Clinical Practice Guidelines for Treatment of Kawasaki Disease

Developed by:

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This clinical guideline is intended as an evidence-based guide for clinical care and not as a replacement for clinical decision making. These guidelines will be reviewed and updated as necessary every three years.

Purpose: *To develop standardization of care of patients diagnosed with Kawasaki disease at JDCH*

Introduction

Kawasaki disease is an acute, self-limited, systemic vasculitis of undetermined etiology that is characterized by fever and muco-cutaneous signs and occurs predominantly in infants and young children. It is the leading cause of acquired heart disease in children in developed countries. It is known to occur in both endemic and community-wide epidemic forms across the globe. Coronary artery aneurysms or ectasia develop in approximately 15-25% of untreated children with the disease and may lead to myocardial infarction, sudden death, or ischemic heart disease.

Clinical Findings

Diagnostic Clinical Findings

≥ 5 days of fever with ≥ 4 of these 5 principle clinical features. All clinical features are not usually present simultaneously and there is no typical order of appearance.

- *Acute or sub-acute changes in the extremities (50-85%)*
  - *Erythema of the palms / soles*
  - *Painful induration of the hands or feet*
  - *Desquamation of the fingers or toes*
- *Polymorphous exanthem (70-90%)*
- *Bilateral bulbar, non-exudative conjunctivitis with sparing of the limbus (>75%)*
- *Changes in lips and oral cavity (90%)*
  - *Erythema, dryness, fissuring, peeling, cracking, bleeding of the lips*
  - *"Strawberry tongue"*
  - *Erythema of the oropharyngeal mucosae*
- *Cervical lymphadenopathy: usually unilateral and > 1.5cm in diameter (25-70%)*

Non-diagnostic Clinical Findings

- *Arthritis or arthralgia (10-20%)*
- *Diarrhea, vomiting, or abdominal pain (61%)*
- *Irritability (50%)*
- *Vomiting (44%)*
- *Cough or rhinorrhea (35%)*
- *Decreased intake (37%)*
- *Meningismus with CSF pleocytosis (40%)*
- *Gallbladder hydrops (<10%)*
- *Myocarditis with CHF (<5%)*

Diagnostic Studies

Laboratory findings associated with acute Kawasaki Disease

- *Leukocytosis, neutrophilia, bandemia*
- *Elevated CRP (≥3mg/dL)*
- *ESR (≥40mm/hr)*
- *Anemia*
- *Abnormal plasma lipids*
- *Hypoalbuminemia*
- *Hyponatremia*
- *Elevated GGT*
- *Elevated ALT/AST*
- *CSF pleocytosis*
- *Synovial fluid leukocytosis*
- *Thrombocytosis (>450k/mm^3) generally occurring after 2nd week of illness*
- *Sterile pyuria (clean catch or bag specimen)*

EKG may show

- *A dysrhythmia*
- *Prolonged PR interval*
- *Non-specific ST and T wave changes*

Differential Diagnosis

- Viral infections such as
  - EBV
  - Parvovirus B-19,
  - Enterovirus,
  - Adenovirus,
  - Measles
- Scarlet Fever
- Staphylococcal Scalded Skin Syndrome
- Toxic Shock Syndrome
- Bacterial cervical lymphadenitis
- Drug hypersensitivity reactions
- Stevens-Johnson Syndrome
- Juvenile rheumatoid arthritis
- Rocky Mountain Spotted Fever
- Leptospirosis
- Mercury hypersensitivity reaction
- Rheumatologic conditions

Incomplete Kawasaki Disease

A well-described variant to classic Kawasaki Disease is the incomplete form of the disease. Incomplete Kawasaki Disease is more common in young infants than in older children. Laboratory findings are similar in both classic and incomplete Kawasaki Disease. The incomplete form should be considered in all children with unexplained fever for more than 5 days associated with at least 2 of the principal clinical features of Kawasaki Disease. Because young infants may present with fever and few, if any, principal clinical features, echocardiography should be considered in any infant less than 6 months of age with fever for seven or more days duration, laboratory evidence of systemic inflammation, and no other explanation for the febrile illness. It is broadly agreed that Kawasaki Disease can be diagnosed in the absence of full criteria when coronary abnormalities are present.

In cases where the gold standard for diagnosis is absent, an algorithm for evaluation of an incomplete form of the disease has been developed:

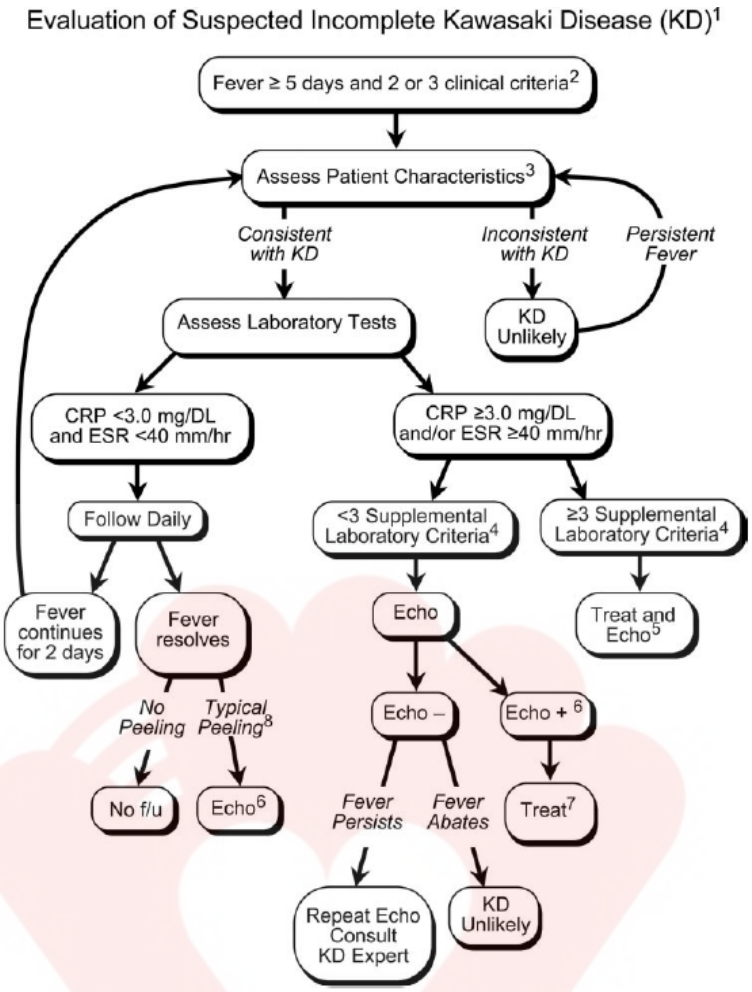

Fig 1. Evaluation of suspected incomplete Kawasaki disease. (1) In the absence of gold standard for diagnosis, this algorithm cannot be evidence based but rather represents the informed opinion of the expert committee. Consultation with an expert should be sought anytime assistance is needed. (2) Infants ≤6 months old on day ≥7 of fever without other explanation should undergo laboratory testing and, if evidence of systemic inflammation is found, an echocardiogram, even if the infants have no clinical criteria. (3) Patient characteristics suggesting Kawasaki disease are listed in Table 1. Characteristics suggesting disease other than Kawasaki disease include exudative conjunctivitis, exudative pharyngitis, discrete intraoral lesions, bullous or vesicular rash, or generalized adenopathy. Consider alternative diagnoses (see Table 2). (4) Supplemental laboratory criteria include albumin ≤3.0 g/dL, anemia for age, elevation of alanine aminotransferase, platelets after 7 days ≥450 000/mm^3, white blood cell count ≥15 000/mm^3, and urine ≥10 white blood cells/high-power field. (5) Can treat before performing echocardiogram. (6) Echocardiogram is considered positive for purposes of this algorithm if any of 3 conditions are met: z score of LAD or RCA ≥2.5, coronary arteries meet Japanese Ministry of Health criteria for aneurysms, or ≥3 other suggestive features exist, including perivascular brightness, lack of tapering, decreased LV function, mitral regurgitation, pericardial effusion, or z scores in LAD or RCA of 2–2.5. (7) If the echocardiogram is positive, treatment should be given to children within 10 days of fever onset and those beyond day 10 with clinical and laboratory signs (CRP, ESR) of ongoing inflammation. (8) Typical peeling begins under nail bed of fingers and then toes.

Recommended evaluation of suspected Kawasaki Disease

1. *CBC*
2. *CMP*
3. *CRP*
4. *ESR*
5. *UA*
6. *ECG – 12 lead*
7. *ECHO to be read by JDCH Inpatient Cardiologist*
8. *Gallbladder U/S in patients with abdominal pain*
9. *Consultation to Pediatric Infectious Disease*
10. *Consultation to JDCH Inpatient Cardiology*

Cardiovascular Effects

Coronary artery changes infrequently occur as early as 4-7 days after the onset of fever. Most commonly they occur 1 to 4 weeks later and development after 6 weeks is extremely rare. Echocardiography should be performed once the diagnosis has been established clinically or as a diagnostic tool in cases where the diagnosis is uncertain. Follow-up echocardiography is imperative and the treating cardiologist, based on the initial echo results and patient risk factors for developing coronary artery lesions, will determine the interval between subsequent studies.

Risk factors for developing coronary artery disease include:

- *male gender,*
- *age less than 12 months or greater than 8 years,*
- *fever for more than 10 days,*
- *baseline relative neutrophil and band count greater than 80%*
- *peripheral white blood cell count greater than 15,000/mm^3*
- *hemoglobin concentration of less than 10 g/dL*
- *hypoalbuminemia, hyponatremia, or thrombocytopenia at presentation.*
- *poor response to initial IVIG infusion*

Classification of Coronary Artery Abnormalities:

Z-Score Classification

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

One caveat to be considered when using Z scores is that a small error in measurement of the coronary artery diameter can translate into a larger difference in Z scores, such that the patient's risk category might change. In addition, accurate measurement of weight and particularly height is important to enable calculation of an accurate BSA. For irritable young infants and toddlers, measurement of height might need to be rechecked if it was initially obtained under less than ideal circumstances.

Treatment

Treatment of Kawasaki Disease in the acute phase is directed at reducing inflammation in the coronary artery wall and preventing coronary thrombosis. Long-term therapy in individuals who develop coronary aneurysms is aimed at preventing myocardial ischemia or infarction. Given the potential seriousness of these complications, together with the efficacy and safety of early treatment, high sensitivity of the treatment criteria is more important than is high specificity.

Initial Treatment:

Aspirin

Aspirin is used for its anti-inflammatory properties at moderate (30-50 mg/kg/day) to high doses (80-100 mg/kg/day) and for its anti-platelet effects at low doses (3-5 mg/kg/day). Moderate to high dose aspirin is prescribed in 4 divided doses until the patient has been afebrile for 48-72 hours. At this point the dose is reduced to 3-5mg/kg/day in a single daily dose until the patient has shown no evidence of coronary artery changes by 6-8 weeks after the onset of illness.

Concomitant use of ibuprofen antagonizes the anti-platelet effect of aspirin and should be avoided. Although it is unknown whether low-dose aspirin therapy increases the risk of Reye syndrome, children on long-term salicylate therapy should receive an annual influenza vaccine.

Alternatives to long-term aspirin therapy: Clinical reasons may exist to consider long term anticoagulation therapy other than aspirin. In these unique circumstances dipyridamole (2-6mg/kg/day in 3 divided doses), low molecular weight heparin, warfarin, and clopidogrel (1mg/kg/day) have been used successfully.

IVIG

IVIG has a generalized anti-inflammatory effect. There appears to be a dose-response effect with higher doses given in a single infusion having the greatest effect. Patients should be treated with IVIG within 10 days of the onset of fever at a dose of 2 grams per kilogram body weight, infused over 10-12 hours. Treatment sooner than day 5 is no more effective in preventing cardiac sequelae than treating on days 5-7 of fever. Treatment after day 10 of fever should be considered in patients who remain febrile without another explanation, or have coronary aneurysms and ongoing systemic inflammation as manifested by elevated ESR or CRP.

Treatment with IVIG within the first 10 days of fever reduces the incidence of transient coronary artery dilatation to about 5%, and the incidence of giant aneurysms to 1%. After an initial dose of IVIG, approximately 10% of patients with Kawasaki Disease fail to defervesce or have a recrudescence of fever within 36 hours.

Concomitant therapy: In patients with coronary artery aneurysm on initial echocardiogram with Z score ≥ 2.5, concurrent use of steroids or infliximab along with IVIG should be considered to prevent coronary artery aneurysm progression. Steroids are usually given as methylprednisolone 2mg/kg/day for 48 hours or until patient is afebrile, then change to oral prednisolone at 2mg/kg/day and tapered over about 2 weeks at the time of outpatient follow up if inflammatory markers remain low. Infliximab is administered at 10mg/kg.

Treatment for Refractory Disease:

IVIG resistance: Approximately 10–15% of patients with KD fail to respond to an initial single dose of IVIG and oral aspirin with persistent fever ≥36 h after completion of the initial IVIG infusion and elevated CRP. Other children may show an initial response, but become febrile again after a short period of being afebrile. Risk factors for IVIG non-response may include male gender, higher CRP (>8 mg/dL), low hemoglobin, low albumin and low sodium.

Subsequent doses of IVIG: A second dose of IVIG 2 g/kg is recommended by many experts in patients who fail to defervesce after the initial dose of IVIG. Although there are no controlled studies demonstrating effectiveness, a second dose is common practice and appears effective in alleviating symptoms in most patients. The incidence of coronary artery lesions is not affected. There is no evidence that more than 2 doses of IVIG is efficacious.

Infliximab (REMICADE): A retrospective review of 2 centers that consistently administered either a second dose of IVIG or infliximab to IVIG-resistant patients suggested that patients receiving infliximab had shorter hospitalization and fewer days of fever, but coronary artery outcomes and adverse events were similar. Infliximab can be considered as an alternative to a second infusion of IVIG for resistant patients.

Steroids:
Systemic corticosteroids have been used to treat patients recalcitrant to initial IVIG-Aspirin therapy. There have been reports of successful management of IVIG-resistant patients and patients with serious complications of KD receiving additional steroid therapy resulting in no serious adverse effects. One study of IVIG-resistant patients did show that IV methylprednisolone followed by oral steroids for 7 days did not improve clinical or coronary artery outcomes compared with IVIG retreatment. Another retrospective study of IVIG-resistant patients showed that IV prednisolone followed by an oral taper (2mg/kg/day tapered over 2 weeks after CRP normalized) had significantly lower rates of persistent or recrudescent fever and coronary artery abnormalities than the group that received IVIG monotherapy, which could be attributed to suppression of persistent vascular inflammation. The optimal steroid regimen is not known, and both pulsed and longer-term steroid therapy are options.

Follow-up

The patient's primary care physician will be instrumental in ensuring adequate follow-up and should be advised of the plan prior to discharge. Cardiology follow-up will be done by a pediatric cardiologist in community-based practice. The JDCH cardiologist who did the inpatient consult will perform a hand-off to the community cardiology prior to discharge. Unless otherwise specified by cardiology, then a repeat echocardiogram should be performed at 2 weeks and 6 weeks after discharge. Cardiology follow-up should occur in approximately 2 weeks after discharge. Follow-up in Infectious Disease Clinic should be 2-4 weeks after discharge. Other follow-up is at the discretion of the inpatient treatment team.

Immunizations

Annual influenza vaccine is strongly recommended in all children who are taking aspirin. Administration of live-attenuated vaccines should be delayed until nine to eleven months after receiving IVIG. Other childhood vaccinations should not be delayed or withheld.

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Memorial Physician Group

New Pediatric Clinical Guideline Setup Checklist

Guideline Name: Kawasaki Disease Clinical Guideline
Goal of Clinical Guideline: To provide guidance in diagnosis and treatment of Kawasaki Disease

Does the proposed guideline meet the below four criteria?

- ☐ The intervention is a structured **multidisciplinary** plan of care
- ☐ The intervention is used to translate guidelines or evidence into local structures
- ☐ The intervention details the steps in a course of treatment or care in a plan, pathway, algorithm, guideline, protocol or other 'inventory of actions' (i.e. the intervention had time-frames or criteria-based progression)
- ☐ The intervention aims to standardize care for a specific population

(Lawal et al. What is a clinical pathway? Refinement of an operational definition to identify clinical pathway studies for a Cochrane systematic Review. BMC Medicine (2016) 14:35)

CHECKLIST

- ☐ Physician (or an alternate author) submitting the clinical guideline must be able (directly or through virtual meeting) to attend Clinical Guidelines Meeting
- ☐ All participants in the clinical guideline development should be listed and primary author identified
- ☐ Participants who are submitting clinical guideline should sign off and include the division chief(s) from all involved specialties (for purposes of disseminating to entire division)
- ☐ All clinical guidelines should include a disclaimer ...*"this clinical guideline is intended as an evidence-based guide for clinical care and not as a replacement for clinical decision making"*
- ☐ Clinical guideline authors should submit an estimated revision schedule, i.e. every 3 years.
- ☐ References must be included in the submission.
- ☐ Authors of the guideline must identify 1-2 quality metrics that can be measured to gauge impact on care

Signature of Contributing Pathway Developers:

Dept. Name	MD Developer Name	Signature
Pediatric Hospital Medicine	Dr. Ronald Ford and Dr. Angelique Martinez	
Pediatric Infectious Disease	Dr. Pilar Gutierrez and Dr. Robert Reid	
Pediatric Cardiology	Dr. Lazaro Hernandez	