within 10 days of the onset.[27] IVIG is also indicated in patients who present after 10 days with risk factors for complications such as fever or raised acute phase markers (ESR and/or CRP). This is considered to be the most current treatment regimen and has been successful in reducing the duration of fever and the prevalence of coronary artery aneurysms in Kawasaki disease (KD).[28] 3[A]Evidence High-dose aspirin is an important adjunct to IVIG therapy and is thought to have an additive anti-inflammatory effect in KD. Variation exists among medical centres concerning when aspirin dose should be reduced either: 48 to 72 hours after defervescence, or 14 days after the onset of symptoms and when the patient has been afebrile for at least 48 to 72 hours.[25]

Two-thirds of patients will be afebrile and improve within 24 hours of completion of the IVIG infusion, and 90% will be afebrile by 48 hours. This therapy regimen is effective in reducing the prevalence of coronary artery abnormalities from 20% to 25% down to 2% to 4%.[28]

Approximately 10% of patients may have persistent or recrudescent fever 48 hours after a single dose of IVIG infusion. These patients are at increased risk of developing coronary artery abnormalities and may benefit from a second IVIG infusion.[29] 4[B]Evidence

Patients refractory to immunoglobulin (IVIG)

A small subset of patients (2% to 3%) will be refractory and remain febrile, despite a second dose of immunoglobulin therapy.[30] It has been shown that corticosteroids are beneficial in refractory KD. Although conflicting reports exist in the literature on the use of oral and intravenous pulse corticosteroid therapy in KD, several case reports and case series suggest that pulse methylprednisolone therapy given intravenously, may be beneficial in patients with IVIG-resistant KD.5[B]Evidence 6[B]Evidence 7[A]Evidence Until more data are available, the small subset of patients with KD that are IVIG-resistant and/or with life-threatening complications should be given the option of pulsed corticosteroid therapy.[35] [36] Further prospective, multicentre, randomised controlled trials are needed to determine the efficacy of pulsed or oral doses of corticosteroids in the treatment of IVIG-resistant KD. A susceptibility gene has been identified on chromosome 19. This gene codes inositol 1,4,5-triphosphate 3-kinase C (ITPKC). It was shown that ITPKC gene is significantly more predominant in IVIG-resistant KD patients and in those with coronary artery lesions.[14]

The discovery that pro-inflammatory cytokines, such as TNF-alpha, play a major role in the pathogenesis of rheumatoid arthritis, spondyloarthropathies, and other inflammatory conditions, including vasculitis, has led to biological anti-cytokine therapy being increasingly used in these conditions.[37] This has opened a window of opportunity to use these new biologicals in the management of KD. The TNF-alpha antagonist infliximab has been used in patients refractory to IVIG and methylprednisolone.[38] In the US,

2.3% of KD patients received infliximab for IVIG resistance between 2001 and 2006.[39] A randomised, double-blind, placebo-controlled trial to assess the benefit of adding infliximab to the primary standard therapy of KD showed that adding a dose of infliximab prior to the IVIG treatment did not reduce the IVIG treatment resistance as measured by coronary artery z-scores at 5 weeks, although reduction of fever and inflammatory markers were significantly more pronounced in the infliximab group.[40] Furthermore, another study from Japan was designed to assess the benefit of adding plasma exchange rescue (PER) to KD patients who were IVIG and infliximab non-responders. The study showed that the addition of PER resulted in disappearance of fever and other acute symptoms and improvement of laboratory data and coronary outcomes. This study has its limitations of being a retrospective study and therefore its results are questionable pending future randomised trials.[41]

Patients with refractory KD in whom a second dose of IVIG, corticosteroids, and infliximab have failed should receive ciclosporin. Finally, very rarely, administration of other biological agents such as anakinra (an interleukin-1 [IL-1] receptor antagonist), cytotoxic agents (such as cyclophosphamide), or plasma exchange may be considered in refractory KD patients who have failed to respond to all of the above regimens.[1]

Presentation after 10 days of onset without risk factors for cardiac complications

Patients with KD that present after day 10 without persistent fever, and when their acute phase markers (ESR and/or CRP) are normal, are regarded as without risk of developing coronary aneurysms.

If their initial and subsequent echocardiograms are normal, they should be treated with low-dose aspirin until 8 weeks from the onset. If echocardiogram at 8 weeks is normal, low-dose aspirin can be discontinued.

However, if ESR or CRP is raised and/or echocardiograms show evidence of coronary abnormalities (dilatations and/or aneurysms), the patient should be treated with IVIG and low-dose aspirin.

Long-term management

In guidelines published by the American Heart Association, a stratification system to categorise patients by their risk level for development of myocardial ischaemia has been proposed.[1]

- Low-risk level: patients without detectable CAA. Data from long-term follow-up (10 to 20 years after onset) have shown that their morbidity and mortality are similar to those in the general paediatric population. Angiography is not necessary in these patients, and they do not need antiplatelet therapy (low-dose aspirin) beyond the recommended 8 weeks after onset. Careful assessment with counselling every 5 years is recommended to determine the future risk of ischaemic heart disease. No restriction of physical activity beyond 8 weeks is necessary.
- Moderate-risk level: patients with regressed CAAs. In this group of patients with KD, individuals have 50% regression of their CAAs to the level of normal lumen diameter, as shown by angiography. The rate of CAA resolution is inversely related to its size. Studies have revealed that, although regression had occurred, it was through intimal thickening and endothelial dysfunction. These patients need to be treated with low-dose aspirin, at least until aneurysm regression is demonstrated. Cardiology follow-up should be performed annually, with ECG and echocardiogram. Stress test and myocardial perfusion studies twice a year are highly recommended. Angiography is needed if evidence of ischaemia is present. High-impact physical activity should be limited and guided. If regression of aneurysms occurred by 8 weeks from onset, no restrictions beyond the first

8 weeks are needed. Careful assessment with counselling every 3 to 5 years is recommended to determine the future risk of ischaemic heart disease.

- High-risk level: patients with angiographic evidence of large or giant aneurysms, or coronary obstruction. These patients with KD need long-term antiplatelet therapy and warfarin (to keep INR at 2 to 3), or low molecular weight heparin (to keep anti-factor Xa level at 0.5 to 1 units/mL). Beta-blockers are needed to reduce myocardial oxygen consumption. Beta-blockers are not part of the standard treatment of KD.[1] However, beta-blockers can be considered on an individual basis when dealing with high-risk KD patients with large or giant aneurysms. For indication and dosage, the cardiology specialist would need to be consulted. Contact or high-impact sport should be avoided to reduce the risk of bleeding. Cardiology follow-up with ECG and echocardiogram, and stress test with myocardial perfusion scan performed twice a year are highly recommended, and would be followed by angiography if ischaemia is present.

Treatment details overview

Consult your local pharmaceutical database for comprehensive drug information including contraindications, drug interactions, and alternative dosing. (see Disclaimer)

Acute (summary)

Patient group	Tx line	Treatment
presentation within 10 days of onset or with risk factor for cardiac complications	**1st**	**intravenous immunoglobulin (IVIG)**
	plus	**high-dose aspirin**
	2nd	**pulse methylprednisolone**
	plus	**high-dose aspirin**
	3rd	**infliximab**
	plus	**high-dose aspirin**
	4th	**other immunomodulatory drug**
	plus	**high-dose aspirin**
presentation more than 10 days after onset without risk factor for cardiac complications	**1st**	**low-dose aspirin**

Ongoing (summary)

Patient group	Tx line	Treatment
■ **low**	**1st**	**cardiovascular risk assessement**
■ **moderate**	**1st**	**low-dose aspirin + cardiology follow-up**

Ongoing			(summary)
high	1st	aspirin + cardiology follow-up
high	plus	warfarin or low molecular weight heparin
high	adjunct	clopidogrel or dipyridamole
high	adjunct	beta-blocker

Treatment options

Acute

Patient group	Tx line	Treatment
presentation within 10 days of onset or with risk factor for cardiac complications	**1st**	**intravenous immunoglobulin (IVIG)** » The main goal of treatment is to prevent coronary artery disease and to relieve symptoms by controlling the inflammatory process. This is monitored by the defervescence and the resolution of all acute symptoms. » IVIG as a single infusion is the standard treatment and comprises the mainstay of therapy, and has been successful in reducing the duration of fever and the prevalence of coronary artery aneurysms in Kawasaki disease (KD).[28] 3[A]Evidence » The best results are achieved when treatment is instituted within 10 days or even within 7 days. However, there is no advantage of giving the treatment before day 5 from disease onset. » A minority of patients (approximately 10%) fail to defervesce within 36 to 48 hours. These patients are at increased risk of developing coronary artery abnormalities and should be given a second dose of IVIG.[29] 4[B]Evidence **Primary options** » immunoglobulin (human): 2 g/kg intravenously as a single dose, may repeat dose 36-48 hours later if patient fails to defervesce
	plus	**high-dose aspirin** » High-dose aspirin has been part of the traditional treatment of KD for many years. It should be given in conjunction with intravenous immunoglobulin. » Aspirin appears to have no effect on the incidence or the development of coronary artery aneurysms, despite treatment before or after 5 days of therapy. » Some clinicians will reduce the dose of aspirin to a low dose 48 to 72 hours after the fever stops. Others will continue the high dose for 14 days or when erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) normalise.

Acute

Patient group	Tx line	Treatment
		» The low-dose aspirin has antiplatelet effects and is maintained until 8 weeks from the onset of the disease. Further continuation of aspirin beyond 8 weeks depends on the long-term risk of myocardial ischaemia: low, moderate, or high risk. **Primary options** » aspirin: 80-100 mg/kg/day orally given in 4 divided doses for 24-72 hours after fever cessation (up to 14 days), followed by 3-5 mg/kg once daily for 8 weeks Doses of 30-50 mg/kg/day may be recommended in some countries, including Japan and Western Europe.
	2nd	**pulse methylprednisolone** » When 2 infusions of IVIG have been given without effect on the fever and/or the acute inflammatory markers, an intravenous pulse dose of methylprednisolone may be given. » These patients comprise a small group of less than 2% of the patients with KD and are regarded as IVIG-resistant, with increased risk for coronary aneurysms. » Corticosteroid treatment appears to be effective.5[B]Evidence 6[B]Evidence 7[A]Evidence **Primary options** » methylprednisolone: 30 mg/kg/day intravenously for 1-3 days, maximum 1000 mg/day
	plus	**high-dose aspirin** » High-dose aspirin has been part of the traditional treatment of KD for many years. It should be given in conjunction with intravenous immunoglobulin. » Aspirin appears to have no effect on the incidence or the development of coronary artery aneurysms, despite treatment before or after 5 days of therapy. » Some clinicians will reduce the dose of aspirin to a low dose 48 to 72 hours after the fever stops. Others will continue the high dose for 14 days or when ESR and CRP normalise. » The low-dose aspirin has antiplatelet effects and is maintained until 8 weeks from the onset

Acute

Patient group	Tx line	Treatment
		of the disease. Further continuation of aspirin beyond 8 weeks depends on the long-term risk of myocardial ischaemia: low, moderate, or high risk.
		Primary options
		» aspirin: 80-100 mg/kg/day orally given in 4 divided doses for 24-72 hours after fever cessation (up to 14 days), followed by 3-5 mg/kg once daily for 8 weeks Doses of 30-50 mg/kg/day may be recommended in some countries, including Japan and Western Europe.
	3rd	**infliximab**
		» The TNF-alpha antagonist infliximab has been used in patients refractory to IVIG and methylprednisolone.[38] These patients comprise an extremely small group of less than 1% of the patients with KD. In the US, 2.3% of KD patients received infliximab for IVIG resistance between 2001 and 2006.[39] These patients should receive a trial of intravenous infusion of infliximab.[38]
		» Infliximab is a chimeric monoclonal antibody to TNF-alpha. Its efficacy in other inflammatory conditions, including vasculitis, supports its use in refractory cases of KD.
		Primary options
		» infliximab: 5 mg/kg intravenously as a single dose
	plus	**high-dose aspirin**
		» High-dose aspirin has been part of the traditional treatment of KD for many years. It should be given in conjunction with intravenous immunoglobulin.
		» Aspirin appears to have no effect on the incidence or the development of coronary artery aneurysms, despite treatment before or after 5 days of therapy.
		» Some clinicians will reduce the dose of aspirin to a low dose 48 to 72 hours after the fever stops. Others will continue the high dose for 14 days or when ESR and CRP normalise.
		» The low-dose aspirin has antiplatelet effects and is maintained until 8 weeks from the onset of the disease. Further continuation of aspirin beyond 8 weeks depends on the long-term risk

Acute

Patient group	Tx line	Treatment
		of myocardial ischaemia: low, moderate, or high risk. **Primary options** » aspirin: 80-100 mg/kg/day orally given in 4 divided doses for 24-72 hours after fever cessation (up to 14 days), followed by 3-5 mg/kg once daily for 8 weeks Doses of 30-50 mg/kg/day may be recommended in some countries, including Japan and Western Europe.
	4th	**other immunomodulatory drug** » Patients with refractory KD in whom a second dose of IVIG, corticosteroids, or infliximab have failed should receive ciclosporin. » Very rarely, administration of other biological agents such as anakinra (an interleukin-1 [IL-1] receptor antagonist), cytotoxic agents (e.g., cyclophosphamide), or plasma exchange may be considered.[1] **Primary options** » ciclosporin: consult specialist for guidance on dose **OR** **Secondary options** » anakinra: consult specialist for guidance on dose **OR** **Secondary options** » cyclophosphamide: consult specialist for guidance on dose
	plus	**high-dose aspirin** » High-dose aspirin has been part of the traditional treatment of KD for many years. It should be given in conjunction with intravenous immunoglobulin. » Aspirin appears to have no effect on the incidence or the development of coronary artery aneurysms, despite treatment before or after 5 days of therapy. » Some clinicians will reduce the dose of aspirin to a low dose 48 to 72 hours after the fever

Acute

Patient group	Tx line	Treatment
		stops. Others will continue the high dose for 14 days or when ESR and CRP normalise. » The low-dose aspirin has antiplatelet effects and is maintained until 8 weeks from the onset of the disease. Further continuation of aspirin beyond 8 weeks depends on the long-term risk of myocardial ischaemia: low, moderate, or high risk. **Primary options** » aspirin: 80-100 mg/kg/day orally given in 4 divided doses for 24-72 hours after fever cessation (up to 14 days), followed by 3-5 mg/kg once daily for 8 weeks Doses of 30-50 mg/kg/day may be recommended in some countries, including Japan and Western Europe.
presentation more than 10 days after onset without risk factor for cardiac complications	**1st**	**low-dose aspirin** » Patients with KD who present after day 10 without persistent fever, and with normal acute-phase markers (ESR and/or CRP) and normal initial echocardiogram, are regarded as without risk of developing coronary aneurysms. » In this group, it is unnecessary to treat with intravenous immunoglobulin, but they should continue low-dose aspirin until 8 weeks. Further continuation of aspirin beyond 8 weeks depends on the long-term risk of myocardial ischaemia: low, moderate, or high risk. **Primary options** » aspirin: 3-5 mg/kg/day orally for 8 weeks

Ongoing

Patient group	Tx line	Treatment
low	**1st**	**cardiovascular risk assessement** » Patients without detectable CAA are at low risk for developing myocardial ischaemia. Data from long-term follow-up (10 to 20 years after onset) have shown that their morbidity and mortality are similar to those in the general paediatric population. Angiography is not necessary in these patients, and they do not need antiplatelet therapy (low-dose aspirin)

Ongoing

Patient group	Tx line	Treatment
		beyond the recommended 8 weeks after onset. Careful assessment with counselling every 5 years is recommended to determine the future risk of ischaemic heart disease. No restriction of physical activity beyond 8 weeks is necessary.[1]
moderate	**1st**	**low-dose aspirin + cardiology follow-up** » Patients with regressed CAAs are at low-moderate risk for developing myocardial ischaemia. In this group of patients with KD, individuals have 50% regression of their CAAs to the level of normal lumen diameter, as shown by angiography. The rate of CAA resolution is inversely related to its size. Studies have revealed that, although regression had occurred, it was through intimal thickening and endothelial dysfunction.[1] » These patients need to be treated with low-dose aspirin, at least until aneurysm regression is demonstrated. Cardiology follow-up should be performed annually, with ECG and echocardiogram. Stress test and myocardial perfusion studies twice a year are highly recommended. Angiography is needed if evidence of ischaemia is present. » High-impact physical activity should be limited and guided. If regression of aneurysms occurred by 8 weeks from onset, no restrictions beyond the first 8 weeks are needed.[1] » Careful assessment with counselling every 3 to 5 years is recommended to determine the future risk of ischaemic heart disease.[1] **Primary options** » aspirin: 3-5 mg/kg/day orally Treatment should continue at least until aneurysm regression is demonstrated.
high	**1st**	**aspirin + cardiology follow-up** » Patients with angiographic evidence of large or giant aneurysms or coronary obstruction are at high risk for developing myocardial ischaemia. These patients with KD need long-term antiplatelet therapy plus warfarin (to keep INR at 2 to 3), or low molecular weight heparin (to keep anti-factor Xa level at 0.5 to 1 units/mL). » Cardiology follow-up with ECG and echocardiogram, and stress test with myocardial perfusion scan performed twice a year are highly recommended, and would be followed by

Ongoing

Patient group	Tx line	Treatment
		angiography if ischaemia is present. Contact or high-impact sport should be avoided to reduce the risk of bleeding.[1] **Primary options** » aspirin: 3-5 mg/kg/day orally
high	plus	**warfarin or low molecular weight heparin** » These patients with KD need long-term warfarin (to keep INR at 2 to 3), or a low molecular weight heparin such as enoxaparin (to keep anti-factor Xa level at 0.5 to 1 units/mL) in addition to aspirin therapy. » Low molecular weight heparin is preferred as an alternative to warfarin for infants and toddlers in whom blood drawing for INR testing is difficult.[1] **Primary options** » warfarin: 0.2 mg/kg orally as a loading dose, followed by 0.1 mg/kg/day, titrate dose to achieve an INR of 2-3 **OR** **Primary options** » enoxaparin: 1 to 1.5 mg/kg subcutaneously every 12 hours
high	adjunct	**clopidogrel or dipyridamole** » Clopidogrel or dipyridamole may be added to aspirin and anticoagulant therapy. **Primary options** » clopidogrel: 0.2 to 1 mg/kg/day orally **OR** **Primary options** » dipyridamole: 1-5 mg/kg/day orally
high	adjunct	**beta-blocker** » Beta-blockers may be considered to reduce myocardial oxygen consumption.[1] They are not part of the standard treatment of KD; however, beta-blockers can be considered on an individual basis when dealing with high-risk KD patients with large or giant aneurysms. For indication and dosage the cardiology specialist would need to be consulted.

Emerging

Intravenous immunoglobulin (IVIG) plus corticosteroid

Two meta-analyses suggest that the addition of corticosteroids to the conventional regimen of IVIG as an initial treatment strategy could reduce the risk of coronary abnormalities.[42] [43] In one randomised, open-label, blinded-endpoints trial, the authors concluded that addition of prednisone to the standard regimen of IVIG in Japanese patients with severe Kawasaki disease (KD) might improve coronary artery outcomes.[44] In addition, fever and inflammation (based on C-reactive protein measurement) resolved more quickly with immunoglobulin plus prednisone than with IVIG alone.[44] KD risk scores used to predict IVIG failure (or resistance) in these studies were developed in Japan and other parts of Asia and do not seem to apply to other populations.[45] [46] An evidence-based randomised trial conducted in the US assessed the use of a single intravenous methylprednisolone dose immediately prior to treatment with IVIG as primary treatment for KD. The study showed no benefit regarding coronary outcomes when compared with IVIG treatment alone.[34] Therefore, experts suggest that until these high risk scores are successfully defined and tested worldwide, IVIG alone (without the addition of corticosteroids) will remain the gold standard initial treatment of KD outside Japan.[45] [46]

Recommendations

Monitoring

Patients will be discharged home on high-dose aspirin if afebrile for 24 hours. C-reactive protein should be repeated within 1 week and, if normalised, aspirin dosing will be switched to low-dose regimen. Patients with known giant aneurysms during the acute phase of KD are likely to have cardiovascular comorbidities as young adults. These patients should be followed up by a cardiologist. The number of patients with myocardial and vascular complications in adulthood, however, has decreased since the introduction of intravenous immunoglobulin (IVIG) treatment.[52]

In addition:

- Patients who present with the classic manifestations of Kawasaki disease (KD) and who had an uncomplicated disease course can be followed-up with echocardiogram at 8 weeks. If normal, low-dose aspirin can be discontinued. Patients with coronary artery aneurysms (CAAs) should be referred to cardiology.
- Patients who present with the classic manifestations of KD, but with a more protracted course of fever, should be followed-up with echocardiogram at 2 weeks. If normal, follow-up should be rescheduled for 6 to 8 weeks from disease onset and, if the echocardiogram is normal, low-dose aspirin can be discontinued and no further follow-up is needed. If CAAs are detected at any stage, refer to cardiologist.

Patient instructions

KD is self-limiting. However, if treated properly, the rate of complications, especially the coronary morbidity, would be reduced significantly. Following the diagnosis and treatment, the patient should be followed up (as outlined in Preventive Actions). In addition, parents should notify the primary care physician for any change in the clinical status of their child with KD, in order to determine if his/her risk level has changed.

Parents should be advised that patients treated with 2 g/kg IVIG should have their MMR and varicella vaccinations delayed for 11 months due to specific antiviral antibodies in the IVIG that may interfere with the body's immune response to live-virus vaccines.

To reduce the risk of Reye's syndrome, patients receiving long-term aspirin treatment should receive annual influenza vaccination, and varicella vaccination should be strongly considered.[54]

Complications

Complications	Timeframe	Likelihood
myocarditis	**short term**	**high**
Is common, but rarely causes congestive heart failure (CHF). Responds promptly to intravenous immunoglobulin.		
pericarditis with small pericardial effusions	**short term**	**medium**

FOLLOW UP

Complications	Timeframe	Likelihood
Complete resolution with intravenous immunoglobulin. Occurs in 25% of patients who are acutely unwell before intravenous immunoglobulin treatment.		
coronary aneurysms	**short term**	**low**
There are diffuse coronary artery ectasia, [Fig-1] small aneurysms (internal luminal diameter <5 mm), and giant aneurysms (≥8 mm). Small aneurysms can resolve in up to 2 years. Giant coronary artery aneurysms (CAAs) are associated with morbidity and mortality. If the echocardiogram findings are abnormal at any stage in the course of illness, the patient should be referred to a paediatric cardiologist for a complete cardiac work-up and follow-up care. The risk of CAAs is the highest in: children with Kawasaki disease (KD) who missed their opportunity to receive intravenous immunoglobulin (IVIG) within the recommended period from the onset of fever (<10 days); patients who have persistent fever despite IVIG treatment; patients with laboratory findings suggesting persistent inflammation (increased erythrocyte sedimentation rate [ESR], C-reactive protein [CRP], or both); and young children (<6 months old) or older children (>8 years old) and males are also at higher risk. In IVIG-treated patients, the following are also associated with higher risk: higher counts of neutrophils, bands and platelets; anaemia; and a lack of defervescence within the first day of the IVIG treatment.[47] [48] Other treatment failure predictors after IVIG include: increase in CRP, lactate dehydrogenase, and bilirubin levels.[48] [49] Some data suggest that sodium levels of less than 135 mmol/L (135 mEq/L) at initial presentation may predict giant CAA development.[50] Black ethnicity background may play a protective role for the development of coronary abnormalities.[51] If CAAs are indeed confirmed, an additional antiplatelet agent, for example, dipyridamole, should be added and the patient should continue to be monitored with cardiology. Patients with known giant aneurysms during the acute phase of KD are likely to have cardiovascular comorbidities as young adults. These patients should be followed up by a cardiologist. The number of patients with myocardial and vascular complications in adulthood, however, has decreased since the introduction of IVIG treatment.[52] A study of patients from 1979 to 2014 in the US found that overall CAA regression rate was approximately 75%, with a low regression rate of 16% in patients with large/giant CAA and a high regression rate of 85% in those with small CAA at diagnosis. Notably, the overall regression rate was higher in the most recent 5-year period (90%). These rates are higher than those previously reported and may be related to better recognition of KD.[53]		
valvulitis	**short term**	**low**
Rarely merits valve replacement. Usually mitral, occurs in only 1% of patients.		
arthritis	**short term**	**low**
Responds promptly to intravenous immunoglobulin and high-dose aspirin.		

Complications	Timeframe	Likelihood
mild hepatic dysfunction, rarely jaundice	**short term**	**low**
In the acute phase. Occurs in 10% to 30% of patients; responds promptly to intravenous immunoglobulin.		
gall bladder disease	**short term**	**low**
Hydrops (diagnosed by means of ultrasonography) occurs in less than 10% of patients. It usually resolves without surgical intervention.		
pneumonitis	**short term**	**low**
Responds promptly to intravenous immunoglobulin.		
aseptic meningitis	**short term**	**low**
Rare, but can occur as a manifestation of KD or as a consequence of intravenous immunoglobulin treatment. Complete spontaneous resolution.		
coronary thrombosis	**long term**	**low**
Medical or surgical interventions as recommended by the cardiologist. Treatment of thrombotic coronary occlusion is based upon recommendations for treatment of adults with acute coronary syndromes. Thrombolytic therapy consists of use of streptokinase, urokinase, or alteplase (tissue plasminogen activator) in combination with aspirin and heparin (unfractionated or low molecular weight).		
myocardial infarction	**long term**	**low**
Medical or surgical interventions as recommended by the cardiologist.		
rupture of giant coronary artery aneurysms	**long term**	**low**
Extremely rare and can be associated with haemopericardium. Most complications relate to healing with stenosis or persistence of giant coronary artery aneurysms. Medical or surgical interventions as recommended by the cardiologist.		
systemic artery aneurysms	**long term**	**low**
Rare, but can occur in the following arteries: femoral, subclavian, iliac, brachial, axillary, and others. Surgical intervention may be needed.		
peripheral extremity gangrene	**long term**	**low**
Vascular surgeon needs to be consulted.		
bowel ischaemia and necrosis	**long term**	**low**

FOLLOW UP

Complications	Timeframe	Likelihood
Paediatric general surgeon needs to be consulted.		

Prognosis

Kawasaki disease (KD) is an acute, self-limiting illness. However, in untreated patients it is associated with significant morbidity and mortality. The immediate outcome has improved dramatically, with a decrease in the frequency of coronary artery aneurysms to less than 3% following the introduction of intravenous immunoglobulin therapy. Overall, the mortality rate is less than 0.5%. It remains to be seen whether other anti-inflammatory agents, such as new immunosuppressive therapies or new anti-cytokine biologicals, will further improve management and outcome of KD.

Diagnostic guidelines

Europe

Fever in under 5s: assessment and initial management

Published by: National Institute for Health and Care Excellence **Last published:** 2013

Summary: Evidence-based guidelines including recommendations for the assessment of feverish illness in children aged younger than 5 years.

North America

Diagnosis, treatment, and long-term management of Kawasaki disease

Published by: American Heart Association **Last published:** 2017

Summary: Discusses clinical criteria for diagnosis of KD and common clinical and laboratory features. Flowcharts with recommendations for work-up of KD.

Treatment guidelines

North America

Diagnosis, treatment, and long-term management of Kawasaki disease

Published by: American Heart Association **Last published:** 2017

Summary: Recommendations for treatment of Kawasaki disease. Provides guidance on risk stratification.

Evidence scores

1. Aetiology: there is medium-quality evidence from a case control study that found no relationship between Kawasaki disease (KD) and coronavirus NL63.[9]
Evidence level B: Randomized controlled trials (RCTs) of <200 participants, methodologically flawed RCTs of >200 participants, methodologically flawed systematic reviews (SRs) or good quality observational (cohort) studies.

2. Aetiology: there is medium-quality evidence from an observational genetic (cohort) study that links KD with a susceptibility gene present at a locus on chromosome 12q24.[22]
Evidence level B: Randomized controlled trials (RCTs) of <200 participants, methodologically flawed RCTs of >200 participants, methodologically flawed systematic reviews (SRs) or good quality observational (cohort) studies.

3. Resolution of fever and inflammation: there is good-quality evidence from a large US randomised controlled trial that a single dose of intravenous immunoglobulin (2 g/kg) is superior to sequential smaller doses in reducing fever, acute inflammatory markers, and prevalence of coronary artery abnormalities in KD.[28]
Evidence level A: Systematic reviews (SRs) or randomized controlled trials (RCTs) of >200 participants.

4. Resolution of fever and inflammation: there is medium-quality evidence from an observational (cohort) study that re-treatment with a second course of intravenous immunoglobulin improves the clinical course.[29]
Evidence level B: Randomized controlled trials (RCTs) of <200 participants, methodologically flawed RCTs of >200 participants, methodologically flawed systematic reviews (SRs) or good quality observational (cohort) studies.

5. Clinical outcome: there is medium-quality evidence that patients refractory to intravenous immunoglobulin treatment benefit from treatment with corticosteroid pulsed therapy.[31] [32]
Evidence level B: Randomized controlled trials (RCTs) of <200 participants, methodologically flawed RCTs of >200 participants, methodologically flawed systematic reviews (SRs) or good quality observational (cohort) studies.

6. Clinical course and coronary artery outcome: there is medium-quality evidence from a randomised controlled trial that a combination of corticosteroids and intravenous immunoglobulin improves clinical course and coronary artery outcome, compared with intravenous immunoglobulin alone.[33]
Evidence level B: Randomized controlled trials (RCTs) of <200 participants, methodologically flawed RCTs of >200 participants, methodologically flawed systematic reviews (SRs) or good quality observational (cohort) studies.

7. Clinical outcome: there is high-quality evidence from a large multicentre trial in the US that the routine use of pulsed methylprednisolone, as an adjunct to intravenous immunoglobulin therapy, does not improve clinical outcome in KD.[34]
Evidence level A: Systematic reviews (SRs) or randomized controlled trials (RCTs) of >200 participants.

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Images

Figure 1: Coronary artery ectasia

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