Kawasaki Disease Clinical Guideline

Definition:

Kawasaki disease (KD), also known as Kawasaki syndrome and mucocutaneous lymph node syndrome, is an acute febrile illness of unknown cause that primarily affects children over 6 months up to 5 years of age, although it can occur in young infants, older children, and adults. The disease was first described in Japan by Tomisaku Kawasaki in 1967, and the first cases outside of Japan were reported in Hawaii in 1976.

The clinical signs include a high fever lasting longer than 5 days, rash, swelling of the hands and feet, conjunctivitis (irritation and redness of the whites of the eyes), swollen lymph glands in the neck, and irritation and inflammation of the mouth, lips, and throat. KD is one of the most common vasculitides of childhood. It is characterized by inflammation of blood vessels throughout the body, including the coronary arteries. It is typically a self-limited condition, with fever and manifestations of acute inflammation lasting for an average of 12 days without therapy. However, complications such as coronary artery (CA) aneurysms, depressed myocardial contractility and heart failure, myocardial infarction, arrhythmias, and peripheral arterial occlusion may develop and lead to significant morbidity and mortality.[43]

Incidence:

Studies of hospital discharge records by the United States Centers for Disease Control (CDC) estimated an overall annual incidence of 20 per 100,000 children younger than five years in the United States. [11] Annual incidence was highest among Asians and Pacific Islanders (30 per 100,000), intermediate among non-Hispanic African Americans (17 per 100,000) and Hispanics (16 per 100,000), and lowest among Caucasians (12 per 100,000) [11]. A winter-spring predominance of cases is characteristic, and the peak incidence of illness is at less than one year of age [11]. In contrast to Japan, surveillance in the United States is passive, and many cases may be missed. The overall incidence was 22 per 100,000 children less than five years of age in San Diego County during a six-year period from 1998 to 2003 [3]. The rates based upon ethnicity were 15, 25, 20, and 46 per 100,000 children less than five years of age for non-Hispanic whites, non-Hispanic African Americans, Hispanics, and Asian/Pacific Islanders, respectively.

Etiology:

The exact cause of Kawasaki disease is not well understood, but it is believed to be a complex interplay between genetic, environmental, and immunological factors. There is some evidence to suggest that an infectious agent, such as a virus or bacteria, may trigger the immune response that leads to Kawasaki disease. However, no specific infectious agent has been definitively identified as the cause of the disease. One line of investigation suggests a novel RNA virus that enters through the upper respiratory tract. [49-50] Intracytoplasmic inclusion

bodies in bronchial epithelial cells and multiple other cell types throughout the body appear to contain RNA and could be linked to the KD agent.[45] Investigation is ongoing.

There may also be a genetic component to Kawasaki disease, as it tends to run in families and is more common in people of Asian descent. Some studies have identified certain genes that may be associated with an increased risk of developing the disease. In addition, there is evidence to suggest that Kawasaki disease may be an autoimmune disorder, in which the body's own immune system attacks healthy tissues, leading to inflammation and damage to the blood vessels.

Immune-mediated presentation, such as bacterial or other toxins acting as superantigens, leading to nonselective T cell activation has been postulated; studies have varied regarding the isolation of superantigen-producing organisms, superantigen proteins, or the presence of immunologic signature of superantigen activity. The innate immune system plays a vital role in the pathogenesis of Kawasaki disease. Neutrophils are important factors in the initial inflammatory response on coronary artery walls. Recent studies also demonstrate increased expression of innate immunity-associated genes during the acute phase of Kawasaki's disease.[2]
Impaired immune regulation has been found to also play a role in the pathogenesis of KD as studies of acute and subacute sera from KD patients have shown a decrease in the population of T regulatory cells in the acute phase with normalization following treatment with IVIG. The role of B cells has not been clearly defined; IgA plasma cells have been found in coronary artery lesions from fatal cases of KD. Their specific role is unknown.[3]

Genetic predisposition to respond to multiple triggers in a common pathway has also been postulated, given that multiple infectious agents have been found in patients with KD. Infections may trigger vasculitis. Recent studies have described functional single nucleotide polymorphisms in the inositol, 1, 4, 5, triphosphate 3-kinase C (ITPKC) gene with increased risk of susceptibility to KD, more severe coronary artery disease, and IVIG resistance. This gene acts as a negative regulator of T-cell activation; signaling alterations may lead to immunoregulatory dysfunction.[4]

Overall, the exact cause of Kawasaki disease remains unclear.

Guideline Inclusion Criteria:
Patients with symptoms concerning for possible Kawasaki Disease

- Prolonged febrile illness (>5 days) in a patient with any of the principle clinical features of KD
- Patient exam with 4 or 5 principal clinical features and fever < 5 days
- Prolonged fever in an infant < 6 months without any principle clinical features

Guideline Exclusion Criteria:
Patient > 18 years old
Incomplete Kawasaki Disease
Kawasaki Disease with complicating morbidities
Recurrent/Refractory Kawasaki Disease
Pre-existing medications that modulate immune response
Covid related MIS-C
CAR–T (cell therapy-related cytokine release syndrome)
PolyArteritis Nodosa

Complicating existing diagnoses:

- MAS
- Hematologic
- Immunologic
- Rheumatic diseases
- Major Chronic inflammatory/immunologic diseases
- Significant congenital heart disease
- Infectious disease(s)
- Active uveitis
- Suspected systemic JIA with active systemic features

Not exclusive to these diagnoses, review **Differential Diagnosis**.

Differential Diagnosis:

Infections predominate in the list of differential diagnoses for Kawasaki Disease. (See Table) However, the finding of a concomitant infection does not rule out the possibility of KD as one study reports up to 30% of children with complete presentation had laboratory evidence of at least one infection.[5] Detailed history regarding exposures, presenting signs and symptoms, and associated physical findings may help support one process over another. Infections may also stimulate an inflammatory process with vasculitis.[6]

Adenovirus, EBV and measles infection are often considered. Distinguishing features of the viral infections may involve exudative conjunctivitis or pharyngitis; in the case of measles, immunization history and possible exposure is critical in a child with significant cough and coryza. Flaviviruses may also present with mucocutaneous inflammation; exposure history, and laboratory findings may help with differentiation. For Flavivirus infections, consider Dengue, West Nile Virus, and Yellow Fever.

Bacterial illnesses such as those related to acute Group A streptococcus and S. aureus may present with acute lymphadenitis, and mucocutaneous inflammation. Toxin-mediated illness secondary to bacterial illness (Staphylococcal or Streptococcal disease) need to be considered, specifically Scarlet Fever, Toxic Shock Syndrome, Acute Rheumatic Fever. Rickettsial infection specifically, Rocky Mountain Spotted Fever (RMSF) and Murine Typhus.. Hypotension may be important in the presentation of these disorders.

Acute Gastroenteritis (AGE) due to Yersinia should be considered as a differential diagnosis when evaluating cases, they can present with fever and some symptoms that might overlap with those of Kawasaki disease.

Hypersensitivity syndromes such as Stevens - Johnson syndrome, and drug hypersensitivity, mercury poisoning, and autoimmune disorders such as systemic juvenile idiopathic arthritis should also be considered.[6]

Diagnostic Evaluation:

CLINICAL PRESENTATION

(Some of these findings may come during the febrile period and then resolve before diagnosis but still count as being present.)

Fever (>38.0°C or 100.4°F rectally or orally) for at least 5 days in the presence of 4 of the 5 following criteria:

1. Bilateral congestion of the ocular conjunctivae (94%)$^{\alpha}$
2. Changes of the lips and oral cavity (at least one of the following):

   a. dryness, erythema, fissuring of lips (70%)
   b. strawberry tongue (71%)
   c. diffuse erythema of oral and pharyngeal mucosa without discrete lesions (70%)
3. Changes of the extremities (at least one of the following):
   a. erythema of palms and soles (80%)
   b. indurative edema (67%)
   c. periungual desquamation of fingers and toes (29%)
4. Polymorphous exanthem (92%)
5. Non-suppurative cervical adenopathy (>1.5 cm) (42%)

$^{\alpha}$ (%) indicates the percentage of U.S. patients manifesting this clinical sign within the first ten days after the onset of fever.

LABORATORY TESTS

Laboratory tests, even though are nonspecific, can provide diagnostic support in patients with clinical features that are suggestive but not diagnostic of Kawasaki disease.

1. Complete blood count
   a. Leukocytosis is typical during the acute stage of Kawasaki disease with a predominance of immature and mature granulocytes. About 50% have white blood cell counts >15 000/mm3.
   b. Anemia may develop with more prolonged active inflammation.
   c. Thrombocytosis is rare in the 1st week of illness but may appear in the 2nd week (peaking in the 3-4th week)with a mean peak platelet count of ≈ 700 000/ mm3.
2. Complete metabolic panel
   a. Hyponatremia can be noted.
   b. Mild to moderate elevations in serum transaminases occur in ≤40% of patients.
   c. Mild hyperbilirubinemia can occur in ≈ 10% of patients.
   d. Hypoalbuminemia is common and is associated with more severe and prolonged acute disease.
3. Erythrocyte sedimentation rate
   a. Elevation of acute phase reactants is nearly universal in Kawasaki disease. Elevation of ESR (but no of CRP) can be caused by IVIG therapy; therefore, ESR should not be used as the sole determinant of the degree of inflammatory activity in IVIG-treated patients.
4. C-reactive protein
   a. CRP should improve quickly with effective treatment, continue to improve 2 weeks into Rx, and should be normal soon after that. Elevation of CRP is seen but should return to normal by 3-4 weeks after onset of illness.
5. Urine analysis
   a. Urinalysis reveals intermittent mild to moderate sterile pyuria in ≈ 33% of patients. Cells originate in the urethra and a catheterized specimen may not contain these cells.
6. Gold Top for further workup (not routinely needed)

IMAGING TESTS

* indicates a required imaging test.

1. Abdominal ultrasound – Acute acalculous distention of the gallbladder (hydrops) occurs in ≈ 15% of patients during the first 2 weeks of the illness and can be identified by imaging.
2. Echocardiography* - The major sequelae of Kawasaki disease are related to the cardiovascular and, more specifically, the coronary arterial system, so cardiac imaging is a critical part of the evaluation of all patients with suspected Kawasaki disease. Long-term follow-up for patients with abnormal coronary arteries must be individualized and should be performed by an experienced pediatric cardiologist.

   Echocardiography for KD
   In cases where acute KD is suspected, echocardiography is used in the initial assessment for potential coronary artery involvement; however, normal findings at echocardiography do not exclude coronary involvement. Accurate identification and assessment of Coronary Artery Aneurysms (CAA) in the acute phase and sequentially during the chronic phase of KD is fundamental to the treatment plan for these patients.[44]

   DEFINITION of Aneurysm

   Dilation or small aneurysms are defined as a localized dilation of the internal lumen diameter but <4 mm, or if the child is ≥5 years of age, dilation but with an internal diameter of a segment measuring ≤1.5 times that of an adjacent segment.

   Medium aneurysms are defined as an internal lumen diameter >4 mm but ≤8 mm, or if the child is ≥5 years of age, an internal diameter of a segment measuring 1.5 to 4 times that of an adjacent segment.

   Large or giant aneurysms are defined as those with an internal lumen diameter >8 mm, or if the child is >5 years of age, an internal diameter of a segment measuring >4 times that of an adjacent segment.

   These criteria do not account for patient size, which can substantially affect normal coronary artery dimensions, potentially leading to underdiagnosis and underestimation of the true prevalence of coronary artery dilation

   Z-Score Classification

   1. No involvement: Always <2
   2. Dilation only: 2 to <2.5; or if initially <2, a decrease 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

   Aortic root Z scores >2 have been reported for 10% of KD patients

Critical Points of Evidence

Evidence Supports *provides evidence to support an intervention*

- IVIG and Moderate Dose(MD) aspirin should be used in combination as first-line therapy - ESR and CRP values could be used as markers for inflammatory response to treatment.
- IVIG therapy should be used as the first line therapy for patients diagnosed with either complete or incomplete Kawasaki Disease
    - Use of the current established Japanese scoring systems to identify high risk patients in the US population*:
      • Kobayashi score
      • Egami score
      • Sano score
      (*the scoring systems that are valuable for Japanese children are not valuable in general for children in the US.)
- IVIG resistance/unresponsive should be considered if the patient is febrile or refractory 36 hours after starting IVIG
- Intravenous pulse methylprednisolone (IVMP) should be considered for second-line therapy in patients that are unresponsive to an initial treatment of IVIG
- Recrudescence of fever should be used to determine inflammatory response to treatment.

Evidence Lacking/Inconclusive

- There is still clinical equipoise regarding the best second treatment for IVIG-resistant patients with a second infusion of IVIG and infliximab as the two leading candidates. [57]
- The latest guidelines of the American Heart Association suggest that reasonable therapy for resistant KD includes a second dose of IVIG or a short course of high-dose steroids or infliximab. The guidelines also mention the anti–interleukin-1 (anti-IL-1) anakinra among the different drugs that can be used in refractory forms, but leave the choice of the drug to individual physicians. [58]

Anticoagulation Guidance

(Adapted from Table 7 of 2017 AHA Kawasaki Disease Scientific Statement)

Anticoagulation (Warfarin or LMWH)*
Should be considered:

- Large and Giant Aneurysm (Z-score ≥10, or absolute dimension ≥8 mm), Current or Persistent

  Low-Molecular-Weight Heparin (LMWH) (i.e. Lovenox*): Goal Anti-Xa level 0.5-1 (dosing per our institutional guidelines)
  Warfarin*: Goal INR 2-3 (dosing per our institutional guidelines)

***Hematology should be consulted if anticoagulation (e.g. lovenox or warfarin) is being considered**

Dual Anti-platelet (ASA + Clopidogrel)
May be considered:

- Medium Aneurysm (Z-score ≥5 to <10, and absolute dimension < 8 mm), Current or Persistent
- Medium Aneurysm, regressed to small aneurysm

- Medium Aneurysm regressed to normal or dilation only, if inducible myocardial ischemia present
- Along with anticoagulation for current/persistent large or giant aneurysm if very extensive or distal coronary aneurysms or if history of coronary artery thrombosis

Should be considered

- Large or giant aneurysm, regressed to medium aneurysm

  Aspirin: 3-5 mg/kg/day, maximum 81-325mg/day
  Clopidogrel: 0.2-1 mg/kg/day

DOACs (as of April 2023, edoxaban and apixaban) are being studied as a potential alternative mode of thromboprophylaxis; for now would still start with warfarin or LMWH as these are more easily monitored and if needed reversed (additionally there may be cost/insurance/availability issues). Transition from warfarin/LMWH to a DOAC may be considered later on.

Outcome Measures

Day of fever that first dose IVIG administered
Utilization of steroids
Utilization of IVIG

Kawasaki Disease Diagnosis Pathway

Evidence Based Outcome Center

High Risk Clinical or Initial Echo features: 1

The following patients require rapid recognition, treatment, and planning for next step therapy if not responding to initial therapy. Initial therapy includes steroids.

- Children ≤ to 6 months
- KD with shock and KD with MAS. Mild tachycardia and irritability is expected with KD but blood pressure and perfusion changes should trigger PICU evaluation.
- Abnormal ECHO(s): (hyperlink to cards write-up about echos) LAD or RCA z score >/equal 2.5
- Rheumatology consultation is needed for high risk populations not responding to initial therapy.

Discharge Criteria: 2

- Vital signs normal:
  - Afebrile > 36 hours after treatment complete
  - Tachycardia resolved
- CRP down-trending
- Clinical symptoms resolving(ed)
- Tolerating oral medication

KD Discharge Tasks: 3

- Prescription for ASA: low-dose 3-5 mg/kg day. Provide 30-day supply. Educate family to not stop ASA until instructed by Cardiology
- Complete KD Action Plan
- **Schedule** follow-up appointments with ID and Cardiology in 2-3 weeks

Abnormal Echo Criteria: 4

ECHO is abnormal if any of these 3 conditions are met:

- Z score of Left Anterior Descending (LAD) or Right Coronary Artery (RCA) 2.5
- Coronary artery aneurysm is observed
- 3 other suggestive features are present: (i.e. decreased LV function, MR, pericardial, effusions, other significant cardiac abnormalities (in discussion with Cardiology)

Team Meeting: 5

- Cardiology, ID, Rheumatology, PCRS to review clinical case, plan treatment and follow-up

Kawasaki Disease (KD) Suspected

- Less/equal to 18 years of age
- **Complete KD:** Prolonged febrile illness ≥ 4 days with 4/5 principal clinical findings
- **Incomplete KD:** Prolonged febrile illness ≥ 5 days with 2-3/5 principal clinical findings
  OR Infant < 6 mo with prolonged febrile illness ≥ 7d without explanation

KD w/MAS, KD w/ Shock or Hemodynamic Instability?

No → **Evaluation**
Labs: CBC, CMP, ESR, CRP, UA (bag, clean catch ok)
EKG
ECHO: within 24 hours (non urgent) for Complete KD or timing as needed to confirm incomplete KD
Assess for High Risk KD 1

Yes → **ADMIT to PICU** 1 Consult/treatment for High Risk KD

KD Unlikely

Consider ddx/ **Mange Off Pathway**

Incomplete KD

CRP < 3 AND/OR ESR <40

- Evaluate DDx
- Perform serial clinical and laboratory reevaluation if fever persists
- ECHO if no clear source and /or skin peeling occurs
- Infectious Disease consult

Meets diagnostic criteria for Incomplete KD?

No → KD Unlikely
Non KD source identified
MANAGE OFF-PATHWAY

Yes → (Initial Treatment)

CRP ≥ 3 AND/OR ESR ≥ 40

- Assess for ≥ 3 supplemental lab findings
- Leukocytosis (WBC > 15 K)
- Anemia for age
- Thrombocytosis (PI> 450K after 1st wk of illness)
- Albumin <3 g/dl
- Elevated ALT
- Sterile pyuria (WBC > 10 WBC/pf
  OR
- ECHO: Abnormal EchoFindings 4

<3 supplemental laboratory criteria and normal ECHO → (Initial Treatment)

≥ 3 supplemental laboratory criteria OR abnormal ECHO 4 → (Initial Treatment)

Complete KD

Initial Treatment

- **IVIG:** Intravenous immunoglobulin 2g/kg single infusion per protocol
- **ASA:** (moderate dosing)
  (Do not delay treatment for Echo)
- If abnormal echo 4 and/or <6months old, add **Steroids** to treatment

Discharge Criteria Met? 2

Yes → **DISCHARGE** 3

No → Persistent or recrudescent fever >24 hrs. after IVIG treatment?

Abnormal ECHO and/or < 6 months of age 4

Subsequent Treatment
In consultation with KD team, administer additional treatment of one or more:

- Repeat IVIG
- Steroids
- Infliximab*
- Cyclosporin*
- Cyclophosphamide*
- Other

*Consult Rheumatology

Normal Echo

Subsequent Treatment

- Repeat CRP, ESR
- Repeat Echo per ID and Cardiology
- Second round of IVIG and steroids

Discharge Criteria Met? 2

Yes → **DISCHARGE** 2 3

No → Persistent or Recurrent fever >24 hours after subsequent treatment, **TEAM HUDDLE** 5 and Manage Off Pathway

KD Diagnosis / Treatment Tips:

- KD has a broad ddx and many mimics. Specific history questions to assess for presence of KD symptoms at any time during course of illness is needed.
- Children with significant congenital heart disease, current rheumatic, immunologic, hematologic disease should NOT be managed on this pathway. Although KD may be on the differential, individualized diagnostic and treatment plans need to be utilized. Broad subspecialty involvement with these populations is recommended.
- ECHO is not required for the diagnosis of Complete KD. ECHO is non-urgent and treatment should not be delayed awaiting ECHO results if diagnostic criteria are met.
- Children meeting diagnostic criteria for KD (complete or incomplete) without hemodynamic changes should be admitted to PCRS. A team approach to KD management is essential and consults will be notified by PCRS. Consultation does not need to occur in the ED.
- MIS-C should be considered if initial laboratory values show lymphopenia < 1k, Na+ < 135, platelets < 150.
- Children with abnormal ECHOs may need anticoagulation. Consult Hematology to assess when needed.

Last Updated: January 2024

Kawasaki Disease Management – Echocardiogram Pathway

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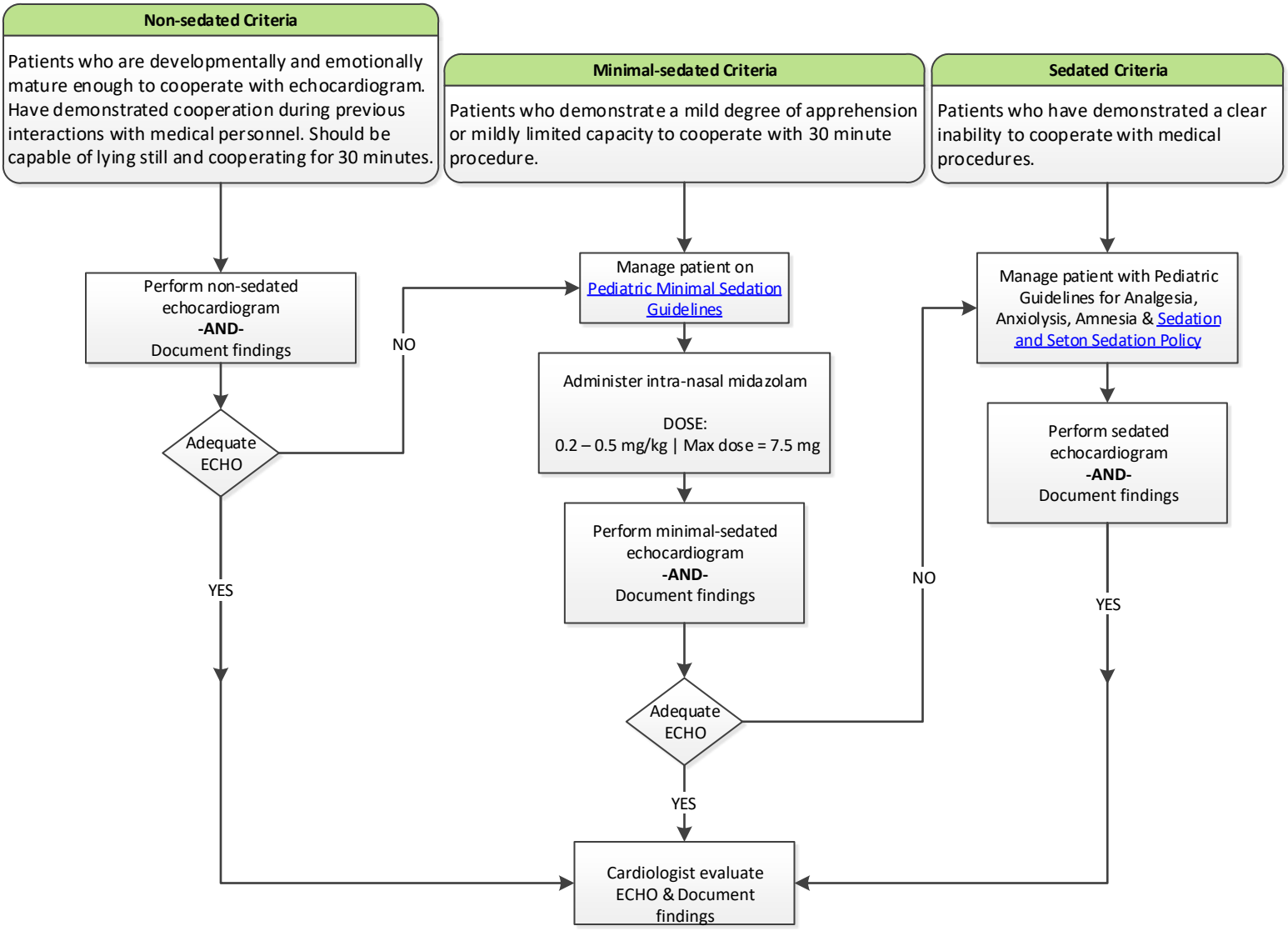

Last Updated: January 2024

Addendum 1:

Principal Clinical Findings for Kawasaki Disease
- Bilateral conjunctival congestion
- Changes in lips and oral cavity: reddening of lips, strawberry tongue, diffuse injection of oral pharyngeal mucosa
- Polymorphous exanthema
- Changes in peripheral extremities: reddening of palms and soles, indurative edema (initial stage), membranous desquamation from fingertips (convalescent stage)
- Acute non-purulent cervical lymphadenopathy

Other clinical and laboratory findings:	
Cardiovascular:	**Gastrointestinal:**
Congestive heart failure, myocarditis, pericarditis, valvular regurgitation	Diarrhea, vomiting, abdominal pain
Coronary artery abnormalities	Hepatic dysfunction
Aneurysms of medium-size noncoronary arteries	Hydrops of gallbladder
Raynaud's phenomenon	
Peripheral gangrene	
Musculoskeletal system:	**Genitourinary system:**
Arthritis, arthralgia	Uretrhitis/meatitis
Central Nervous System:	**Other findings:**
Irritability	Anterior uveitis (mild)
Aseptic Meningitis	Desquamating rash in groin
Sensorineural hearing loss	

Laboratory findings in Kawasaki Disease:
Normal or elevated WBC with predominance of neutrophils
Elevated ESR (> 40 mm/h) and/ or CRP (> 3 mg/dL)
Anemia for age
Albumin < 3 mg/dL
Hyponatremia
Thrombocytosis (platelets > 450,000 /mm3)
Sterile pyuria (> 10 WBC/hpf)
Elevated serum tramsaminases with or without elevated serum GGT or bilirubin
CSF pleocytosis
Leukocytosis in synovial fluid (WBC > 15,000 /mm3)

Differential Diagnosis for Kawasaki Disease:
Viral infections (adenovirus, EBV, enterovirus, measles infection)
Flavivirus infections (Dengue, West Nile Virus, and Yellow Fever)
Scarlet fever
Staphylococcal scalded skin syndrome
Toxic shock syndrome
Acute rheumatic fever
Bacterial cervical lymphadenitis
Drug hypersensitivity reactions
Stevens-Johnson Syndrome
Juvenile idiopathic arthritis
Rocky Mountain Spotted Fever
Murine Typhus
Acute Gastroenteritis (AGE) due to Yersinia
Leptospirosis
Mercury hypersensitivity reaction

Medication

Medication	Dosing
Aspirin	See full table (KD Aspirin Dosing Table)
IVIG	2 g/kg/dose
Methylprednisolone	1 mg/kg/dose Q12hr (max 60 mg/day) For pulse dosing: 30 mg/kg/dose Q24 hr (max 1 g) for 3 days
Prednisolone	1 mg/kg/dose BID (max 60 mg/day)
Infliximab*	10 mg/kg/dose (*Consult Rheumatology)
Famotidine	0.5 mg/kg/dose BID (or per pharmacy protocol)

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KD Aspirin Dosing Table

Initial (Acute) Phase Dosing Recommendation: **Moderate Dose** 30-50 mg/kg/day divided Q6H			
Weight Range		**Dose**	**Total Daily Dose (mg)**
Low kg	**High kg**		
++++'	2.9	Individualized Weight Based Dosing	
3 (54 mg/kg)	5.9 (27.4 mg/kg)	40.5 mg (0.5 tab) Q6H	162
6 (54 mg/kg)	9.9 (32.7 mg/kg)	81 mg (1 tab) Q6H	324
10 (48.6 mg/kg)	12.9 (37.7 mg/kg)	121.5 mg (1.5 tabs) Q6H	486
13 (49.8 mg/kg)	19.9 (32.5 mg/kg)	162 mg (2 tabs) Q6H	648
20 (48.6 mg/kg)	29.9 (32.5 mg/kg)	243 mg (3 tabs) Q6H	972
30 (43.2 mg/kg)	39.9 (32.5 mg/kg)	324 mg (4 tabs) Q6H	1296
40 (40.5 mg/kg)	49.9 (32.5 mg/kg)	405 mg (5 tabs) Q6H	1620
50	++++'	Individualized Weight Based Dosing	
Maintenance (Step-Down) Dosing Recommendations **Low Dose** 3-5 mg/kg/day			
Weight Range		**Dose**	**Total Daily Dose (mg)**
Low kg	**High kg**		
++++'	2.9	Individualized Weight Based Dosing	
4 (10 mg/kg)	13.9 (3 mg/kg)	40.5 mg (0.5 tab) Qday	40.5
14 (5.8 mg/kg)	++++'	81 mg (1 tab) Qday	81

- Aspirin 81 mg tablets may be crushed/chewed and mixed with flavoring for immediate single dose administration. Aspirin 81 mg tablets CANNOT be compounded into a suspension for multi-dose administration.
- Aspirin 325 mg tablets are enteric coated (EC) and CANNOT be crushed or chewed.
- Substitution with 325 mg tablets may be considered for patients on high doses and patients able to tolerate swallowing tablets whole.
- Maximum daily dose = 4000 mg/day or 120 mg/kg/day, whichever is less.
- Long-term, high-dose aspirin therapy puts children at increased risk for Reye's syndrome.

Back

Kawasaki Disease Action Plan
Evidence Based Outcome Center

This action plan is your "checklist" to make sure you and your child are prepared after your recent hospitalization for Kawasaki Disease. You should complete this form along with your care team before you leave the hospital.

- I received patient information packet on Kawasaki disease

  ☐ No anomaly/aneurysm

  ☐ Possible coronary anomaly/aneurysm

- Our first **Cardiology Clinic** visit will be in 2-3 weeks:

  Date of visit: _____

  Provider: _____

  Phone number for office contact: _____

- Our first **Infectious Disease Clinic** visit is in 2-3 weeks:

  Date of visit: _____

  Provider: _____

  Phone number for office contact: _____

- At my child's first visits, the Cardiology and Infectious Disease Teams will arrange for future follow-up visits.
- I understand my child is to continue aspirin until instructed to stop by the cardiologist seen outside the hospital (Aspirin usually continues for 6-8 weeks).

I understand the following symptoms should make me worry. If any of the following are present, I will contact the Infectious Disease Doctors at 512-628-1820:

- Fever over 100.4°F
- Conjunctivitis (redness of the eyes)
- Red lips and mouth
- Rash
- Unusual irritability
- Swelling of hands or feet
- Vomiting

- I understand live virus vaccines like the measles vaccine or the chicken pox vaccine should not be given to my child for 11 months after treatment with IVIG for Kawasaki Disease
- I understand that children on aspirin and their families should receive the influenza vaccination.

-Primary aim
- -Identify coronary artery involvement, pericarditis, and/or myocarditis

-Timing of echocardiography
- -Uncomplicated Kawasaki
  - -At time of diagnosis
  - -Two-three weeks
  - -Six to eight weeks
- -Complicated Kawasaki
  - -At minimum, should adhere to echocardiography timing for uncomplicated Kawasaki
  - -Increased frequency of imaging may be necessary and should be determined by clinical provider

-Optimization of overall image assessment (improving quality and resolution)
- -Plan for possible sedation in children between 12mo-3yrs
- -Use highest possible frequency transducer
- -Use cine loops/still frame images in conjunction with color Doppler imaging
- -Reduce two-dimensional gain and compression
- -Use low Nyquist limit to optimize visualization of normal diastolic coronary flow

-Echocardiographic report content
- -Coronary arteries
  - -Visualization and location of coronary arteries
  - -Presence and description of coronary abnormalities
  - -Summary comment in conclusions about presence/absence of coronary involvement
- -Valvular function
- -Biventricular systolic function
- -Presence of pericardial effusion
- -Presence of pleural effusions

-Coronary artery assessment
- -Should be performed in multiple imaging planes
- -Optimal views to attain imaging of each coronary should be attempted
- -Method of measurement
  - - inner edge to inner edge of the vessel wall and not measured at the level of normal branching
- -Descriptions of coronaries should use specific descriptive terms

-Additional resources
- -Normal coronary artery diameters with mean and standard deviation
- -Additional information about Kawasaki
- -Atypical Kawasaki-Echocardiographic Assessment
- -KD Coronary Echo Nomenclature

Optimal Views to Image Coronary Arteries

-Left main coronary artery (LMCA):
- -parasternal short axis at level of aortic valve
- -parasternal long axis toward PA
- -subcostal left ventricular long axis

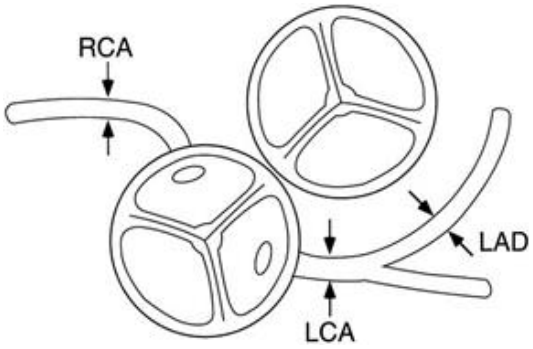
-Left anterior descending (LAD):
- -parasternal short axis at level of aortic valve
- -parasternal long axis toward PA
- -parasternal short axis of left ventricle

-Left circumflex (LCx):
- -parasternal short axis at level of aortic valve
- -apical 4-chamber in MV AV groove

-Right coronary artery (RCA):
- -proximal segment:
  - -parasternal short axis at level of aortic valve
  - -parasternal long axis toward the TV
  - -subcostal coronal projection of RVOT
  - -subcostal short axis at level of AV groove
- -middle segment:
  - -parasternal long axis of left ventricle toward TV
  - -apical 4-chamber
  - -subcostal left ventricular long axis
  - -subcostal short axis at level of AV groove
- -distal segment
  - -apical 4-chamber (inferior)
  - -subcostal atrial long axis (inferior)

-Posterior descending artery (PDA):
- -apical 4-chamber (inferior)
- -subcostal atrial long axis (inferior)
- -parasternal long axis (inferior tangential) imaging
- -posterior interventricular groove

Method of Measurement (inner-to-inner)



-Left main coronary artery (LMCA)
- Measure in the mid-position, distal to the flaring often seen near the aortic orifice and before the first bifurcation

-Left anterior descending (LAD)
- Measure distal to the bifurcation and before the first marginal branch

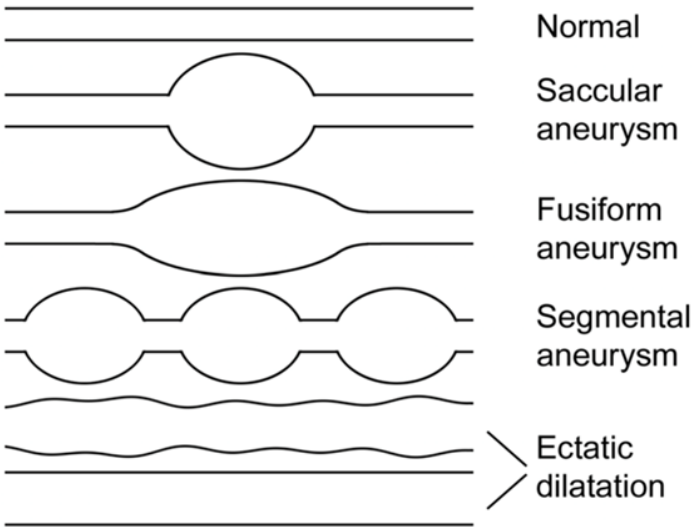
-Right coronary artery (RCA)
- Measure in the relatively straight section of artery just after the initial rightward turn from the anterior facing sinus of Valsalva

Coronary Descriptors

-Specific terminology should be used to describe coronary abnormalities seen in patients with Kawasaki disease in order to improve interoperator reliability between reports

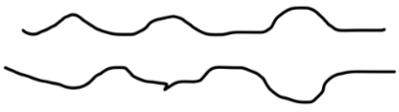
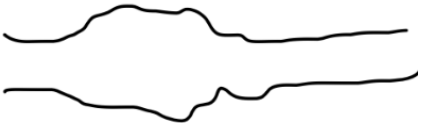
-Main features of coronary artery involvement:
- -Dilatation (intra-luminal diameter Z-score of ≥ 2.5mm)
  - -Ectatic:
    - -Uniform: dilated long segment
    - -Segmented: multiple dilatations joined by normal or stenotic areas
  - -Lack of tapering of the distal coronary vessel
  - -Perivascular brightness
  - -Aneurysm formation
    - -Fusiform: spindle-shaped, gradual tapering from normal to dilated segment

-Saccular: spherical, acute transition from normal to dilated segment



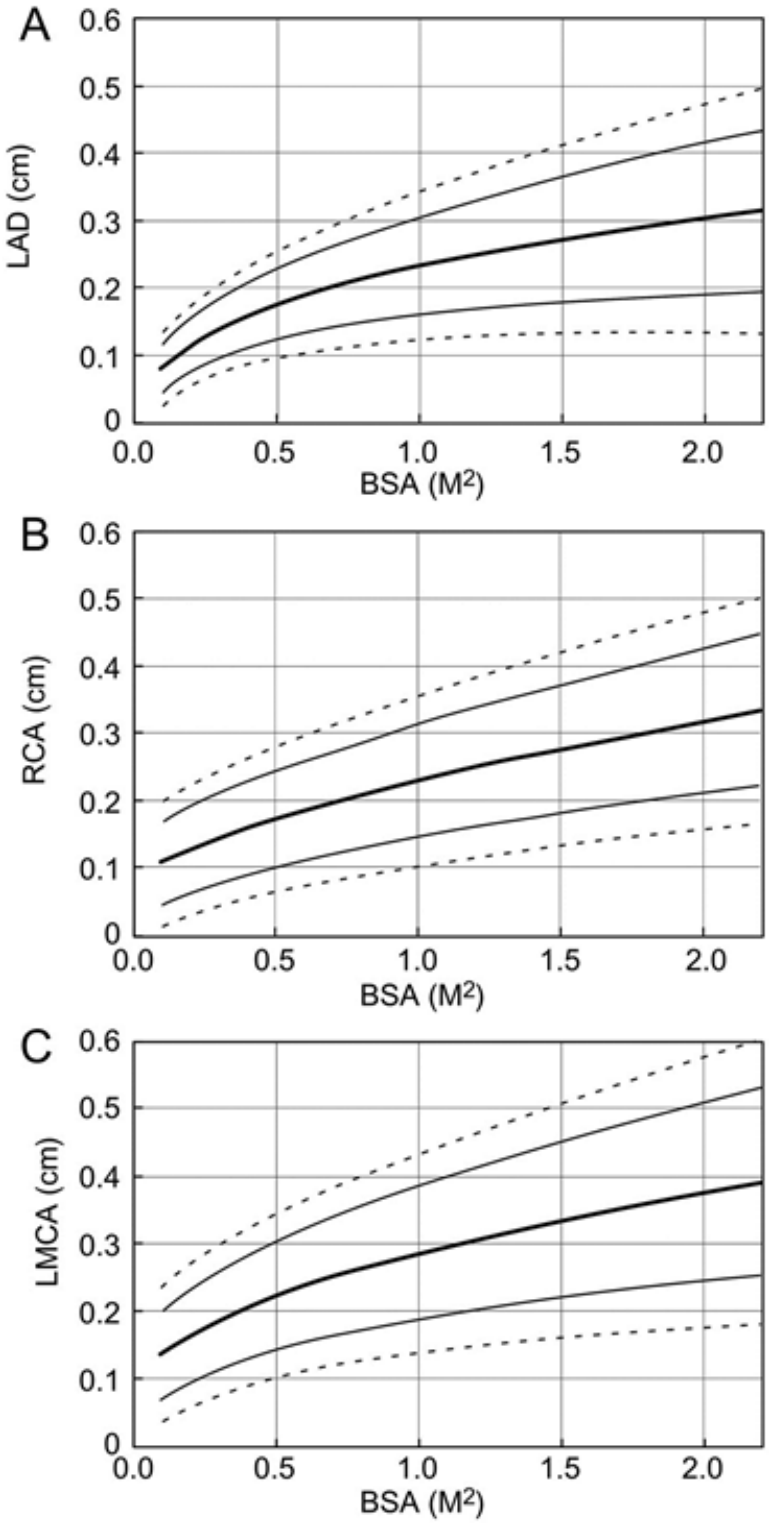
Back

KD Coronary Echo Nomenclature

	Associated Nomenclature	Description	Clinical Relevance
	Normal, No aneurysm or ectasia, Unremarkable	Z score less than +2.5, qualitatively regular lumen and wall appearance	
	Echo-bright, Prominent	Z score normal, no significant wall contour irregularity, qualitative appearance is bright or mildly dilated	**No clinical significance** but meant to call attention to target area on subsequent interrogation
	Somewhat irregular, mildly dilated, mild ectasia	Z score normal or borderline, irregular contour of walls, +/- echobright,	Limited clinical significance, may indicate potential for future aneurysm. Does not dictate need for therapeutic intervention
	Saccular aneurysm	Z score of dilated area > +2.5. Surrounding area may be normal size	Abnormal
	Ectasia, multiple small aneurysms, dilated	Z scores > +2.5. Diffusely irregular contour to vessel walls	Abnormal
	Fusiform aneurysm	Z scores > +2.5, frequently larger. Aneurysm extends over millimeters and is of varied diameters	

Normal Coronary Diameters

-Mean and prediction limits for 2 and 3 SDs for size of LAD (A), proximal RCA (B), and LMCA (C) according to body surface area for children <18 years old. Adapted from de Zorzi, Newburger, J. W. *et al.* Pediatrics 2004;114:1708-33.



Additional Information about Kawasaki

-Common sites of coronary involvement (from highest to lowest frequency):
- -Proximal LAD
- -Proximal RCA
- -LMCA
- -LCx
- -Distal RCA
- -Junction of RCA and PDA

-Risk stratification of aneurysms
- -Smaller aneurysms/fusiform aneurysms have greater chance of resolution
- -Distal coronary artery aneurysms tend to regress more rapidly than proximal aneurysms

-Cardiovascular disease
- -History of Kawasaki disease may increase risk for adult cardiovascular disease
- -Studies show abnormal vascular endothelial function, intimal thickness and abnormal lipid profiles

Methods

Existing External Guidelines/Clinical Pathways

Existing External Guideline/Clinical Pathway	Organization and Author	Last Update
Diagnosis, Treatment, and Long-Term Management of Kawasaki Disease	American Heart Association Jane W. Newburger, MD, et. al.	2004
Guidelines for medical treatment of acute Kawasaki Disease	Japanese society of pediatric cardiology and cardiac surgery. Tsutomu Saji, et. al.	2014
Management of Kawasaki Disease	UCI Institute of Child Health D Eleftheriou, et. al.	2013
Emergency Department and Inpatient Clinical Pathway for Evaluation/Treatment of Children with Kawasaki Disease or Incomplete Kawasaki Disease	Children's Hospital of Philadelphia	2023
Kawasaki Disease (KD) Management	Boston Children's Hospital	2022
Diagnosis and Management of Kawasaki Disease in Children	Texas Children's Hospital	2019

Any published clinical guidelines have been evaluated for this review using the **AGREE II criteria**. The comparisons of these guidelines are found at the end of this document. **AGREE II criteria** include evaluation of: Guideline Scope and Purpose, Stakeholder Involvement, Rigor of Development, Clarity of Presentation, Applicability, and Editorial Independence.

Review of Relevant Evidence: Search Strategies and Databases Reviewed

Search Strategies	Document Strategies Used
Search Terms Used:	Kawasaki disease, complete kawasaki, incomplete/atypical, IVIG, aspirin, IVIG unresponsive, Refractory, IVMP, steroids, inflammatory response, predictors, febrile, coronary abnormalities, methylprednisolone, risk factors
Years Searched - All Questions	2000 -2023
Language	English
Age of Subjects	< 18 years
Search Engines	http://www.cochrane.org/ https://www.ncbi.nlm.nih.gov/pubmed https://scholar.google.com/

EBP Web Sites	http://www.seattlechildrens.org/healthcare-professionals/gateway/pathways/ http://childrenshospital.libguides.com/content.php?pid=114078&sid=1001858 http://www.chop.edu/pathways#.V4Oyfo7F_OE https://www.cincinnatichildrens.org/service/j/anderson-center/evidence-based-care/recommendations/ http://www.texaschildrenshealthplan.org/for-providers/provider-resources/practice-guidelines
Professional Organizations	http://www.kdfoundation.org http://www.kawasakikidsfoundation.org http://patient.info/health/kawasaki-disease-leaflet http://www.vasculitisfoundation.org/education/forms/kawasaki-disease/?gclid=CO2lpaTi8cwCFQEJaQodk4AMnQ http://kidshealth.org/en/parents/kawasaki.html#
Government/State Agencies	http://www.guideline.gov/
Other	

Evidence Found with Searches

Check Type of Evidence Found	Summary of Evidence – All Questions
X	Systematic Reviews
X	Meta-analysis articles
X	Randomized Controlled Trials
X	Non-randomized studies
☐	Review articles
☐	Government/State agency regulations
X	Professional organization guidelines, white papers, ect.

Evaluating the Quality of the Evidence

The GRADE criteria were used to evaluate the quality of evidence presented in research articles reviewed during the development of this guideline. The table below defines how the quality of evidence is rated and how a strong versus a weak recommendation is established.

Recommendation	
Strong	Desirable effects clearly outweigh undesirable effects or vice versa
Weak	Desirable effects closely balanced with undesirable effects
Type of Evidence	
High	Consistent evidence from well-performed RCTs or exceptionally strong evidence from unbiased observational studies
Moderate	Evidence from RCTs with important limitations (e.g., inconsistent results, methodological flaws, indirect evidence, or imprecise results) or unusually strong evidence from unbiased observational studies
Low	Evidence for at least 1 critical outcome from observational studies, from RCTs with serious flaws or indirect evidence
Very Low	Evidence for at least 1 critical outcome from unsystematic clinical observations or very indirect evidence

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EBOC Project Owner: Sarmistha Hauger, MD

Revision History

Date Approved: November 2, 2016

Last Review Date: January 2024 - Literature review post 2016. Updates to Diagnostic Algorithm, definition of Z-scores, expansion of thrombolytic management, high-risk management with steroids.

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