TEXAS CHILDREN'S HOSPITAL
EVIDENCE-BASED OUTCOMES CENTER
Diagnosis and Management of Kawasaki Disease in Children
Evidence-Based Guideline

Definition: Kawasaki disease (KD), also known as mucocutaneous lymph node syndrome, is an acute, self-limiting vasculitic syndrome of unknown etiology that primarily affects children younger than 5 years of age. [(1)] First described in Japan in 1967 by Tomisaku Kawasaki, KD is the leading cause of acquired heart disease in children. [(2)] The most common and dangerous long-term sequelae of KD are coronary artery abnormalities (aneurysms or ectasia) that develop in up to 25% of untreated children and may lead to sudden death or ischemic heart disease. [(3)] Classic or complete KD is defined by the Centers for Disease Control (CDC) as an illness characterized by fever of 5 or more days duration and the presence of at least 4 of the following 5 clinical criteria: rash; cervical lymphadenopathy (at least 1.5 cm in diameter); bilateral conjunctival injection; oral mucosal changes; and peripheral extremity changes. Incomplete KD is an atypical presentation of Kawasaki disease which should be considered in any infant or child with prolonged unexplained fever, fewer than 4 of the principal clinical findings, and compatible laboratory or echocardiographic findings.

Epidemiology: According to the CDC, the estimated overall annual incidence of KD is approximately 25 per 100,000 children younger than five years in the United States. [(2)] This information was collected via passive national reporting to the CDC, private insurance databases, or administrative databases (i.e., Pediatric Hospital Information Service). There is prominent ethnic variation in the KD incidence rate for the United States with higher rates among Pacific Islanders and Japanese Americans (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). [(4)] Males are more commonly affected than females, and 90% of the cases occur in children younger than five years. Disease occurrence is most common in winter and early spring in North America.

Etiology: KD is an acute systemic inflammatory disease of unknown etiology. Several theories have attempted to determine whether the source of KD is infectious, genetic or a host immune response. However, none of the etiological agents have been found to be causative. The seasonality of KD is associated with increased incidence in geographic areas and may suggest a transmissible factor. Studies are ongoing to determine the etiology of KD. [(5)]

Pathophysiology: KD is an acute, self-limiting, multisystem vasculitis. The innate immune system plays a vital role in the pathogenesis of Kawasaki's 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. [(6)] Impaired immune regulation has been found to also play a role in 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.

Inclusion Criteria
- Patients <18 years of age
- Prolonged febrile illness (≥5 days) in a patient with ≥2 of the principal clinical features of Kawasaki disease.
- Patients with fever and ≥4 principal clinical features
- Infants with fever for ≥7 days without other explanation

Exclusion Criteria
- Patients ≥18 years of age
- Complicating existing diagnoses:
  - Immunologic
  - Rheumatologic disease
  - Major chronic inflammatory diseases
  - Significant congenital heart disease
- Macrophage activation syndrome (MAS)
- **KD shock syndrome (KDSS)**
  - A rare, potentially life-threatening complication of KD characterized by systolic hypotension for age, sustained systolic hypotension (decrease in blood pressure ≥20% from baseline) or clinical signs of poor perfusion [(7)]
  - Laboratory findings
    - Higher levels of inflammatory markers
    - Lower albumin levels
    - Anemia
    - Consumptive coagulopathy
    - Bandemia
    - Hyponatremia
  - Clinical Findings
    - More severe skin rash
    - Myocardial dysfunction
    - More severe coronary artery involvement
    - Poor response to IVIG
  - ***If shock is suspected, exit KD guideline/algorithm and treat accordingly (consider Septic Shock Guideline)**

Differential Diagnosis [(8)]

Infectious and noninfectious conditions:
- Viral infections [**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* [(9)]]
  - Adenovirus
  - Epstein Barr Virus
  - Influenza
  - Measles
  - Mononucleosis
  - Roseola infantum
  - Rubella
- Bacterial infections
  - Lyme Disease
  - Leptospirosis
  - Meningococcemia
  - Retropharyngeal abscess
  - Rocky Mountain Spotted Fever
  - Staphylococcal infection (e.g., Staphylococcal Scalded Skin Syndrome [SSSS]; Toxic Shock Syndrome [TSS])
  - Streptococcal infection (e.g., rheumatic fever, scarlet fever, TSS like syndrome)

- Autoimmune disorders
  - Systemic juvenile rheumatoid arthritis
  - Systematic lupus erythematosus
- Multi-organ system disorders
  - Infantile Polyarteritis Nodosa
- Drug hypersensitivity reactions
  - Stevens-Johnson Syndrome (SJS)
  - Toxic Epidermal Necrolysis (TEN)

Diagnostic Evaluation

History: Assess for presence of fever and principal clinical features

- Fever:
  - Onset (≥5 days of fever with ≥2 clinical criteria or 4 days with all 5 clinical criteria)
  - Response to antipyretics
  - How high was the temperature (typically high spiking; >39°C to 40°C, remittent)
- Bilateral bulbar conjunctival injection without exudate
- Oral mucous membrane changes, including injected or fissured lips, injected pharynx, or strawberry tongue
- Rash: maculopapular, diffuse erythroderma, or erythema multiforme-like (often worse in groin area)
- Peripheral extremity changes, including erythema and edema of hands and feet (acute phase), and periungual desquamation (convalescent phase)
- Cervical lymphadenopathy (at least one lymph node >1.5 cm in diameter), usually unilateral

History: Assess for other clinical findings

- Cough, increased work of breathing, sore throat
- Vomiting
- Diarrhea
- History of illnesses
- Review of current medications
- Family history of autoimmune disease

Physical Examination

- Vital signs
  - Temperature
  - Heart rate
  - Respirations
  - Blood pressure
  - Oxygen saturations
- Assess for presence of diagnostic criteria:
  - Bilateral bulbar conjunctival injection without exudate
  - Oral mucous membrane changes, including injected or fissured lips, injected pharynx, or strawberry tongue
  - Rash: maculopapular, diffuse erythroderma, or erythema multiforme-like (often worse in groin area)
  - Peripheral extremity changes, including erythema and edema of hands and feet (acute phase), and periungual desquamation (convalescent phase)
  - Cervical lymphadenopathy (at least one lymph node >1.5 cm in diameter), usually unilateral

Supplemental Laboratory Tests

****There is no single laboratory test to confirm the diagnosis of KD but certain laboratory findings can assist in the diagnosis of incomplete KD and differentiate KD from other conditions.*

- Complete blood counts with differential white blood cell (WBC) counts
  - 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/mm^3.
  - Anemia may develop with more prolonged active inflammation.
  - Thrombocytosis is rare in the 1st week of illness but may appear in the 2nd week (peaking in the 3rd-4th week) with a mean peak platelet count of ≈ 700,000/ mm^3.
- Complete metabolic panel
  - Hyponatremia can be noted.
  - Mild to moderate elevations in serum transaminases occur in ≤40% of patients.
  - Mild hyperbilirubinemia can occur in ≈ 10% of patients.
  - Hypoalbuminemia is common and is associated with more severe and prolonged acute disease.
- Liver enzymes including aspartate transaminase (AST), alanine transaminase (ALT), and albumin
  - Abnormal results common in patients with acute Kawasaki disease and are associated with IVIG resistance.
- C-reactive protein (CRP)
  - Elevation of CRP is seen but should return to normal by 6-10 weeks after onset of illness.
- Erythrocyte sedimentation rate (ESR)
  - 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.
- Urinalysis
  - 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.
- D-dimer
  - Elevated D-dimer can signify endothelial damage and fibrinolysis which is associated with systemic vasculitis and may help predict coronary artery involvement

Optional laboratory tests

- Consider obtaining NT-pro BNP
  - Can be used as an adjunctive marker to assist with the diagnosis of patients in the acute phase of Kawasaki disease

Echocardiogram

- Transthoracic echocardiography is highly sensitive and specific for the diagnosis of coronary artery involvement. It is important to ensure that the timing or results of the echocardiogram do not delay initial treatment of Kawasaki disease, and that the diagnosis is made predominantly on clinical findings.
- Echocardiogram is considered positive if any of 3 conditions are met:
  - Z score of LAD or RCA ≥2.5
  - Coronary arteries meet criteria for aneurysms
    - 3 other suggestive features exist, including decreased LV function, mitral regurgitation, pericardial effusion, or Z scores in LAD or RCA of 2 - 2.5
- If full criteria are not met and coronary artery abnormalities are present on echocardiography, then the child has incomplete features of Kawasaki disease and treatment with high dose intravenous immunoglobulin should be given.

Electrocardiography (ECG)

- Consider ordering and ECG, especially if the echocardiogram is abnormal.

Critical Points of Evidence*

Evidence Supports

- Patients with complete Kawasaki disease (KD) criteria and those who meet the algorithm criteria for incomplete KD are to be treated with high-dose intravenous immunoglobulin (IVIG) (2 g/kg given as a single intravenous infusion) within 10 days of illness onset but as soon as possible after diagnosis. KD can be diagnosed and treatment initiated on day 4 if all clinical features are present and there is no alternative diagnosis. [10-15] – Strong recommendation, moderate quality evidence
  Remarks: Echocardiogram should not delay the initiation of treatment with IVIG.
- Administration of IVIG therapy to patients presenting after the 10th day of illness (i.e., in whom the diagnosis was missed earlier) if they have either persistent fever without other explanation OR coronary artery abnormalities OR ongoing systemic inflammation, as manifested by elevated erythrocyte sedimentation rate (ESR) or C-reactive protein (CRP >3.0 mg/dL). [10-15] – Strong recommendation, moderate quality evidence
- An echocardiogram should be performed within 24 hours of diagnosis of KD but should not delay treatment. [16,17] – Strong recommendation, moderate quality evidence.
  Remarks: Transthoracic echocardiography is highly sensitive and specific for the diagnosis of coronary artery involvement. It is important to ensure that the timing or results of the echocardiogram do not delay initial treatment of Kawasaki disease, and that the diagnosis is made predominantly on clinical findings.
- For patients who meet the 2017 American Heart Association (AHA) Incomplete Algorithm criteria, an echocardiogram should be obtained within 12 to 24 hours of being ordered but should not delay treatment. [16,18-21] – Strong recommendation, moderate quality evidence
- For patients who do not meet the 2017 AHA Incomplete Algorithm criteria, an echocardiogram should be obtained within 12 hours of being ordered to determine treatment. [16,18-21] – Strong recommendation, moderate quality evidence
  Remarks: If full criteria are not met and coronary artery abnormalities are present on echocardiography, then the child has incomplete features of Kawasaki disease and treatment with high dose intravenous immunoglobulin should be considered.
- For patients who are unable to cooperate enough to obtain a high quality echo, consider sedation. [22-29] – Weak recommendation, low quality evidence
  Remarks: Detailed echocardiographic imaging may be compromised for an uncooperative child, therefore sedation is often needed for those patients <3 years of age and may also be required in older, irritable children. If a poor-quality initial echocardiogram is obtained because sedation was not administered, a sedated study should be repeated as soon as possible within the 48 hours after diagnosis and initial treatment. If sedation is needed for the echocardiogram procedure, please refer to the **Sedation for Transthoracic Echocardiography**.
- For diagnostic echocardiogram for patients with suspected Kawasaki disease assess for significant findings such as, valvular function, biventricular systolic function, presence of pericardial effusion, and presence of pleural effusions. [16,30-37] – Strong recommendation, low quality evidence
- For uncomplicated patients, echocardiography should be repeated at both 1 to 2 weeks and 4 to 6 weeks after initiation of therapy. For patients with important and evolving coronary artery abnormalities (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. [35,38-40] – Strong recommendation, low quality evidence
- For patients presenting with 2 to 3 AHA clinical criteria and incomplete KD is being considered, obtain erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP), in addition to the American Heart Association/American Academy of Pediatrics (AHA/AAP) recommended laboratory evaluations (complete blood count [CBC] with differential; white blood cell [WBC] count; urinalysis [U/A], preferably clean catch; serum alanine aminotransferase level [ALT]; and serum albumin). [35,41-63] – Strong recommendation, moderate quality evidence.
  Remarks: No laboratory studies are included among the diagnostic criteria for typical KD for any guidelines. However, certain findings may support the diagnosis of KD, particularly in incomplete cases. Typical manifestations of systemic inflammation may include elevation of acute-phase reactants (e.g., C-reactive protein [CRP] or erythrocyte sedimentation rate [ESR]), thrombocytosis that generally develops after the seventh day of illness, leukocytosis, and a left-shift (increased immature neutrophils) in the white blood cell (WBC) count.
- For patients presenting with complete KD and to determine the risk of coronary artery involvement, consider obtaining N-terminal pro b-type natriuretic peptide (NT-pro-BNP) and D-Dimer, in addition to AHA/AAP recommended laboratory evaluation (C-reactive protein (CRP); erythrocyte sedimentation rate (ESR); complete blood count (CBC) with differential white blood cell (WBC) count; urinalysis (U/A), preferably clean catch; serum alanine aminotransferase level; and serum albumin). [35,41-63] – Weak recommendation, low quality evidence
- To consider, in consultation with cardiology and rheumatology, administration of corticosteroids, together with IVIG 2 g/kg and ASA, for treatment of high-risk patients with acute KD. [64-71] – Weak recommendation, low quality evidence
- Administration of a second dose of IVIG (2 g/kg) for patients with refractory Kawasaki disease (patients with persistent or recrudescent fever at least 36 hours after the end of the first IVIG infusion **without** other concerning features, such as coronary abnormalities and/or Kawasaki shock). Consult Rheumatology and/or Cardiology for high risk patients (i.e., patients <1 year of age, the small group who develop early coronary artery changes, and patients with features of hemophagocytic lymphohistiocytosis (HLH), and/or shock). [72-86] – Strong recommendation, moderate quality evidence
- To consider performing an echocardiogram and evaluating NT-proBNP in patients younger than 12 months with fever that has lasted longer than 2 days, regardless of the presence or absence of manifestations associated with KD. [86-95] – Weak recommendation, low quality evidence

Evidence Against

- Perivascular brightness and distal tapering are not significant echocardiogram findings in the diagnosis of suspected Kawasaki disease. [16,30-37] – Strong recommendation, low quality evidence
- Routine administration of adjunctive corticosteroids with IVIG therapy as routine primary therapy for non-high risk patients with KD. [64-71] – Strong recommendation, moderate quality evidence

- Use of the current established Japanese scoring systems to identify high risk patients in the US population (i.e., Kobayashi score, Egami score, and Sano score). [31,36,96-110] – Strong recommendation, moderate quality evidence

Evidence Lacking/Inconclusive

- Administration of oral aspirin (ASA) upon diagnosis of Kawasaki disease at a dose of 30 to 50 mg/kg/DAY until the patient is afebrile for 72 hours and then transition to 3-5 mg/kg/DAY once daily for 6 to 8 weeks until the echocardiogram demonstrates a lack of coronary artery abnormalities. [111-121] – Consensus recommendation
- To consider hospital discharge if patients are afebrile for at least 24 hours following IVIG therapy, are clinically improved **AND** have a normal initial echo. For high risk patients, consider discharge if patients are afebrile for at least 36 hours following IVIG therapy, show clinical improvement **AND** have a normal initial echo. [122-125] – Consensus recommendation
- For the patient to return for follow up labs and imaging (echocardiogram) in 7 to 14 days from discharge **OR** 14 to 21 days from initial fever, whichever occurs sooner. – Consensus recommendation

*NOTE: The references cited represent the entire body of evidence reviewed to make each recommendation.

Condition-Specific Elements of Clinical Management

General

- The goal of therapy is to reduce the systemic and tissue-level inflammation as rapidly as possible. Patients should be treated as soon as the diagnosis is confirmed.
- All patients within the first 10 days of fever onset should be treated with IVIG. Patients diagnosed after 10 days should receive IVIG if they are still febrile, have markedly elevated inflammatory parameters, or have coronary artery dilation.
- Recrudescent fever at least 36 hours after the end of IVIG infusion without other explanation is a marker for persistent inflammation and should prompt immediate and aggressive anti-inflammatory therapy
- Patients with coronary artery dilation (z-score >2.0) should be followed with a repeat echocardiogram at least twice a week until dimensions stabilize; additional anti-inflammatory therapy should be considered.
- Acute phase:
  - Up to 10 days (until resolution of fever)
- Subacute phase:
  - 10-25 days (until resolution of disease)
  - Associated with thrombocytosis, ESR, CRP, and skin peeling of hands and feet
  - 20% of untreated patients will have coronary aneurysms
- Convalescent phase:
  - >1 month
  - Well-appearing but evolution of coronary dilatation and resolution
  - Increased ESR, CRP, and platelets

Treatment Recommendations:

Initial Treatment

- The primary goal of treatment is the prevention of coronary artery aneurysms, since the etiology is unknown
- Intravenous Immunoglobulin (IVIG)
  - 2g/kg as a single infusion
  - Most benefit when given in first 10 days of illness. There may be benefit even when given up to 60 days later
  - If fever persists, administer a second IVIG infusion
  - Do not check ESR following IVIG administration
- Aspirin
  - Administration of oral aspirin (ASA) upon diagnosis of Kawasaki disease at a dose of 30 to 50 mg/kg/DAY until the patient is afebrile for 72 hours and then transition to 3-5 mg/kg/DAY once daily for 6 to 8 weeks until the echocardiogram demonstrates a lack of coronary artery abnormalities.
- Corticosteroids
  - To consider, in consultation with Cardiology and Rheumatology, administration of corticosteroids, together with IVIG 2 g/kg and ASA, for treatment of high-risk patients with acute KD.

Admission Criteria

- All children with diagnosed or suspected Kawasaki disease should be admitted for inpatient observation.

Discharge Criteria

- Consider hospital discharge once the patient has been afebrile for at least 24 hours following completion of IVIG therapy.
- For high-risk patients, consider longer period of observation (at least 36 hours).
- Echocardiogram completed

Consults/Referrals

- Cardiology
- Rheumatology, if needed

Follow-Up Care

- Patient to return for follow up labs and imaging (echocardiogram) in 7-14 days from discharge OR 14-21 days from initial fever, whichever occurs sooner.
- Patient/Family education:
  - Return to EC if fever >38.0°C or recurrence of KD symptoms before follow up with PCP, Cardiology, or Rheumatology
  - Education on side effects of low dose aspirin (i.e., bruising, gastrointestinal bleeding)
  - Patient received inactivated flu vaccine if during flu season; no live vaccines for 11 months
  - Avoid exposure to anyone with the flu or chicken pox to avoid the risk of Reye's syndrome, which has been linked to aspirin use in these illnesses
  - Recommend a low-fat, heart healthy diet, regular exercise and avoid exposure to secondhand cigarette smoke
  - Physical activity

Measures

Process

- Day of fever that KD diagnosis made
- Day of fever that first dose IVIG administered
- Utilization of steroids
- Utilization of Infliximab
- Utilization of IVIG
- Rate of IVIG resistance
- Rate of comprehensive echocardiogram evaluations and documentation
- Rate of post-hospitalization PCP and specialist follow-up

Outcome

- Length of stay
- Readmissions
- Rate of aneurysms
- Rate of progression of coronary involvement (Z score) on follow-up echocardiogram
- Rate of delayed and/or missed diagnosis

TEXAS CHILDREN'S HOSPITAL
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Diagnosis of Suspected Kawasaki Disease Algorithm

Inclusion Criteria
- Patients < 18 years of age
- Prolonged febrile illness (≥5 days) in a patient with ≥2 of the principal clinical features of Kawasaki disease.
- Patients with fever and ≥4 principal clinical features
- Infants with fever for≥7 days without other explanation

Exclusion Criteria
- Patients ≥18 years of age
- Complicating existing diagnoses:
  - Immunologic
  - Rheumatologic disease
  - Major chronic inflammatory diseases
  - Significant congenital heart disease
- Macrophage activation syndrome (MAS)
- **KD shock syndrome (KDSS, see below)**

Patient presents with suspected Kawasaki disease (KD)

Is patient stable?

NO

EXIT ALGORITHM
- If shock is suspected, treat accordingly (consider Septic Shock Guideline)
- Consult Rheumatology if KD shock syndrome is suspected
- Assess for differential diagnosis (see guideline for list of differential diagnoses)

YES

History & Physical
- Assess fever onset and duration
- Assess for presence of Kawasaki disease diagnostic criteria
- Consider differential diagnosis (see guideline for list of differential diagnoses)

Assess supplemental laboratory tests
- C-reactive protein (CRP)
- Erythrocyte sedimentation rate (ESR)
- Liver function tests
- D-dimer
- Complete blood count (CBC) with differential white blood cell (WBC) count
- Urinalysis (U/A, clean catch)

Assess optional laboratory tests
- Consider NT-pro BNP

Kawasaki Disease Principal Clinical Features

Prolonged febrile illness ≥5 days

-AND ≥4 of the following-
- Bilateral conjunctival injection
- Oral mucous membrane changes (injected or fissured lips, injected pharynx or strawberry tongue)
- Rash (maculopapular, diffuse erythroderma or erythema multiforme-like)
- Peripheral extremity changes (erythema and edema of hands and feet; periungual desquamation)
- Cervical lymphadenopathy (at least one lymph node >1.5 cm in diameter), usually unilateral

Fever ≥ 5 days duration with ≥4 principal clinical features

2017 American Heart Association Incomplete Criteria

Fever ≥5 days duration with 2 to 3 of the principal clinical features

OR

Infants with fever for ≥7days without other explanation

Complete Kawasaki Disease

CRP ≥3 mg/dL **AND/OR** ESR ≥40 mm/h

CRP <3 mg/dL **AND** ESR <40 mm/h

Assess for ≥3 supplemental labs findings:
- Leukocytosis (WBC≥ 15,000/mm^3)
- Anemia for age
- Thrombocytosis (platelet count≥ 450,00 after 1st week)
- Albumin ≤3.0 g/dL
- Elevated ALT
- Sterile pyuria (urine ≥10 WBC/hpf)

OR

*Order echocardiogram and assess for **POSITIVE ECHOCARDIOGRAM FINDINGS** (see echocardiogram recommendations below)

EXIT ALGORITHM
- Reassess for differential diagnosis
- If diagnosis is unclear, consult Infectious Disease
- Treat as indicated
- Discharge if clinically stable
- Schedule follow-up with PCP after discharge
- Re-evaluation of serial clinical and laboratory tests if fever persists 24 hours
- Echocardiogram if typical peeling develops

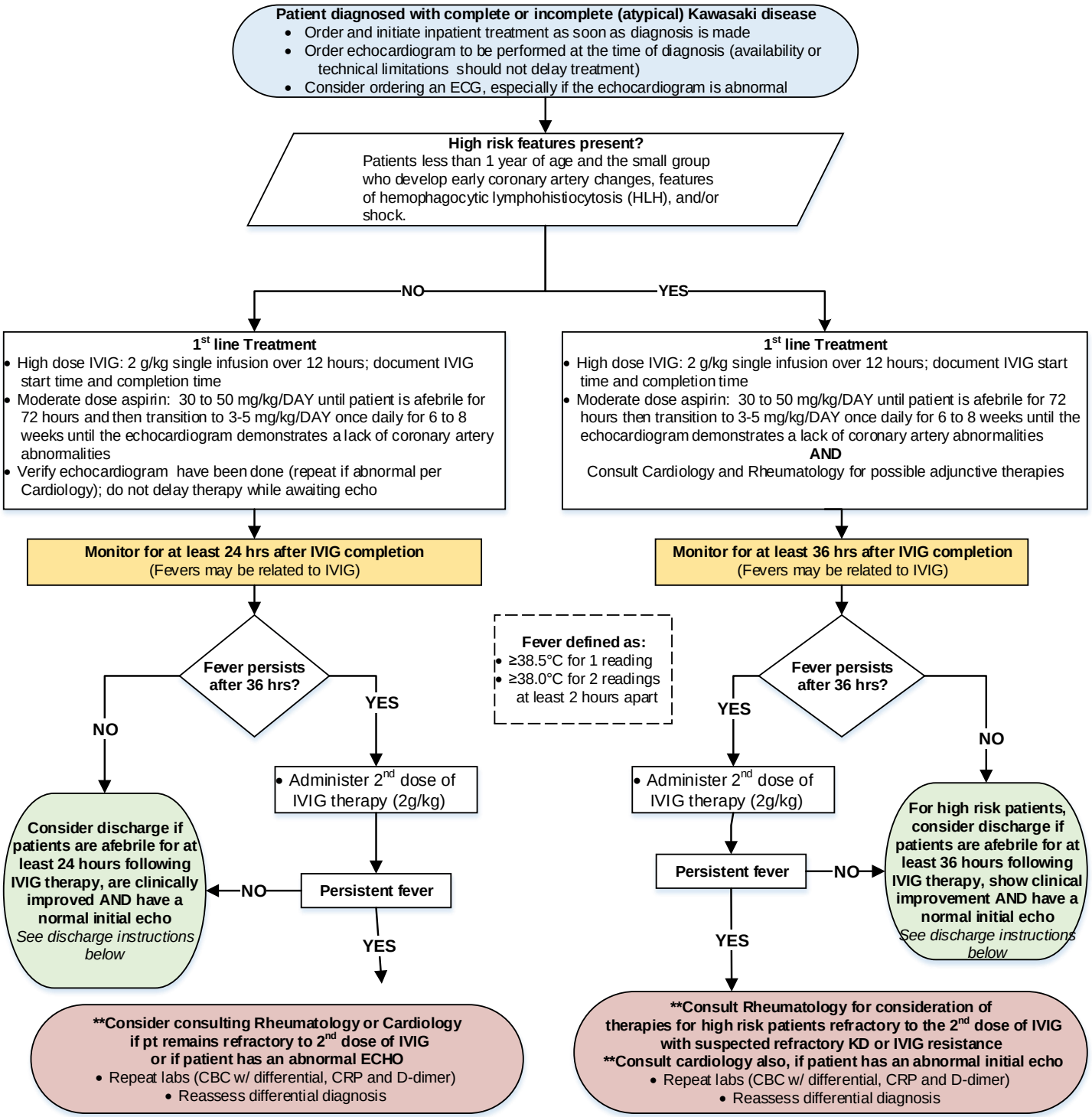
Incomplete Kawasaki Disease

Proceed to Management of Kawasaki Disease Algorithm
*Order echocardiogram (if not already performed) but do not delay treatment (see echocardiogram recommendations below)

***Echocardiogram**
- An echocardiogram should be performed within 24 hours of diagnosis of KD but should not delay treatment Assess for significant findings such as, valvular function, biventricular systolic function, presence of pericardial effusion, and presence of pleural effusions
- For patients who meet the 2017 American Heart Association (AHA) Incomplete Algorithm criteria, an echocardiogram should be obtained within 12 to 24 hours of being ordered but should not delay treatment.
- For patients who do not meet the 2017 AHA Incomplete Algorithm criteria, an echocardiogram should be obtained within 12 hours of being ordered to determine treatment.
- For patients who are unable to cooperate enough to obtain a high quality echo, consider sedation. Detailed echocardiographic imaging may be compromised for an uncooperative child, therefore sedation is often needed for those patients <3 years of age and may also be required in older, irritable children. If a poor-quality initial echocardiogram is obtained because sedation was not administered, a sedated study should be repeated as soon as possible within the 48 hours after diagnosis and initial treatment. **If sedation is needed for the echocardiogram procedure, please refer to the** Sedation for Transthoracic Echocardiogram Algorithm

Clinical standards are developed for 80% of the patient population with a particular disease. Each practitioner must use his/her clinical judgment in the management of any specific patient.

TEXAS CHILDREN'S HOSPITAL
EVIDENCE BASED OUTCOMES CENTER
Management of Kawasaki Disease Algorithm



Discharge Instructions

- Patient to return for follow up clinical evaluation, labs and imaging (echocardiogram) in 7 to 14 days from discharge **OR** 14 to 21 days from initial fever, whichever occurs sooner.
- Parents should monitor their child's temperature and alert their physician if the child has symptoms of fever.
- Patient should receive inactivated flu vaccine if in season

Clinical standards are developed for 80% of the patient population with a particular disease. Each practitioner must use his/her clinical judgment in the management of any specific patient.

Appendix A: Kawasaki Disease Terminology (McCrindle 17, Kanagaye 09)

Acute phase: Stage which begins with an abrupt onset of fever and lasts approximately 7-14 days. The fever is typically high-spiking and remittent, with peak temperatures ranging from 102-104°F (39-40°C) or higher.

Classic Kawasaki disease: An illness characterized by fever of 5 or more days duration and the presence of at least 4 of the following 5 clinical criteria: rash; cervical lymphadenopathy (at least 1.5 cm in diameter); bilateral conjunctival injection; oral mucosal changes; and peripheral extremity changes**.**

Convalescent phase: Stage begins when clinical signs disappear and continues until the erythrocyte sedimentation rate becomes normal, usually six to eight weeks after the onset of illness.

Incomplete (Atypical) Kawasaki disease: Atypical presentation of Kawasaki disease which should be considered in any infant or child with prolonged unexplained fever, fewer than 4 of the principal clinical findings, and compatible laboratory or echocardiographic findings.

Intravenous immunoglobulin (IVIG) resistance: Persistent or recrudescent fever at least 36 hours and <7 days after completion of first IVIG infusion.

Kawasaki disease shock syndrome: A rare, potentially life-threatening complication of KD characterized by systolic hypotension for age, sustained systolic hypotension (decrease in blood pressure ≥20% from baseline) or clinical signs of poor perfusion.

Plasma exchange: Therapeutic process to remove large-molecular-weight substances such as harmful antibodies from the plasma. In the case of Kawasaki disease, this process can be considered as a third line therapy in consultation with Rheumatology to remove antibodies which may be causing resistance to disease treatment. It is usually carried out using an automated blood cell separator to ensure fluid balance and maintain a normal plasma volume.

Refractory Kawasaki disease: The development or continuation of fever greater than 36 hours after completion of the IVIG infusion. These patients are at increased risk of developing cardiac abnormalities and will need additional treatment.

Subacute phase: This stage is from the end of the fever to about day 25. During this phase, patients may have desquamation of the fingers and toes, arthritis and arthralgia, and thrombocytosis.

Tumor Necrosis Factor (TNF) α blockers: An inflammatory cytokine that plays an important role in host defense against infections and in immune responses (Fiers 1991). Natural production of TNF-α is protective, but excessive production of TNF-α may be harmful and even lethal to the host. Overproduction of TNF-α has been associated with the chronic inflammation observed in immune-modulated inflammatory disorders, such as Kawasaki disease. It should be considered as third line therapy in consultation with Rheumatology.

References

1. Maddox, R. A., Holman, R. C., Uehara, R., Callinan, L. S., Guest, J. L., Schonberger, L. B., ... & Belay, E. D. (2015). Recurrent Kawasaki disease: USA and Japan. *Pediatrics International*, *57*(6), 1116-1120.
2. Centers for Disease Control and Prevention. Kawasaki syndrome [Website]. Retrieved from http://www.cdc.gov/kawasaki/.
3. Newburger J. W., Takahashi, M., Gerber, M. A., Gewitz, M. H., Tani, L. Y., Burns, J. C., ... & Taubert, K. A. (2004). Diagnosis, treatment, and long-term management of Kawasaki disease: A statement for health professionals from the Committee on Rheumatic Fever, Endocarditis, and Kawasaki Disease, Council on Cardiovascular Disease in the Young, American Heart Association. *Pediatrics, 114*(6), 1708-1733.
4. de Zorzi, A., Colan, S. D., Gauvreau, K., Baker, A. L., Sundel, R. P., & Newburger, J. W. (1998). Coronary artery dimensions may be misclassified as normal in Kawasaki disease. *Journal of Pediatrics, 133*(2), 254–258.
5. Ayusawa, M., Sonobe, T., Uemura, S., Ogawa, S., Nakamura, Y., Kiyosawa, N., ... & Harada, K. (2005). Revision of diagnostic guidelines for Kawasaki disease (the 5th revised edition). *Pediatrics International*, *47*(2), 232-234.
6. Chang, F. Y., Hwang, B., Chen, S. J., Lee, P. C., Meng, C. C., & Lu, J. H. (2006). Characteristics of Kawasaki disease in infants younger than six months of age. *Pediatric Infectious Disease Journal, 25*(3), 241-244.
7. Kanegaye, J. T., Wilder, M. S., Molkara, D., Frazer, J. R., Pancheri, J., Tremoulet, A. H., ... & Burns, J. C. (2009). Recognition of a Kawasaki disease shock syndrome. *Pediatrics*, *123*(5), e783.
8. Cox, J. R., & Sallis, R. E. (2009). Recognition of Kawasaki disease. *Permanente Journal*, *13*(1), 57.
9. McCrindle, B. W., Rowley, A. H., Newburger, J. W., Burns, J. C., Bolger, A. F., Gewitz, M., ... & Kobayashi, T. (2017). Diagnosis, treatment, and long-term management of Kawasaki disease: A scientific statement for health professionals from the American Heart Association. *Circulation*, *135*(17), e927-e999.
10. Chen, J., Ma, B., Lin, L. X., & Xue, Y. M. (2012). Treatment of Kawasaki disease by different doses of immunoglobulin: A meta analysis of efficacy and safety. *Translational Pediatrics*, *1*(2), 99-107.
11. Oates-Whitehead, R. M., Baumer, J. H., Haines, L., Love, S., Maconochie, I. K., Gupta, A., ... & Flynn, I. (2003). Intravenous immunoglobulin for the treatment of Kawasaki disease in children. *Cochrane Database of Systematic Reviews, 4,* CD004000.
12. Bal, A. K., Prasad, D., Pamintuan, M. A. U., Mammen-Prasad, E., & Petrova, A. (2014). Timing of intravenous immunoglobulin treatment and risk of coronary artery abnormalities in children with Kawasaki disease. *Pediatrics & Neonatology*, *55*(5), 387-392.
13. Ho, C. L., Fu, Y. C., Lin, M. C., & Jan, S. L. (2015). Early immunoglobulin therapy and outcomes in Kawasaki disease: A nationwide cohort study. *Medicine*, *94*(39), e1544.
14. Qiu, H., He, Y., Rong, X., Ren, Y., Pan, L., Chu, M., ... & Shi, H. (2018). Delayed intravenous immunoglobulin treatment increased the risk of coronary artery lesions in children with Kawasaki disease at different status. *Postgraduate Medicine*, *130*(4), 442-447.
15. Shiozawa, Y., Inuzuka, R., Takahiro, S., Mafune, R., Hayashi, T., Hirata, Y., ... & Oda, Y. (2018). Effect of intravenous immunoglobulin within day 4 of illness in Kawasaki disease. *Pediatrics International, 60*(4), 334-341.
16. Dominguez, S. R., Anderson, M. S., El-Adawy, M., & Glodé, M. P. (2012). Preventing coronary artery abnormalities: A need for earlier diagnosis and treatment of Kawasaki disease. *Pediatric Infectious Disease Journal*, *31*(12), 1217-1220.
17. Fuse, S., Mori, T., Kuroiwa, Y., & Hirakawa, S. (2017). On what day of illness does the dilatation of coronary arteries in patients with Kawasaki disease begin? *Circulation Journal*, *82*(1), 247-250.
18. Ha, K. S., Jang, G., Lee, J., Lee, K., Hong, Y., Son, C., & Lee, J. (2013). Incomplete clinical manifestation as a risk factor for coronary artery abnormalities in Kawasaki disease: A meta-analysis. *European Journal of Pediatrics*, *172*(3), 343-349.
19. Baer, A. Z., Rubin, L. G., Shapiro, C. A., Sood, S. K., Rajan, S., Shapir, Y., ... & Bierman, F. Z. (2006). Prevalence of coronary artery lesions on the initial echocardiogram in Kawasaki syndrome. *Archives of Pediatrics & Adolescent Medicine*, *160*(7), 686-690.
20. Bratincsak, A., Reddy, V. D., Purohit, P. J., Tremoulet, A. H., Molkara, D. P., Frazer, J. R., ... & Melish, M. A. (2012). Coronary artery dilation in acute Kawasaki disease and acute illnesses associated with fever. *Pediatric Infectious Disease Journal*, *31*(9), 924-926.
21. Satoh, K., Wakejima, Y., Gau, M., Kiguchi, T., Matsuda, N., Takasawa, R., ... & Shimohira, M. (2018). Risk of coronary artery lesions in young infants with Kawasaki disease: Need for a new diagnostic method. *International Journal of Rheumatic Diseases*, *21*(3), 746-754.
22. Miller, J., Xue, B., Hossain, M., Zhang, M. Z., Loepke, A., & Kurth, D. (2016). Comparison of dexmedetomidine and chloral hydrate sedation for transthoracic echocardiography in infants and toddlers: A randomized clinical trial. *Pediatric Anesthesia*, *26*(3), 266-272.
23. Salehi, F., Riasi, H. R., Ebrahimzadeh, A., & Askari Janatabadi, S. (2017). The effect of oral midazolam and chloral hydrate before echocardiography in pediatric patients: A randomized double-blind clinical trial. *Global Pediatric Health*, *4*, 2333794X17735972.
24. Tsze, D. S., Ieni, M., Fenster, D. B., Babineau, J., Kriger, J., Levin, B., & Dayan, P. S. (2017). Optimal volume of administration of intranasal midazolam in children: A randomized clinical trial. *Annals of Emergency Medicine, 69*(5), 600-609.
25. Li, B. L., Ni, J., Huang, J. X., Zhang, N., Song, X. R., & Yuen, V. M. (2015). Intranasal dexmedetomidine for sedation in children undergoing transthoracic echocardiography study--A prospective observational study. *Pediatric Anesthesia*, *25*(9), 891-896.
26. Lorenzoni, R. P., Choi, J., Choueiter, N. F., Munjal, I. M., Katyal, C., & Stern, K. W. (2018). Predictors of inadequate initial echocardiography in suspected Kawasaki disease: Criteria for sedation. *Congenital Heart Disease*, *13*(3), 470-475.
27. Margossian, R., Lu, M., Minich, L. L., Bradley, T. J., Cohen, M. S., Li, J. S., ... & Colan, S. D. (2011). Predictors of coronary artery visualization in Kawasaki disease. *Journal of the American Society of Echocardiography*, *24*(1), 53-59.
28. Miller, J. W., Divanovic, A. A., Hossain, M. M., Mahmoud, M. A., & Loepke, A. W. (2016). Dosing and efficacy of intranasal dexmedetomidine sedation for pediatric transthoracic echocardiography: A retrospective study. *Canadian Journal of Anesthesia 63*(7), 834-841.
29. Stern, K. W., Gauvreau, K., Geva, T., & Benavidez, O. J. (2014). The impact of procedural sedation on diagnostic errors in pediatric echocardiography. *Journal of the American Society of Echocardiography*, *27*(9), 949-955.
30. Crystal, M. A., Manlhiot, C., Yeung, R. S., Smallhorn, J. F., & McCrindle, B. W. (2009). Coronary artery dilation after Kawasaki disease for children within the normal range. *International Journal of Cardiology*, *136*(1), 27-32.
31. Friedman, K. G., Gauvreau, K., Hamaoka-Okamoto, A., Tang, A., Berry, E., Tremoulet, A. H., ... & Newburger, J. W. (2016). Coronary artery aneurysms in Kawasaki disease: Risk factors for progressive disease and adverse cardiac events in the US population. *Journal of the American Heart Association*, *5*(9), e003289.
32. Giacchi, V., Sciacca, P., Stella, I., Filippelli, M., Barone, P., La Rosa, M., & Leonardi, S. (2014). Assessment of coronary artery intimal thickening in patients with a previous diagnosis of Kawasaki disease by using high resolution transthoracic echocardiography: Our experience. *BMC Cardiovascular Disorders*, *14*(1), 106.
33. Gaur, L., Waloff, K., Schiller, O., Sable, C. A., & Frank, L. H. (2014). Noncoronary inflammation in Kawasaki disease is associated with abnormal myocardial deformation in the acute phase. *Journal of the American Society of Echocardiography*, *27*(12), 1329-1335.
34. Muniz, J. C. G., Dummer, K., Gauvreau, K., Colan, S. D., Fulton, D. R., & Newburger, J. W. (2013). Coronary artery dimensions in febrile children without Kawasaki disease. *Circulation: Cardiovascular Imaging*, *6*(2), 239-244.
35. Printz, B. F., Sleeper, L. A., Newburger, J. W., Minich, L. L., Bradley, T., Cohen, M. S., ... & Takahashi, M. (2011). Noncoronary cardiac abnormalities are associated with coronary artery dilation and with laboratory inflammatory markers in acute Kawasaki disease. *Journal of the American College of Cardiology*, *57*(1), 86-92.

36. Son, M. B. F., Gauvreau, K., Kim, S., Tang, A., Dedeoglu, F., Fulton, D. R., ... & Newburger, J. W. (2017). Predicting coronary artery aneurysms in Kawasaki disease at a North American center: An assessment of baseline z scores. *Journal of the American Heart Association*, *6*(6), e005378.
37. Tamaki, W., Tsuda, E., Takehiro, I., Tanaka, N., & Fujieda, M. (2015). Importance of evaluation of the right coronary artery by two-dimensional echocardiography in patients after Kawasaki disease: A right parasternal approach. *Heart and Vessels*, *30*(2), 178-185.
38. Chih, W. L., Wu, P. Y., Sun, L. C., Lin, M. T., Wang, J. K., & Wu, M. H. (2016). Progressive coronary dilatation predicts worse outcome in Kawasaki disease. *Journal of Pediatrics*, *171*, 78-82.
39. Dallaire, F., Fournier, A., Breton, J., Nguyen, T. D., Spigelblatt, L., & Dahdah, N. (2012). Marked variations in serial coronary artery diameter measures in Kawasaki disease: A new indicator of coronary involvement. *Journal of the American Society of Echocardiography*, *25*(8), 859-865.
40. Liu, M. Y., Liu, H. M., Wu, C. H., Chang, C. H., Huang, G. J., Chen, C. A., ... & Wang, J. K. (2017). Risk factors and implications of progressive coronary dilatation in children with Kawasaki disease. *BMC Pediatrics*, *17*(1), 139.
41. Lin, K. H., Chang, S. S., Yu, C. W., Lin, S. C., Liu, S. C., Chao, H. Y., ... & Lee, C. C. (2015). Usefulness of natriuretic peptide for the diagnosis of Kawasaki disease: A systematic review and meta-analysis. *BMJ Open*, *5*(4), e006703.
42. Yu, J., Li, H. H., & Dong, L. (2016). Meta-analysis: Diagnostic value of N-terminal pro-brain natriuretic peptide for Kawasaki disease. *Clinical Laboratory*, *62*(10), 1903-1910.
43. Buonsenso, D., Macchiarulo, G., Supino, M. C., La Penna, F., Scateni, S., Marchesi, A., ... & Boccuzzi, E. (2018). Laboratory biomarkers to facilitate differential diagnosis between measles and Kawasaki disease in a pediatric emergency room: A retrospective study. *Mediterranean Journal of Hematology and Infectious Diseases*, *10*(1), e2018033.
44. Chen, Y. L., Wang, J. L., & Li, W. Q. (2014). Prediction of the risk of coronary arterial lesions in Kawasaki disease by serum 25-hydroxyvitamin D3. *European Journal of Pediatrics*, *173*(11), 1467-1471.
45. Kwon, H., Lee, J. H., Jung, J. Y., Kwak, Y. H., Kim, D. K., Jung, J. H., ... & Kim, K. (2016). N-terminal pro-brain natriuretic peptide can be an adjunctive diagnostic marker of hyper-acute phase of Kawasaki disease. *European Journal of Pediatrics*, *175*(12), 1997-2003.
46. Lee, S. H., Song, E. S., Yoon, S., Hong, S., Cho, H. J., Yang, E. M., ... & Cho, Y. K. (2017). Usefulness of age-stratified N-terminal prohormone of brain natriuretic peptide for diagnosing Kawasaki disease. *Disease Markers*, *2017*, 6263121.
47. Seo, Y. M., Kang, H. M., Lee, S. C., Yu, J. W., Kil, H. R., Rhim, J. W., ... & Lee, K. Y. (2018). Clinical implications in laboratory parameter values in acute Kawasaki disease for early diagnosis and proper treatment. *Korean Journal of Pediatrics*, *61*(5), 160-166.
48. Wang, Z., Weng, F., Li, C., Shi, H., Tang, Z., Qiu, H., ... & Chu, M. (2018). Neutropenia after intravenous immunoglobulin therapy is associated with coronary artery lesions in children with Kawasaki disease: A case control study. *BMC Pediatrics*,*18*(1), 76.
49. Xu, H., Fu, S., Wang, W., Zhang, Q., Hu, J., Gao, L., ... & Gong, F. (2016). Predictive value of red blood cell distribution width for coronary artery lesions in patients with Kawasaki disease. *Cardiology in the Young*, *26*(6), 1151-1157.
50. Ye, Q., Shao, W. X., Shang, S. Q., Zhang, T., Hu, J., & Zhang, C. C. (2015). A comprehensive assessment of the value of laboratory indices in diagnosing Kawasaki disease. *Arthritis & Rheumatology*, *67*(7), 1943-1950.
51. Ha, K. S., Jang, G. Y., Lee, J., Lee, K. C., & Son, C. S. (2018). Laboratory markers in incomplete Kawasaki disease according to coronary artery outcome. *Korean Circulation Journal*, *48*(4), 287-295.
52. Öner, T., Yilmazer, M. M., Güven, B., Devrim, İ., Çilengiroglu, Ö. V., Demirpence, S., ... & Vitrinel, A. (2012). An observational study on peripheral blood eosinophilia in incomplete Kawasaki disease. *Anatolian Journal of Cardiology, 12*(2), 160-164.
53. Iwashima, S., Kimura, M., Ishikawa, T., & Ohzeki, T. (2011). Importance of C-reactive protein level in predicting non-response to additional intravenous immunoglobulin treatment in children with Kawasaki disease. *Clinical Drug Investigation*, *31*(3), 191-199.
54. Kuo, H. C., Liang, C. D., Wang, C. L., Yu, H. R., Hwang, K. P., & Yang, K. D. (2010). Serum albumin level predicts initial intravenous immunoglobulin treatment failure in Kawasaki disease. *Acta Paediatrica*, *99*(10), 1578-1583.
55. Nakagama, Y., Inuzuka, R., Hayashi, T., Shindo, T., Hirata, Y., Shimizu, N., ... & Takamizawa, M. (2016). Fever pattern and C-reactive protein predict response to rescue therapy in Kawasaki disease. *Pediatrics International*, *58*(3), 180-184.
56. Seo, E., Yu, J. J., Jun, H. O., Shin, E. J., Baek, J. S., Kim, Y. H., & Ko, J. K. (2016). Prediction of unresponsiveness to second intravenous immunoglobulin treatment in patients with Kawasaki disease refractory to initial treatment. *Korean Journal of Pediatrics*, *59*(10), 408-413.
57. Carbone, I., Cannata, D., Algeri, E., Galea, N., Napoli, A., De Zorzi, A., ... & Passariello, R. (2011). Adolescent Kawasaki disease: Usefulness of 64-slice CT coronary angiography for follow-up investigation. *Pediatric Radiology*, *41*(9), 1165-1173.
58. Duan, Y., Wang, X., Cheng, Z., Wu, D., & Wu, L. (2012). Application of prospective ECG-triggered dual-source CT coronary angiography for infants and children with coronary artery aneurysms due to Kawasaki disease. *British Journal of Radiology*, *85*(1020), e1190-e1197.
59. Gutierrez, N. G., Shirinsky, O., Gagarina, N., Lyskina, G., Fukazawa, R., Ogawa, S., ... & Kahn, A. M. (2017). Assessment of coronary artery aneurysms caused by Kawasaki disease using transluminal attenuation gradient analysis of computerized tomography angiograms. *American Journal of Cardiology*, *120*(4), 556-562.
60. Han, B. K., Lesser, A., Rosenthal, K., Dummer, K., Grant, K., & Newell, M. (2014). Coronary computed tomographic angiographic findings in patients with Kawasaki disease. *American Journal of Cardiology*, *114*(11), 1676-1681.
61. Kim, J. W., & Goo, H. W. (2013). Coronary artery abnormalities in Kawasaki disease: Comparison between CT and MR coronary angiography. *Acta Radiologica*, *54*(2), 156-163.
62. Schäfer, M., Truong, U., Ivy, D. D., Fonseca, B., Malone, L., DiMaria, M., ... & Browne, L. P. (2018). Children with Kawasaki disease present elevated stiffness of great arteries: Phase-contrast MRI study. *Journal of Magnetic Resonance Imaging, 48*(5), 1228-1236.
63. Tsujii, N., Tsuda, E., Kanzaki, S., & Kurosaki, K. (2016). Measurements of coronary artery aneurysms due to Kawasaki disease by dual-source computed tomography (DSCT). *Pediatric Cardiology*, *37*(3), 442-447.
64. Chen, S., Dong, Y., Kiuchi, M. G., Wang, J., Li, R., Ling, Z., ... & Liu, S. (2016). Coronary artery complication in Kawasaki disease and the importance of early intervention: A systematic review and meta-analysis. *JAMA Pediatrics*, *170*(12), 1156-1163.
65. Wardle, A. J., Connolly, G. M., Seager, M. J., & Tulloh, R. M. (2017). Corticosteroids for the treatment of Kawasaki disease in children. *Cochrane Database of Systematic Reviews*, *1*, CD011188.
66. Zhu, B. H., Lv, H. T., Sun, L., Zhang, J. M., Cao, L., Jia, H. L., ... & Shen, Y. P. (2012). A meta-analysis on the effect of corticosteroid therapy in Kawasaki disease. *European Journal of Pediatrics*, *171*(3), 571-578.
67. Ebato, T., Ogata, S., Ogihara, Y., Fujimoto, M., Kitagawa, A., Takanashi, M., & Ishii, M. (2017). The clinical utility and safety of a new strategy for the treatment of refractory Kawasaki disease. *Journal of Pediatrics*, *191*, 140-144.
68. Kibata, T., Suzuki, Y., Hasegawa, S., Matsushige, T., Kusuda, T., Hoshide, M., ... & Uchida, M. (2016). Coronary artery lesions and the increasing incidence of Kawasaki disease resistant to initial immunoglobulin. *International Journal of Cardiology*, *214*, 209-215.
69. Kim, H. J., Lee, H. E., Yu, J. W., & Kil, H. R. (2016). Clinical outcome of patients with refractory Kawasaki disease based on treatment modalities. *Korean Journal of Pediatrics*, *59*(8), 328-334.
70. Lim, Y. J., & Jung, J. W. (2014). Clinical outcomes of initial dexamethasone treatment combined with a single high dose of intravenous immunoglobulin for primary treatment of Kawasaki disease. *Yonsei Medical Journal*, *55*(5), 1260-1266.
71. Zhao, C. N., Du, Z. D., & Gao, L. L. (2016). Corticosteroid therapy might be associated with the development of coronary aneurysm in children with Kawasaki disease. *Chinese Medical Journal*, *129*(8), 922.
72. Xue, L. J., Wu, R., Du, G. L., Xu, Y., Yuan, K. Y., Feng, Z. C., ... & Hu, G. Y. (2017). Effect and safety of TNF inhibitors in immunoglobulin-resistant Kawasaki disease: A meta-analysis. *Clinical Reviews in Allergy & Immunology*, *52*(3), 389-400.

73. Mori, M., Hara, T., Kikuchi, M., Shimizu, H., Miyamoto, T., Iwashima, S., ... & Suzuki, Y. (2018). Infliximab versus intravenous immunoglobulin for refractory Kawasaki disease: A phase 3, randomized, open-label, active-controlled, parallel-group, multicenter trial. *Scientific Reports*, *8*(1), 1994.
74. Ebato, T., Ogata, S., Ogihara, Y., Fujimoto, M., Kitagawa, A., Takanashi, M., & Ishii, M. (2017). The clinical utility and safety of a new strategy for the treatment of refractory Kawasaki disease. *Journal of Pediatrics*, *191*, 140-144.
75. Jone, P. N., Anderson, M. S., Mulvahill, M. J., Heizer, H., Glodé, M. P., & Dominguez, S. R. (2018). Infliximab plus intravenous immunoglobulin (IVIG) versus IVIG alone as initial therapy in children with Kawasaki disease presenting with coronary artery lesions: Is dual therapy more effective? *Pediatric Infectious Disease Journal, 37*(1), 976-980.
76. Koizumi, K., Hoshiai, M., Katsumata, N., Toda, T., Kise, H., Hasebe, Y., ... & Kagami, K. (2018). Infliximab regulates monocytes and regulatory T cells in Kawasaki disease. *Pediatrics International*, 60(9), 796-802.
77. Masuda, H., Kobayashi, T., Hachiya, A., Nakashima, Y., Shimizu, H., Nozawa, T., ... & Suzuki, Y. (2018). Infliximab for the treatment of refractory Kawasaki disease: A nationwide survey in Japan. *Journal of Pediatrics*, *195*, 115-120.
78. Mori, M., Imagawa, T., Hara, R., Kikuchi, M., Hara, T., Nozawa, T., ... & Yokota, S. (2012). Efficacy and limitation of infliximab treatment for children with Kawasaki disease intractable to intravenous immunoglobulin therapy: Report of an open-label case series. *Journal of Rheumatology, 39*(4), 864-867.
79. Sonoda, K., Mori, M., Hokosaki, T., & Yokota, S. (2014). Infliximab plus plasma exchange rescue therapy in Kawasaki disease. *Journal of Pediatrics*, *164*(5), 1128-1132.
80. Hamada, H., Suzuki, H., Abe, J., Suzuki, Y., Suenaga, T., Takeuchi, T., ... & Yamaga, H. (2012). Inflammatory cytokine profiles during cyclosporin treatment for immunoglobulin-resistant Kawasaki disease. *Cytokine*, *60*(3), 681-685.
81. Suzuki, H., Terai, M., Hamada, H., Honda, T., Suenaga, T., Takeuchi, T., ... & Yamaga, H. (2011). Cyclosporin A treatment for Kawasaki disease refractory to initial and additional intravenous immunoglobulin. *Pediatric Infectious Disease Journal*, *30*(10), 871-876.
82. Jang, H., Kim, K. Y., & Kim, D. S. (2018). Clinical outcomes of low-dose methotrexate therapy as a second-line drug for intravenous immunoglobulin-resistant Kawasaki disease. *Yonsei Medical Journal*, *59*(1), 113-118.
83. Fujimaru, T., Ito, S., Masuda, H., Oana, S., Kamei, K., Ishiguro, A., ... & Abe, J. (2014). Decreased levels of inflammatory cytokines in immunoglobulin-resistant Kawasaki disease after plasma exchange. *Cytokine*, *70*(2), 156-160.
84. Hokosaki, T., Mori, M., Nishizawa, T., Nakamura, T., Imagawa, T., Iwamoto, M., & Yokota, S. (2012). Long-term efficacy of plasma exchange treatment for refractory Kawasaki disease. *Pediatrics International*, *54*(1), 99-103.
85. Koné-Paut, I., Cimaz, R., Herberg, J., Bates, O., Carbasse, A., Saulnier, J. P., ... & Piram, M. (2018). The use of interleukin 1 receptor antagonist (anakinra) in Kawasaki disease: A retrospective cases series. *Autoimmunity Reviews, 17*(8), 768-774.
86. Clark, D. E., Denby, K. J., Kaufman, L. M., Fill, M. A., Piya, B., Krishnaswami, S., ... & Halasa, N. (2018). Predictors of intravenous immunoglobulin nonresponse and racial disparities in Kawasaki disease. *Pediatric Infectious Disease Journal, 37*(12), 1227-1234.
87. Dietz, S. M., Kuipers, I. M., Tacke, C. E., Koole, J. C., Hutten, B. A., & Kuijpers, T. W. (2017). Giant aneurysms: A gender-specific complication of Kawasaki disease? *Journal of Cardiology*, *70*(4), 359-365.
88. Downie, M. L., Manlhiot, C., Collins, T. H., Chahal, N., Yeung, R. S., & McCrindle, B. W. (2017). Factors associated with development of coronary artery aneurysms after Kawasaki disease are similar for those treated promptly and those with delayed or no treatment. *International Journal of Cardiology*, *236*, 157-161.
89. Flores-Montes, O. A., Valle-Leal, J., Arreguin-Reyes, R., & Armenta-Velderrain, J.M. (2018). Risk factors related to cardiovascular complications in patients with Kawasaki disease in Northwestern Mexico. *Boletin Medico del Hospital Infantil de Mexico, 75*(3), 145-152.
90. Maric, L. S., Knezovic, I., Papic, N., Mise, B., Roglic, S., Markovinovic, L., & Tesovic, G. (2015). Risk factors for coronary artery abnormalities in children with Kawasaki disease: a 10-year experience. *Rheumatology International*, *35*(6), 1053-1058.
91. Salgado, A. P., Ashouri, N., Berry, E. K., Sun, X., Jain, S., Burns, J. C., & Tremoulet, A. H. (2017). High risk of coronary artery aneurysms in infants younger than 6 months of age with Kawasaki disease. *Journal of Pediatrics*, *185*, 112-116.
92. Song, D., Yeo, Y., Ha, K., Jang, G., Lee, J., Lee, K., ... & Lee, J. (2009). Risk factors for Kawasaki disease-associated coronary abnormalities differ depending on age. *European Journal of Pediatrics*, *168*(11), 1315.
93. Tulloh, R. M., Mayon-White, R., Harnden, A., Ramanan, A. V., Tizard, E. J., Shingadia, D., ... & Craggs, P. (2018). Kawasaki disease: A prospective population survey in the UK and Ireland from 2013 to 2015. *Archives of Disease in Childhood*, *104*(7), 640-646.
94. Yeo, Y., Kim, T., Ha, K., Jang, G., Lee, J., Lee, K., ... & Lee, J. (2009). Incomplete Kawasaki disease in patients younger than 1 year of age: A possible inherent risk factor. *European Journal of Pediatrics*, *168*(2), 157.
95. Yoon, Y. M., Yun, H. W., & Kim, S. H. (2016). Clinical characteristics of Kawasaki disease in infants younger than six months: A single-center study. *Korean Circulation Journal*, *46*(4), 550-555.
96. Sleeper, L. A., Minich, L. L., McCrindle, B. M., Li, J. S., Mason, W., Colan, S. D., ... & Newburger, J. W. (2011). Evaluation of Kawasaki disease risk-scoring systems for intravenous immunoglobulin resistance. *Journal of Pediatrics*, *158*(5), 831-835.
97. Arane, K., Mendelsohn, K., Mimouni, M., Mimouni, F., Koren, Y., Simon, D. B., ... & Glatstein, M. (2018). Japanese scoring systems to predict resistance to intravenous immunoglobulin in Kawasaki disease were unreliable for Caucasian Israeli children. *Acta Paediatrica, 107*(12), 2179-2184.
98. Berdej-Szczot, E., Małecka-Tendera, E., Gawlik, T., Firek-Pędras, M., Szydłowski, L., & Gawlik, A. (2017). Risk factors of immunoglobulin resistance and coronary complications in children with Kawasaki disease. *Kardiologia Polska (Polish Heart Journal)*, *75*(3), 261-266.
99. Cho, H. J., Bak, S. Y., Kim, S. Y., Yoo, R., Baek, H. S., Yang, S., ... & Ban, J. E. (2017). High neutrophil: lymphocyte ratio is associated with refractory Kawasaki disease. *Pediatrics International*, *59*(6), 669-674.
100. Davies, S., Sutton, N., Blackstock, S., Gormley, S., Hoggart, C. J., Levin, M., & Herberg, J. A. (2015). Predicting IVIG resistance in UK Kawasaki disease. *Archives of Disease in Childhood, 100*(4), 366-368.
101. Ha, K. S., Lee, J., Jang, G. Y., Lee, J., Lee, K. C., Son, C. S., & Lee, J. W. (2015). Value of neutrophil-lymphocyte ratio in predicting outcomes in Kawasaki disease. *American Journal of Cardiology*, *116*(2), 301-306.
102. Hua, W., Sun, Y., Wang, Y., Fu, S., Wang, W., Xie, C., ... & Gong, F. (2017). A new model to predict intravenous immunoglobin-resistant Kawasaki disease. *Oncotarget*, *8*(46), 80722.
103. Kanamitsu, K., Kakimoto, H., Shimada, A., Nakata, Y., Ochi, H., Watanabe, H., ... & Miyazawa, M. (2016). Verification of risk scores to predict I.V. immunoglobulin resistance in incomplete Kawasaki disease. *Pediatrics International*, *58*(2), 146-151.
104. Kawamura, Y., Takeshita, S., Kanai, T., Yoshida, Y., & Nonoyama, S. (2016). The combined usefulness of the neutrophil-to-lymphocyte and platelet-to-lymphocyte ratios in predicting intravenous immunoglobulin resistance with Kawasaki disease. *Journal of Pediatrics*, *178*, 281-284.
105. Loomba, R. S., Raskin, A., Gudausky, T. M., & Kirkpatrick, E. (2016). Role of the Egami score in predicting intravenous immunoglobulin resistance in Kawasaki disease among different ethnicities. *American Journal of Therapeutics*, *23*(6), e1293-e1299.
106. Qian, W., Tang, Y., Yan, W., Sun, L., & Lv, H. (2018). A comparison of efficacy of six prediction models for intravenous immunoglobulin resistance in Kawasaki disease. *Italian Journal of Pediatrics*, *44*(1), 33.
107. Sánchez-Manubens, J., Antón, J., Bou, R., Iglesias, E., Calzada-Hernandez, J., Borlan, S., ... & Kawasaki Disease in Catalonia Working Group. (2016). Role of the Egami score to predict immunoglobulin resistance in Kawasaki disease among a Western Mediterranean population. *Rheumatology International*, *36*(7), 905-910.

108. Song, R., Yao, W., & Li, X. (2017). Efficacy of four scoring systems in predicting intravenous immunoglobulin resistance in children with Kawasaki disease in a children's hospital in Beijing, North China. *Journal of Pediatrics*, *184*, 120-124.
109. Takeshita, S., Kanai, T., Kawamura, Y., Yoshida, Y., & Nonoyama, S. (2017). A comparison of the predictive validity of the combination of the neutrophil-to-lymphocyte ratio and platelet-to-lymphocyte ratio and other risk scoring systems for intravenous immunoglobulin (IVIG)-resistance in Kawasaki disease. *PloS One*, *12*(5), e0176957.
110. Tewelde, H., Yoon, J., Van Ittersum, W., Worley, S., Preminger, T., & Goldfarb, J. (2014). The Harada score in the US population of children with Kawasaki disease. *Hospital Pediatrics*, *4*(4), 233-238.
111. Baumer, J. H., Love, S., Gupta, A., Haines, L., Maconochie, I. K., & Dua, J. S. (2006). Salicylate for the treatment of Kawasaki disease in children. *Cochrane Database of Systematic Reviews, 4,* CD004175.
112. Amarilyo, G., Koren, Y., Bar-Meir, M., Bahat, H., Helou, M. H., Mendelson, A., ... & Barkai, G. (2017). High-dose aspirin for Kawasaki disease: Outdated myth or effective aid? *Clinical and Experimental Rheumatology*, *35*(1), 209-212.
113. Dallaire, F., Fortier-Morissette, Z., Blais, S., Dhanrajani, A., Basodan, D., Renaud, C., ... & Saulnier, H. (2017). Aspirin dose and prevention of coronary abnormalities in Kawasaki disease. *Pediatrics*, *139*(6), e20170098.
114. Dhanrajani, A., Chan, M., Pau, S., Ellsworth, J., Petty, R., & Guzman, J. (2017). Aspirin dose in Kawasaki disease: The ongoing battle. *Arthritis Care & Research, 70*(10), 1536-1540.
115. Huang, X., Huang, P., Zhang, L., Xie, X., Xia, S., Gong, F., ... & Jin, L. (2017). Is aspirin necessary in the acute phase of Kawasaki disease? *Journal of Paediatrics and Child Health, 54*(6), 661-664.
116. Lee, G., Lee, S. E., Hong, Y. M., & Sohn, S. (2013). Is high-dose aspirin necessary in the acute phase of Kawasaki disease? *Korean Circulation Journal*, *43*(3), 182-186.
117. Kim, G. B., Yu, J. J., Yoon, K. L., Jeong, S. I., Song, Y. H., Han, J. W., ... & Joo, C. U. (2017). Medium-or higher-dose acetylsalicylic acid for acute Kawasaki disease and patient outcomes. *Journal of Pediatrics*, *184*, 125-129.
118. Kuo, H. C., Lo, M. H., Hsieh, K. S., Guo, M. M. H., & Huang, Y. H. (2015). High-dose aspirin is associated with anemia and does not confer benefit to disease outcomes in Kawasaki disease. *PloS One*, *10*(12), e0144603.
119. Migally, K., Braunlin, E. A., Zhang, L., & Binstadt, B. A. (2018). Duration of high-dose aspirin therapy does not affect long-term coronary artery outcomes in Kawasaki disease. *Pediatric Research*.
120. Rahbarimanesh, A., Taghavi-Goodarzi, M., Mohammadinejad, P., Zoughi, J., Amiri, J., & Moridpour, K. (2014). Comparison of high-dose versus low-dose aspirin in the management of Kawasaki disease. *Indian Journal of Pediatrics*, *81*(12), 1403-1403.
121. Yoo, J. W., Kim, J. M., & Kil, H. R. (2016). The outcome of short-term low-dose aspirin treatment in Kawasaki disease based on inflammatory markers. *Korean Journal of Pediatrics*, *59*(12), 24-29.
122. Callinan, L. S., Holman, R. C., Vugia, D. J., Schonberger, L. B., & Belay, E. D. (2014). Kawasaki disease hospitalization rate among children younger than 5 years in California, 2003-2010. *Pediatric Infectious Disease Journal*, *33*(7), 781-783.
123. Davison, M., Meridis, G., & Strehle, E. M. (2013). Ten-year audit of Kawasaki disease in a district general hospital. *Human Genetics & Embryology*, *3*(106), 2161-0436.
124. Holman, R. C., Belay, E. D., Christensen, K. Y., Folkema, A. M., Steiner, C. A., & Schonberger, L. B. (2010). Hospitalizations for Kawasaki syndrome among children in the United States, 1997-2007. *Pediatric Infectious Disease Journal*, *29*(6), 483-488.
125. Sexson Tejtel, S. K., Ramirez, A., Liou, A., Seery, T., Canter, D., DeGuzman, M., & Altman, C. (2015). Abstract 23: Trends in Kawasaki disease incidence - 2004-2014. *Circulation, 131 (Suppl_2).*

Clinical Standards Preparation

This clinical standard was prepared by the Evidence-Based Outcomes Center (EBOC) team in collaboration with content experts at Texas Children's Hospital. Development of this clinical standard supports the TCH Quality and Patient Safety Program initiative to promote clinical standards and outcomes that build a culture of quality and safety within the organization.

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No relevant financial or intellectual conflicts to report.

Development Process

This clinical standard was developed using the process outlined in the EBOC Manual. The literature appraisal documents the following steps:

1. Review Preparation
   - PICO questions established
   - Evidence search confirmed with content experts
2. Review of Existing External Guidelines
   - Kawasaki Disease Clinical Guideline
   - Diagnosis, Treatment and Long-Term Management of Kawasaki Disease
   - Guidelines for medical treatment of acute Kawasaki Disease
   - Management of Kawasaki Disease
   - Kawasaki Disease, Journal of American College of Cardiology
3. Literature Review of Relevant Evidence
   - Searched: PubMed, Medline, CINAHL, and Cochrane
4. Critically Analyze the Evidence
   - 10 meta-analyses, 5 randomized controlled trials, and 105 nonrandomized studies
5. Summarize the Evidence
   - Materials used in the development of the clinical standard, literature appraisal, and any order sets are maintained in a Diagnosis and Management of Kawasaki Disease evidence-based review manual within EBOC.

Evaluating the Quality of the Evidence

Published clinical guidelines were evaluated for this review using the **AGREE II** criteria. The summary of these guidelines are included in the literature appraisal. AGREE II criteria evaluate Guideline Scope and Purpose, Stakeholder Involvement, Rigor of Development, Clarity and Presentation, Applicability, and Editorial Independence using a 4-point Likert scale. The higher the score, the more comprehensive the guideline.

This clinical standard specifically summarizes the evidence *in support of* or *against* specific interventions and identifies where evidence is *lacking/inconclusive*. The following categories describe how research findings provide support for treatment interventions.
"Evidence Supports" provides evidence to support an intervention
"Evidence Against" provides evidence against an intervention.
"Evidence Lacking/Inconclusive" indicates there is insufficient evidence to support or refute an intervention and no conclusion can be drawn *from the evidence.*

The **GRADE** criteria were utilized to evaluate the body of evidence used to make practice recommendations. The table below defines how the quality of the evidence is rated and how a strong versus weak recommendation is established. The literature appraisal reflects the critical points of evidence.

Recommendation	
STRONG	Desirable effects clearly outweigh undesirable effects or vice versa
WEAK	Desirable effects closely balanced with undesirable effects
Quality	**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, RCTs with serious flaws or indirect evidence
Very Low	Evidence for at least 1 critical outcome from unsystematic clinical observations or very indirect evidence

Recommendations

Practice recommendations were directed by the existing evidence and consensus amongst the content experts. Patient and family preferences were included when possible. The Content Expert Team and EBOC team remain aware of the controversies in the diagnosis/management of Kawasaki disease in children. When evidence is lacking, options in care are provided in the clinical standard and the accompanying order sets (if applicable).

Approval Process

Clinical standards are reviewed and approved by hospital committees as deemed appropriate for its intended use. Clinical standards are reviewed as necessary within EBOC at Texas Children's Hospital. Content Expert Teams are involved with every review and update.

Disclaimer

Practice recommendations are based upon the evidence available at the time the clinical standard was developed. Clinical standards (guidelines, summaries, or pathways) do not set out the standard of care and are not intended to be used to dictate a course of care. Each physician/practitioner must use his or her independent judgment in the management of any specific patient and is responsible, in consultation with the patient and/or the patient's family, to make the ultimate judgment regarding care.

Version History

Date	Comments
Jun 2019	Updated to guideline; previous summaries archived