Kawasaki Disease - Diagnosis

Inpatient

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Principle Clinical Features:
- Bilateral nonexudative conjunctival injection
- Erythema/cracking of lips, strawberry tongue, erythema oral mucosa
- Erythema or swelling of distal extremity or periungual desquamation
- Rash
- Cervical adenopathy (≥ 1.5 cm), usually unilateral

Not all features need to be present at the same time.

Document features **photographically** when possible.

Inclusion Criteria:
- All patients with fever ≥ 4 days without other explanation

Initial Assessment
Child with fever ≥ 4 days without an alternative explanation

- Consider MIS-C pathway (esp. if known exposure to or illness with COVID-19 in last month)
- Consult Infectious Diseases

How many diagnostic criteria are met?

- 0-1 criteria → ≤ 6 months old with fever ≥ 7 days?
- 2-3 criteria → Obtain CRP/ESR
- ≥4 criteria → **Complete KD** Start treatment and obtain baseline echocardiogram

≤ 6 months old with fever ≥ 7 days?

- Yes → Obtain CRP/ESR, supplemental labs & echocardiogram
- No → Consider alternate diagnoses

Obtain CRP/ESR, supplemental labs & echocardiogram → Echo findings suggestive of KD?

- No → Assess for lab criteria and monitor with serial echocardiogram until KD is diagnosed or until patient is afebrile/well for 48 hours.
- Yes → **Incomplete KD** Start treatment

Consider alternate diagnoses → CRP ≥ 3.0mg/dL **OR** ESR ≥40mm/hr

- Yes → Obtain supplemental labs & echocardiogram → ≥ 3 supplemental lab criteria† **OR** abnormal echocardiogram
  - Yes → **Incomplete KD** Start treatment
  - No → Fevers persist after 24-48 hours?
- No → Shared decision-making regarding disposition → Fevers persist after 24-48 hours?

Fevers persist after 24-48 hours?

- Yes →
  - Consider alternate diagnoses
  - Obtain inflammatory markers (and repeat supplemental labs if previously obtained)
  - Obtain echo if > 7 days or periungual desquamation
- No → **KD Unlikely**
  - Consider alternate diagnoses
  - Consult Infectious Diseases if periungual desquamation occurs for late presentation

Consider KD for:
- Infants ≤ 6 months w/ prolonged fever/irritability
- Infants w/ prolonged fever and unexplained aseptic meningitis
- Infants/children with prolonged fever and
  - Unexplained/culture negative shock
  - Cervical lymphadenitis unresponsive to antibiotic treatment
  - Retropharyngeal/ parapharyngeal phlegmon unresponsive to antibiotic treatment

Supplemental Labs:
- CBC with diff
- CMP
- Urinalysis w/micro
- Obtain extra red-top
- Blood culture
- Respiratory viral panel

† Supplemental Lab Criteria:
- Anemia for age
- Platelets ≥ 450k
- Albumin ≤ 3.0g/dL
- Elevated ALT level
- WBC ≥ 15,000/mm^3
- ≥ 10 WBC/hpf on urinalysis

Kawasaki Disease Treatment
Inpatient

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Document IVIG Start and Completion Times

Standard Initial Therapy:
- Begin IVIG administration per institutional practice titration
- Aspirin 30 to 50 mg/kg/day orally in 4 divided doses; maximum 4g/day.

Do not give Ibuprofen or other NSAIDs while on aspirin

Provider team to notify Kawasaki Disease team via email at **KawasakiTreatmentTeam@nationwidechildrens.org**.

*** High-risk KD patients are any of the following:**
- Patients age ≤ 6 months or > 8 years
- Patients with a known max Z score of the LAD or RCA of ≥ 2.5 on baseline echocardiogram or discrete aneurysm or aortic root dilatation
- Patients with shock
- Patients with a CRP > 15 mg/dL and one of the following:
  - WBC > 20,000 with neutrophil predominance
  - Platelet count < 150,000
  - Sodium < 133
  - Albumin < 2.8
  - Hemoglobin < 8
  - ALT > 100

Patient at high risk* for IVIG resistance?

Yes →
- **ADD** Methylprednisolone (1mg/kg IV q12) until afebrile and CRP decreasing with transition to PO prednisolone with 2–3-week taper.

No ↓

Persistence of fever between 36 hours to 2 weeks after the finish of IVIG infusion or recurrence of fever?

Consult Cardiology with any abnormal Echo results for additional guidance on management including aspirin dosing, timing of repeat Echo, and specific discharge needs.

Additional laboratory evaluation to include: §
- Ferritin
- Soluble IL-2 Receptor
- Repeat CBC, CMP, CRP, ESR
- Triglycerides
- Fibrinogen

Yes ↓

Rule out other causes of fever including potential for Macrophage Activation Syndrome (MAS)§

No ←

Clinically improving?
- Patient afebrile for at least 12 hours before discharge and 24 hours post completion of IVIG
- Repeat CRP and CBC roughly 24 hours post IVIG with CRP trending down

KD team consult and echo completed

KD with MAS concerns?
- Cytopenia
- Transaminitis
- Hyperferritinemia
- Drop in ESR

MAS Criteria

Yes → **Off Pathway** Consult Rheumatology

No ↓

‡ Escalation Options
- Anakinra
- Infliximab
- IV pulse methylprednisolone
- Cyclosporine
- Cyclophosphamide

- Retreat with IVIG administration per institutional practice titration
- Consider adding steroids (if not already started)

Clinically improving?
- Patient afebrile for at least 12 hours before discharge and 24 hours post completion of second dose of IVIG
- Repeat CRP and CBC roughly 24 hours post IVIG with CRP trending down

No → **Off Pathway** Discuss escalation options‡ with KD Experts and Rheumatology

Yes →

Yes ↓

Discharge Orders:
- For patients **without** CA abnormalities prescribe 6 week supply of low-dose aspirin (3-5mg/kg/day or 81mg daily)
- For patients **with** CA abnormalities, Cardiology will guide aspirin dosing
- Steroid taper in place, if applicable
- KD clinic follow-up scheduled
- Patient received inactivated flu vaccine if in season
- Family received education materials regarding fever monitoring

Definition & Diagnosis

Kawasaki disease (KD) is an acute, self-limited febrile illness of unknown etiology typically affecting children under the age of 5 years, though it can affect older children. KD is the most common cause of acquired heart disease in children in developed countries.

The highest risk period for coronary aneurysm is the first 6 weeks after diagnosis when the coronary artery dilation can occasionally expand to aneurysm, leading to thrombosis and rupture with ischemia, arrhythmia, and even sudden death.

With treatment, the majority of cardiac findings will resolve.

Definitions:

- **COMPLETE** presentation is defined as:
  - Fever of ≥ 4 days and at least 4 of 5 principal clinical features (conjunctival injection, oropharyngeal changes, unilateral cervical lymphadenopathy, hand/feet changes, and/or rash).
  - *In the presence of > 4 principal clinical features, particularly when redness and swelling of the hands and feet are present, the diagnosis may be made with only 4 days of fever, and for an experienced clinician rarely at day 3 of fever.*

- **INCOMPLETE** presentation is defined as one of the following:
  - Fever of ≥ 4 days and 2-3 principal features in those ≥ 6 months WITH elevated inflammatory markers and ≥ 3 supplemental lab criteria
  - Fever of any duration in any age child with documented coronary artery abnormalities (coronary diameters normalized to height and weight with calculated Z score of ≥ 2.5) with 2-3 cardinal features of the disease.
  - Fever in infants ≤ 6 months with fever of 7 or more days duration, evidence of systemic inflammation and no other explanation for the illness. These infants may have none of the principal clinical features of KD.

McCrindle et al. Diagnosis, treatment, and long term management of Kawasaki disease. American Heart Association. Circulation. 2017;135:e927-e999.

Return to Diagnosis Algorithm

Diagnostic Pearls

In the infant ≤ 6 months of age, prolonged fever and irritability may be the only clinical manifestations of Kawasaki disease (KD), and these children are at high risk of developing coronary artery abnormalities.

In a child with clinical findings compatible with classic KD, the detection of respiratory viruses such as respiratory syncytial virus, metapneumovirus, coronaviruses, parainfluenza viruses, or influenza viruses does not exclude the diagnosis of KD.

In children with some clinical features of KD and a positive rapid test or culture for group A streptococcus who do not improve after 24 to 48 hours of effective antibiotic therapy (streptococcal carriers), the diagnosis of KD should be considered.

McCrindle et al. Diagnosis, treatment, and long term management of Kawasaki disease. American Heart Association. Circulation. 2017;135:e927-e999.

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Principle Clinical Features of KD

Fever:
- Typically high spiking and remittent
- Spontaneous resolution of fever after 7 days should not be regarded as evidence that the diagnosis of KD has been excluded.

Conjunctival injection:
- Often begins shortly after fever and spares the limbus.
- Not typically associated with tearing or discharge.
- Anterior uveitis may be present by slit-lamp exam.
- Subconjunctival hemorrhage/punctate keratitis occasionally observed.
- Conjunctival injection that begins in one eye and then becomes bilateral is more typically associated with adenovirus infection.

Hand/feet swelling/changes:
- Erythema of the palms and soles and firm sometimes painful induration of the hands or feet often occur in the acute phase.
- Desquamation of the fingers and toes (around the nailbed, “periungual”) occurs only 2-3 weeks after fever onset and may extend to palms/soles.

Rash
- Scarlatiniform, erythema multiforme-like, urticarial or micro-pustular.
- Usually extensive, primarily involving the trunk and extremities with accentuation in the groin.
- *KD rashes are typically NOT bullous, vesicular or petechial.*

Oral mucosal changes:
- Erythema, dryness, fissuring, cracking, bleeding or peeling of the lips
- A “strawberry tongue” with erythema and prominent fungiform papillae may be present.
- *KD does NOT typically present with oral ulcers and/or pharyngeal exudate.*

Lymphadenopathy:
- This is the least common of the principal clinical features.
- Lymph node swelling is usually unilateral, > 1.5 cm in diameter, and confined to the anterior cervical triangle.

McCrindle et al. Diagnosis, treatment, and long term management of Kawasaki disease. American Heart Association. Circulation. 2017;135:e927-e999.

Return to Diagnosis Algorithm

Other Clinical Features

Other Clinical Features

Neurologic:

- **Common:**
  - Extreme irritability exceeding that observed in other febrile illnesses
  - Aseptic meningitis
- **Less common:**
  - Transient peripheral facial nerve palsy
  - Sensorineural hearing loss

Cardiovascular:

- **Common:**
  - Myocarditis
  - Inflammation of the pericardium, myocardium, endocardium including valves, and coronary arteries.
- **Less Common**
  - Arrhythmias
  - A shock-like picture, including myocardial dysfunction, valvar dysfunction (MR > TR > AR) and pericardial effusion.

Gastrointestinal:

- **Common:**
  - Hepatitis
  - Diarrhea
  - Vomiting
  - Abdominal pain
  - Gallbladder hydrops
- **Less common:**
  - Pancreatitis
  - Jaundice

Genitourinary:

- **Common:**
  - Urethritis
- **Less common:**
  - Hydrocele
  - Phimosis

Musculoskeletal:

- First week of illness:
  - Arthralgia/arthritis involving small interphalangeal joints and large weight bearing joints
- Second-third week of illness:
  - Predominantly large weight bearing joints, especially knees and ankles (If aspirated, joint fluid may look purulent with a WBC count of 125,000-300,000/mm^3, normal glucose, negative Gram stain and culture)

Respiratory:

- Peribranchial and interstitial infiltrates on chest X-ray; nodular infiltrates occur rarely.

Other:

- Prolonged fever and cervical lymphadenitis unresponsive to antibiotic therapy. Imaging can reveal cluster of lymph nodes.
- Prolonged fever and retropharyngeal or parapharyngeal phlegmon unresponsive to antibiotic therapy.
- Erythema and induration at the site of previous vaccination with bacille Calmette-Guerin.
- Macrophage Activation Syndrome: disseminated intravascular coagulopathy, cytopenia, thrombosis.

Return to Diagnosis Algorithm

Differential Diagnoses

Differential Diagnoses

- Viral infections (EBV, adenovirus, enterovirus, measles)
- Staphylococcal scalded skin syndrome
- Streptococcal toxin-mediated disease
- Drug hypersensitivity reactions including Stevens-Johnson syndrome
- Systemic onset juvenile idiopathic arthritis
- Rocky Mountain spotted fever
- Leptospirosis
- **Macrophage activation syndrome**
- **MIS-C** (Especially if known exposure to or illness with COVID-19 in last month)

- **Features generally NOT consistent with KD:**
  - Exudative conjunctivitis
  - Exudative pharyngitis
  - Oral ulcerations
  - Splenomegaly
  - Vesiculobullous or petechial rashes
  - Acute lymphadenitis in which radiologic imaging reveals a sole node, especially with purulence

- Patients with adenovirus infections typically have conjunctival injection which begins mono-ocular and then becomes bilateral within 24-48 hours and is associated with EITHER tearing or exudate

Return to Diagnosis Algorithm

Cardiovascular Testing

In addition to the laboratory tests listed under clinical findings cardiovascular testing should be performed in all patients evaluated for KD.

Inpatient Echocardiogram for Suspected KD

- Place order for Echocardiogram
- If patient is < 3 yrs old, make NPO for sedated echocardiogram after discussing with Infectious Disease and echocardiogram technologist. Contact procedure center in regards to scheduling.

Consult cardiology with any Echo abnormality to discuss impact on treatment, timing of repeat Echo and follow up needs.

Echo Findings Suggestive of KD

- Z score of left anterior descending coronary artery or right coronary artery ≥ 2.5
- Coronary artery aneurysm is observed
- ≥ 3 other suggestive features exist:
  - Decreased left ventricular function
  - Mitral regurgitation
  - Pericardial effusion
  - Z score in left anterior descending coronary artery or right coronary artery of 2-2.5

Return to Diagnosis Algorithm

Return to Treatment Algorithm

Cardiovascular Severity Assessment

Z-Score Classification

1. No involvement: Always < 2
2. Dilation only: 2 to < 2.5; or if initially < 2, an increase in Z score during follow-up ≥ 1
3. Small aneurysm: ≥ 2.5 to < 5
4. Medium aneurysm: ≥ 5 to < 10, and absolute dimension < 8 mm
5. Large or giant aneurysm: ≥ 10, or absolute dimension ≥ 8 mm

Accurate measurement of weight and particularly height is important to enable calculation of an accurate body surface area. For irritable young infants and toddlers, measurement of height might need to be rechecked if it was initially obtained under less than ideal circumstances.

- **For patients with important and evolving CAA (Z score ≥ 2.5) detected during the acute illness, more frequent echocardiography (at least twice per week) should be performed until luminal dimensions have stopped progressing to determine the risk for and presence of thrombosis.**
- **Cardiology will make all recommendations regarding frequency of Echo and any additional cardiac testing.**

To detect coronary artery thrombosis, it may be reasonable to perform echocardiography for patients with expanding large or giant aneurysms twice per week while dimensions are expanding rapidly and at least once weekly in the first 45 days of illness, and then monthly until the third month after illness onset, because the failure to escalate thromboprophylaxis in time with the rapid expansion of aneurysms is a primary cause of morbidity and mortality. These patient will be followed by cardiology and hematology.

For more info on long term management see table 2 from Jone PN, Tremoulet A, Choueiter N, et al.

Return to Diagnosis Algorithm

Return to Treatment Algorithm

Treatment of Standard Risk KD Patients

- Begin IVIG administration per institutional practice titration
  - Dose: 2,000 mg/kg (2g/kg)
  - Max dose = 100g
  - The ESR is increased after IVIG treatment; therefore, ESR is not a reliable marker of inflammation after IVIG
  - **Document IVIG Start and Completion Times**
- Initial aspirin dosing of 30 to 50mg/kg/day orally in 4 divided doses; maximum 4g/day.
- For patients **without** CA abnormalities plan to transition to low-dose aspirin (3-5mg/kg/day or 81mg daily) prior to or at the time of discharge.
- For patients **with** CA abnormalities, Cardiology will make recommendations in regards to aspirin dosing.
- Do not give Ibuprofen or other NSAIDs while on aspirin
- Notify Kawasaki Treatment team via email when treatment is being started at **KawasakiTreatmentTeam@nationwidechildrens.org**
- Consult Infectious Disease if not on ID service
- Consult Cardiology with any Echo abnormality and/or other KD related cardiac complications

Return to Treatment Algorithm

Treatment of High-Risk KD Patients

Patients believed to be at high risk for development of CA aneurysms may benefit from primary adjunctive therapy

High-risk KD patients are any of the following:

- Patients age ≤ 6 months or > 8 years
- Patients with a known max Z score of the LAD or RCA of ≥ 2.5 on an acute stage echocardiogram, discrete aneurysm, and/ or aortic root dilatation ≥ 2.5 based on Z score from the initial echo for high-risk determination
- Patients with shock
- Patients with a CRP > 15 mg/dL and one of the following:
  - WBC > 20,000 with neutrophil predominance
  - Platelet count < 150,000
  - Sodium < 133
  - Albumin < 2.8
  - Hemoglobin < 8
  - ALT > 100

Provider team to notify Kawasaki Disease team about high-risk KD patients via email at **KawasakiTreatmentTeam@nationwidechildrens.org**.

1. Adjunctive steroid therapy should be started as soon as possible
   - **ADD** Methylprednisolone (1mg/kg IV q12) until afebrile and CRP decreasing with transition to PO prednisolone with 2–3 week taper. Prior to discharge patient should be on once daily steroid dosing.
   - Infants ≤ 6 months of age and younger should remain hospitalized on IV steroids until the CRP normalizes. Other children can be discharged when CRP is decreasing (e.g. roughly 50% each day from initial value) and they are afebrile.

2. Echocardiography should be performed twice weekly until coronary artery size stabilizes.

3. If follow-up echocardiography shows worsening coronary artery Z scores, the child should remain hospitalized.

4. If fever recurs or CRP does not remain normal as prednisone is tapered, please consult with KD team regarding dose adjustment or other therapy.

5. Consider famotidine treatment during steroid therapy in the hospital and at home.

6. Cardiology consult for any patient with coronary artery Z score ≥ 2.5, discrete aneurysm, ventricular disfunction, greater than mild valve disease, and patients presenting with Kawasaki shock.

Cardiology will manage aspirin dosing recommendations and may recommend the addition of Clopidogrel (Plavix) or Warfarin/ Enoxaparin.

z-score 2.5 to < 5: Aspirin with starting dose 30-50mg/kg/day in 4 divided doses (maximum 4g/day).
z-score ≥ 5 to < 10: Dual antiplatelet therapy with the addition of Clopidogrel.
z-score ≥ 10: Dual antiplatelet therapy (Aspirin and Clopidogrel) with addition of Warfarin or Enoxaparin.

Once afebrile for 48-72 hours, can transition to low dose Aspirin (3-5mg/kg/day or 81mg daily).

For more info on long term management see table 2 from Jone PN, Tremoulet A, Choueiter N, et al.

Return to Treatment Algorithm

Retreatment of KD

- Retreatment of KD patients with recurrent fever and/or persistently elevated CRP values who did not receive initial high-risk protocol but are found to have LAD or RCA Z scores of > 4.0 or enlarging coronary arteries at the time of retreatment:
  - Follow the protocol for primary therapy of high-risk patients, using a combination of repeat IVIG and steroid therapy for re-treatment.
- Retreatment of KD patients with recurrent fever who do not have LAD or RCA Z scores of > 4.0 or enlarging coronary arteries at the time of retreatment
  - Consider infliximab
  - If patient refuses infliximab, administer a second dose of IVIG administration per institutional practice titration

- For KD patients who are retreatment failures or otherwise complex, please consult rheumatology. Consider monoclonal antibody therapy (except TNF-α blockers), cytotoxic agents, or (rarely) plasma exchange if second IVIG infusion, infliximab, or extended course of steroids has failed. Clinical judgment is needed to determine whether to consider additional/alternate therapies:

  - High-dose pulse steroids (usually methylprednisolone +/- subsequent course and taper of oral prednisone)
  - Longer (eg, 2–3 weeks) tapering course of prednisolone or prednisone, together with
    - IVIG administration per institutional practice titration
    - Infliximab
    - Anakinra
  - Cyclosporine if second IVIG infusion, infliximab, or a course of steroids has failed per rheumatology consult

Return to Treatment Algorithm

MAS Criteria

2004 HLH/MAS diagnostic criteria, which includes 5 of the following 8 findings:

- Persistent fever > 38.5°C
- Splenomegaly
- Peripheral blood cytopenia, with at least two of the following: hemoglobin < 9 g/dL (for infants < 4 weeks, hemoglobin < 10g/dL); platelets < 100,000/microL; absolute neutrophil count < 1000/microL
- Hypertriglyceridemia (fasting triglycerides > 265mg/dL) and/or hypofibrinogenemia (fibrinogen < 150mg/dL)
- Ferritin > 500ng/mL (many consider a ferritin > 3000ng/mL as more indicative of HLH)
- Hemophagocytosis in bone marrow, spleen, lymph node, or liver not diagnostic and not recommended at this time
- Low or absent NK cell activity newer literature with recommendations to not use this criteria due to the nature of the testing
- Elevated soluble CD25 (soluble IL-2 receptor alpha) two standard deviations above age-adjusted laboratory-specific norms

MAS patients are off pathway. Consult Rheumatology.

Return to Treatment Algorithm

Discharge Criteria & Planning

Discharge Criteria

- Patient afebrile for at least 12 hours before discharge and 24 hours post completion of IVIG
- CRP trending down
- KD team consult and echo completed

Discharge Orders

- For patients **without** CA abnormalities:
  - Prescribe 6-week supply of low-dose aspirin (3-5mg/kg/day or 81mg daily).
  - KD clinic follow-up scheduled in 2 weeks of discharge
  - Patient received inactivated flu vaccine if in season
  - Family received education materials regarding fever monitoring

- For patients **with** CA abnormalities:
  - Cardiology will make recommendations regarding aspirin dosing at the time of discharge
  - Cardiology may recommend the addition of Clopidogrel to low-dose aspirin for patients with moderate coronary artery dilation (Z score ≥ 5 to < 10), or the addition of Warfarin or Enoxaparin +/- Clopidogrel to low-dose aspirin for patients with large/giant coronary artery dilation (Z score ≥ 10). Beta blockers +/-statin therapy may also be recommended by cardiology for patients with severe coronary artery.
  - Follow up within 1 week with Cardiology
  - KD clinic follow-up scheduled in 2 weeks of discharge
  - Patient received inactivated flu vaccine if in season
  - Family received education materials regarding fever monitoring

Return to Treatment Algorithm

Patient & Caregiver Education

- Live vaccines (particularly measles, mumps, varicella) should be deferred for 11 months after receiving high-dose IVIG.
- Children at high risk for measles may receive the vaccination earlier but will require re-immunization 11 months after IVIG administration

Kawasaki Disease Helping Hands

Return to Treatment Algorithm

Metrics

Pathway Goal

- **Evidence based standardized diagnostic approach to patients suspected or confirmed with Kawasaki disease with the timely initiation and escalation, if necessary, of treatment to promote optimal patient outcomes.**

Quality Measures

Outcome Metrics

- Inpatient LOS
- Coronary abnormality rate (acute, ≤ 6 months)

Process Metrics

- Pathway EPIC tool utilization

Balancing Metrics

- Inpatient readmission, all cause, 7 and 30 day

Return to Diagnosis Algorithm

Return to Treatment Algorithm

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Clinical Pathway Development

This clinical pathway was developed using the process described in the NCH Clinical Pathway Development Manual Version 6, 2022. Clinical Pathways at Nationwide Children's Hospital (NCH) are standards which provide general guidance to clinicians. Patient choice, clinician judgment, and other relevant factors in diagnosing and treating patients remain central to the selection of diagnostic tests and therapy. The ordering provider assumes all risks associates with care decisions. NCH assumes no responsibility for any adverse consequences, errors, or omissions that may arise from the use or reliance on these guidelines. NCH's clinical pathways are reviewed periodically for consistency with new evidence; however, new developments may not be represented, and NCH makes no guarantees, representations, or warranties with respect to the information provided in this clinical pathway.

For more information about our pathways and program please contact:
ClinicalPathwaysProgram@NationwideChildrens.org

Return to Diagnosis Algorithm

Return to Treatment Algorithm