Kawasaki Disease

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Author Disclosure
Drs Son and Newburger have disclosed no financial relationships relevant to this article. This commentary does contain discussion of unapproved/investigative use of a commercial product/device.

Practice Gap

1. Clinicians should not dismiss the diagnosis of Kawasaki disease (KD) in children with symptoms commonly attributed to viral illness. For example, severe headache and photophobia should signal the possibility of aseptic meningitis even in the presence of KD. And, right upper quadrant pain may indicate hydrops of the gallbladder.
2. A challenging subset of patients who do not meet the classic case definition are said to have incomplete KD. Patients who have incomplete KD are more likely to be infants and older children and, as such, are also at higher risk for coronary artery lesions (CAL). Of note, infants younger than 6 months of age are at high risk for development of CAL, yet often have fewer clinical features to facilitate the diagnosis. For these reasons, echocardiography is recommended for infants younger than age 6 months with fever of unclear etiology persisting for 7 or more days and elevated inflammatory markers.

Objectives

After reading this article, readers should be able to:

1. Describe the clinical manifestations of Kawasaki disease.
2. Formulate a differential diagnosis for patients with suspected Kawasaki disease.
3. Describe the laboratory values typically seen in Kawasaki disease.
4. Discuss the role of echocardiography in the management of patients who have Kawasaki disease and describe the cardiac complications of the disease.
5. Define primary treatment of Kawasaki disease with intravenous immunoglobulin and aspirin.

Case Study

A 3-year-old previously healthy Hispanic girl is brought to her pediatrician's office with a history of 6 days of fever. The fever has been present daily and has been unremitting, despite administration of antipyretic medications. She has been irritable with decreased appetite. Her mother noticed an erythematous, nonpruritic rash covering her torso 1 day after fever onset. She has developed red eyes in the past 2 days. She has no siblings and attends child care.

On examination, the girl is febrile to 38.9°C and tachycardic at 140 beats per minute. Her blood pressure while crying is 110/60 mm Hg. Her weight is 14.5 kg. She has conjunctival injection with limbal sparing and without exudate. Her lips appear erythematous and cracked, and her oropharynx is diffusely erythematous without exudate. She does not have significant cervical chain lymphadenopathy. A polymorphous maculopapular rash covers her torso and extremities. The dorsa of her hands and feet appear swollen.

She has a total white blood cell count of 15,600/mm^3, a hemoglobin level of 9.8 g/dL, and a platelet count of 670,000/mm^3. The differential count of the white blood cells is 81% neutrophils and 14% lymphocytes. She has mild transaminitis with an alanine aminotransferase level of 68 U/L; her aspartate aminotransferase level is normal. Her

Abbreviations

AHA: American Heart Association
ASA: aspirin
CAL: coronary artery lesions
CRP: C-reactive protein
EBV: Epstein-Barr virus
ESR: erythrocyte sedimentation rate
IVIG: intravenous immunoglobulin
KD: Kawasaki disease
LAD: left anterior descending artery
RCA: right coronary artery

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C-reactive protein (CRP) level is 9.8 mg/dL and her erythrocyte sedimentation rate (ESR) is 65 mm/hour. There are 25 white cells per high-power field on urinalysis.

Overview

Kawasaki disease (KD) is an acute febrile illness of childhood characterized by vasculitis of medium-sized, extraparenchymal arteries, with a predilection for coronary arteries. KD is the leading cause of acquired heart disease in developed countries, although rheumatic heart disease continues to dominate in the developing world. The natural history and treatment of KD are well described, but its etiology remains obscure, hampering efforts to identify a specific diagnostic test and targeted treatments.

In the absence of a specific diagnostic test, KD remains a diagnosis based on clinical criteria. All signs and symptoms of KD resolve following the acute illness, but coronary artery lesions (CALs) develop in 3% to 5% of children treated with intravenous immunoglobulin (IVIG), and up to 25% of untreated children. Its prognosis is predicated entirely on the presence and severity of CALs, which can range from mild dilation to giant aneurysms (Fig 1). It is unclear if children who have normal-appearing coronary arteries during the acute phase of the disease will be at risk for endothelial dysfunction and accelerated atherosclerosis later in the life.

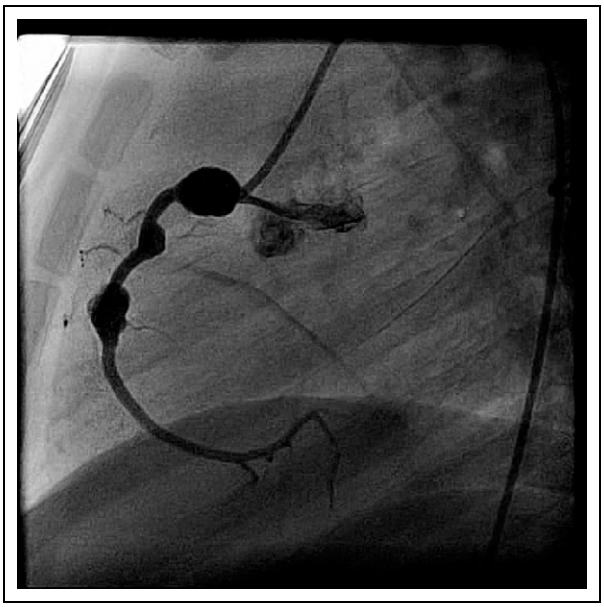

Figure 1. Selective right coronary angiogram demonstrating multiple aneurysms in a child who has KD.

Epidemiology

KD was first described in 1967 by a Japanese pediatrician, Dr Tomisaku Kawasaki, as the mucocutaneous lymph node syndrome. (1) At that time, the cardiac involvement of KD was not apparent, nor was effective treatment described. Within a few years, autopsy cases of patients who had KD demonstrated coronary artery aneurysms and thrombosis, and the cardiac complications of KD became evident. Since Dr Kawasaki's initial report, KD has been described in children around the world, and in virtually all races; however, Japanese children are at the highest risk.

Since 1970, Japan has collected epidemiologic data about KD nearly every 2 years via nationwide surveys. Interestingly, although the birth rate has declined, the numbers of patients diagnosed with KD and the incidence rate in Japan have risen rapidly since the 1990s. There have been three documented epidemics of KD in Japan, in 1979, 1982, and 1986. In 2010, the incidence rate of KD in Japan was 239.6 per 100,000 children age 0 to 4 years, which exceeds the highest rate during any of the epidemics and is the highest rate recorded. The reason for the linear increase in the incidence rate of KD in Japan is unclear. Similar to prior surveys in Japan, the most recent survey in 2009–2010 found that the incidence rate was highest among children age 6 to 11 months and was higher in boys than in girls. As compared with a survey performed in 1999–2000, the proportion of children with coronary artery dilation and aneurysms decreased from 6% to 3%; however, the incidence of giant aneurysms in patients who had KD did not decrease concomitantly. Infants, particularly those younger than 6 months, as well as children at least age 5 years had an increased relative risk of developing CAL.

In contrast to Japan, hospitalization rates associated with KD in the United States have been relatively stable over the past decade. The rate in 1997 was 17.5 per 100,000 children younger than age 5 years, and in 2006, 20.8 per 100,000 children younger than age 5 years. Most hospitalizations occurred in children younger than age 3 years. Children of Asian/Pacific Islander descent had the highest hospitalization rate, demonstrating the likely role of genetics in the pathogenesis of KD. An underlying genetic predisposition is supported further by the findings that siblings of children who have KD have a 10-fold increased risk for the disease, and the parents of children who have KD in Japan today are twice as likely, compared with other adults, to have had KD when they were children.

Risk factors for poor coronary artery outcomes have been studied in several populations. Demographic factors, such as young age, particularly younger than 6 months and

older than 9 years, male gender, Asian and Pacific Islander race, and Hispanic ethnicity have been associated with poor clinical outcomes. Laboratory parameters, such as neutrophilia, thrombocytopenia, hyponatremia, elevated CRP, and transaminitis, have all been associated with poor response to IVIG and the development of CAL. (2) Essentially, patients with evidence of significant and widespread inflammation are at the highest risk.

Pathogenesis

KD's etiology remains unknown. Many aspects of KD mimic infectious processes, such as toxin-mediated illnesses and viral illnesses. Seasonal peaks have occurred in the United States and Japan, with increased incidence in localized areas, suggesting a transmissible vector. Researchers have looked painstakingly and unsuccessfully for an etiologic infectious agent, including Epstein-Barr virus (EBV), adenovirus, human coronavirus, human bocavirus, *Yersinia pseudotuberculosis*, herpes viruses, and others.

Toxins, such as those produced by *Staphylococcus aureus* and *Streptococcus pyogenes,* have been postulated as the causative agents of KD because the rash can resemble an erythroderma, similar to the toxic shock syndromes and staphylococcal scalded skin syndrome. Additionally, the efficacy of treatment with IVIG could be explained by immunoglobulin binding of the toxins, although antigen-independent mechanisms have been postulated as well. Toxins act as superantigens, which nonselectively activate large numbers of T cells, leading to massive cytokine release and inflammation. Studies looking at the role of superantigens in KD have been conflicting. Specifically, isolation of superantigen-producing organisms, isolation of superantigen proteins, and the presence of an immunologic signature of superantigen activity have varied across studies.

To date, no unique agent has been proven to cause KD. An alternative hypothesis posits that many infectious agents trigger a final common pathway in genetically susceptible hosts, which is supported by the finding that many patients diagnosed as having KD have documented concomitant infections. The interplay of infection and vascular inflammation has been described in other forms of vasculitis, such as hepatitis B and polyarteritis nodosa, hepatitis C and cryoglobulinemia, and *Staphylococcus* and granulomatosis with polyangitis (Wegener's). Therefore, the hypothesis that infectious agents may trigger the inflammatory cascade in KD has face validity.

Both the innate and adaptive arms of the immune system have been evaluated in the pathogenesis of KD. The innate immune system includes epithelial barriers and phagocytic cells that provide protection against infection, whereas the adaptive immune response is mediated by antigen-specific lymphocytes stimulated by infectious agents. There is evidence that the innate immune system plays a significant role in the pathogenesis of KD. One study reported that neutrophils are important actors in the initial attack on coronary artery walls. (3) In a murine model of coronary arteritis induced by *Lactobacillus casei* cell wall extract, Toll-like receptor 2 and its downstream adaptor protein, MyD88, are required for the development of coronary artery lesions, establishing a role for the innate immune system. (4) Two recent studies demonstrated increased expression levels of innate immunity-associated genes during the acute phase of KD. (5)(6)

T cells also play an important role in KD. CD8+ T cells have been found in the coronary arteries from autopsy specimens. Studies of acute and subacute sera in patients who have KD showed a decrease in the population of T regulatory cells in the acute phase, with normalization following treatment with IVIG, indicating that impaired immunoregulation has a possible role in the development of KD.

Recent genome-wide association studies have described functional single-nucleotide polymorphisms in the *ITPKC* (inositol 1,4,5 triphosphate 3-kinase C) gene that are associated with increased risks for susceptibility to KD, more severe coronary artery disease, and resistance to IVIG. (7) *ITPKC* acts as a negative regulator of T-cell activation through the calcineurin/NFAT signaling pathway, and alterations in signaling may contribute to immune hyperreactivity in KD.

To date, the role of B cells in the pathogenesis of KD has not been clearly elucidated. Immunoglobulin A plasma cells have been found in lung tissue and coronary arteries from fatal cases of KD, but the precise role of the immunoglobulin A plasma cells remains to be determined. Furthermore, a recent study using the murine model with *Lactobacillus casei* cell wall extract–induced coronary arteritis indicated that B cells are not required for development of CALs. (8)

Clinical Manifestations

Classic clinical criteria with supportive clinical and laboratory findings are listed in Table 1. (9) With the exception of fever, the features of KD can fluctuate, and a thorough medical history is required to determine their presence during the period of illness. Children who have at least 4 days of fever (3 days in expert hands) and 4 or 5 of the principal criteria meet the case definition of KD. The case definition also includes children with fewer than four criteria if they have coronary artery disease.

The hallmark of KD is fever, typically above 39°C, which has abrupt onset and may not remit with antipyretic

Table 1. Clinical and Laboratory Features of Kawasaki Disease

Epidemiologic case definition (classic clinical criteria)
- Fever of at least 5 days' duration
- Presence of at least 4 of the following principal features:
  - Changes in extremities
  - Polymorphous exanthem
  - Bilateral conjunctival injection
  - Changes in lips and oral cavity
  - Cervical lymphadenopathy
- Exclusion of other diseases with similar findings (Table 2)

Other clinical and laboratory findings
- Cardiovascular findings
  - Congestive heart failure, myocarditis, pericarditis, or valvular regurgitation
  - Coronary artery abnormalities
  - Aneurysms of medium-sized noncoronary arteries
  - Raynaud phenomenon
  - Peripheral gangrene
- Musculoskeletal system
  - Arthritis
  - Arthralgia
- Gastrointestinal tract
  - Diarrhea, vomiting, abdominal pain
  - Hepatic dysfunction
  - Hydrops of the gallbladder
- Respiratory tract
  - Pulmonary nodules and interstitial infiltrates
  - Pleural effusion
- Central nervous system
  - Extreme irritability
  - Aseptic meningitis
  - Peripheral facial nerve palsy
  - Sensorineural hearing loss
- Genitourinary system
  - Urethritis/meatitis
  - Testicular swelling
- Other findings
  - Erythema and induration at Bacille Calmette-Guerin site
  - Anterior uveitis
  - Desquamating rash in groin
- Laboratory findings in acute Kawasaki disease (KD)
  - Neutrophilia with immature forms
  - Elevated erythrocyte sedimentation rate
  - Elevated C-reactive protein (CRP) level
  - Elevated serum α1-antitrypsin level
  - Anemia
  - Abnormal plasma lipids
  - Hypoalbuminemia
  - Thrombocytosis after first week of illness
  - Sterile pyuria
  - Elevated serum transaminases
  - Pleocytosis of cerebrospinal fluid
  - Leukocytosis in synovial fluid

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medications. In the absence of treatment, fever typically lasts 11 to 12 days, with rare cases of prolonged fever lasting more than 3 weeks. Although some children treated with IVIG experience immediate improvement during the infusion, others defervesce 1 to 2 days after receiving IVIG. Approximately 15% of children treated with IVIG have persistent or recrudescent fever more than 36 hours after completion of the first IVIG infusion.

More than 90% of children who have KD develop bilateral, nonexudative conjunctivitis that spares the limbus (ie, with clearing around the iris (Fig 2). Anterior uveitis also may be detected on slit-lamp examination during the acute phase of the disease. Oropharyngeal manifestations are common and include a diffusely erythematous oropharynx, red fissured lips, and a strawberry tongue (Fig 3). Discrete oral ulcers and tonsillar exudates are not seen typically in KD.

KD rash usually appears within 5 days of fever onset, and often starts as desquamation in the perineal area that evolves into a diffuse, erythematous, maculopapular rash. Morbilliform rashes, erythema multiforma, and erythroderma also can occur. Bullous or vesicular lesions suggest an alternative diagnosis.

Children afflicted with KD develop firm swelling of the hands and feet, as well as erythema of the palms and soles in the acute phase of the disease. Characteristic, although not pathognomonic, periungual peeling from the fingers and the toes (Fig 4) begins 2 to 3 weeks after the onset of the fever.

Cervical lymph node enlargement is the least common criterion found in patients who have KD. The enlargement is usually unilateral, located in the anterior cervical chain, nonfluctuant, and nontender. The diameter of the involved node

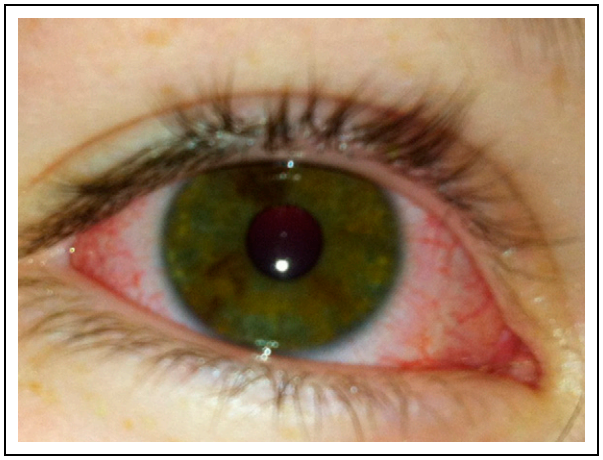

Figure 2. Bilateral nonexudative limbal sparing conjunctivitis is found in up to 90% of children who have KD. Courtesy of Annette L. Baker, NP.

should be ≥1.5 cm. Imaging typically reveals a group of matted nodes without abscess formation.

Children who have KD can have a myriad of other signs and symptoms, including myalgias, arthralgias, and arthritis. Neurologic involvement can include significant irritability, likely because of meningeal inflammation, transient facial palsies, and sensorineural hearing loss. Gastrointestinal complaints occur in up to 30% of patients and include abdominal pain, vomiting, diarrhea, acalculous distention of the gallbladder (hydrops), and hepatomegaly. Rarely, hemophagocytic lymphohistiocytosis, a life-threatening complication in which activated macrophages and T cells cause a cytokine storm, can occur in KD.

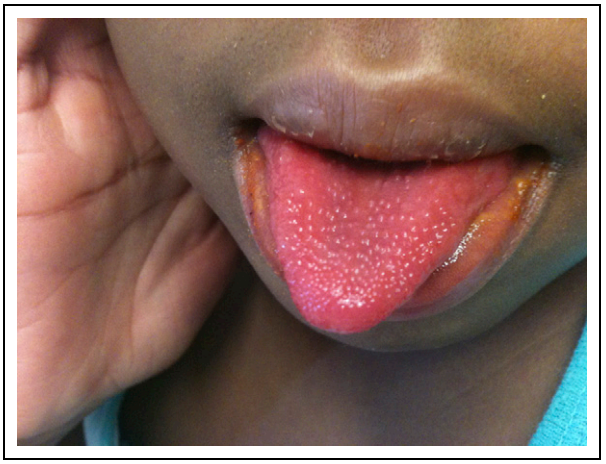

Figure 3. Oropharyngeal changes, including a strawberry tongue, as pictured, are common in children who have KD. Courtesy of Annette L. Baker, NP.

Incomplete KD

A challenging subset of patients who do not meet the classic case definition are said to have incomplete or atypical KD. Children who have incomplete KD do not have atypical features; rather, they have some of the classic features of KD but not enough to meet the case definition. Patients who have incomplete KD are more likely to be infants and older children, and, as such, also are at higher risk for CALs.

Considering the cardiac consequences of failing to treat incomplete KD and the comparative safety of IVIG treatment, the American Heart Association (AHA) published an algorithm for the evaluation and treatment of suspected incomplete KD to assist clinicians (Fig 5). The algorithm uses laboratory values and echocardiography in those children who have only a few clinical features of the disease, and also recommends consultation with a KD expert if needed.

A multicenter retrospective study of patients who have KD with aneurysms presenting before day 21 of illness found that application of the AHA algorithm would have resulted in referral of 97% of patients for IVIG treatment. (10) Of note, infants younger than age 6 months are at high risk for development of CALs, yet often have few clinical features to facilitate the diagnosis. For these reasons, it is recommended that infants younger than age 6 months who have had ≥7 days of fever of unclear etiology and elevated inflammatory markers undergo echocardiography.

Differential Diagnosis

Because KD is a self-limited febrile illness, infections dominate the list of differential diagnoses (Table 2). Measles, adenovirus, enterovirus, and EBV can mimic the clinical presentation of KD. Measles does not occur typically in countries with widespread vaccination; a travel or contact history should be sought in cases in which coryza and cough are conspicuous. Children who have adenoviral or enteroviral illnesses typically are less ill compared with children who have KD, and laboratory studies show less evidence of inflammation, with lower white blood cell counts and inflammatory markers. White blood cell indices typically reveal lymphocytosis.

EBV is associated commonly with an exudative pharyngitis and diffuse lymphadenopathy, neither of which is seen typically in KD. The conjunctivitis and rash of KD can be quite prominent and may appear consistent with Stevens-Johnson syndrome. The absence of other clinical features of KD, or findings of skin pain, skin necrosis, or blisters, favors the diagnosis of Stevens-Johnson syndrome.

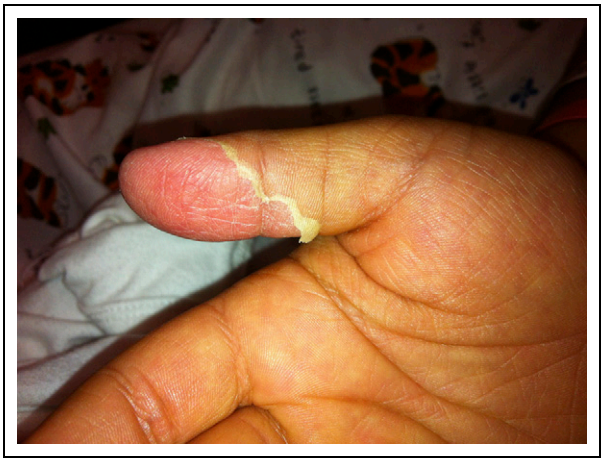

Figure 4. Periungual peeling, first from the finger nailbeds and then the toes, is typically seen 2 to 3 weeks after onset of the fever. Courtesy of Annette L. Baker, NP.

Toxin-mediated syndromes triggered by staphylococcal or streptococcal infections usually are characterized by visceral organ involvement, including renal insufficiency and significant hepatic dysfunction that are quite unusual in KD. Hypotension is also quite prominent in the toxin-mediated illnesses.

Scarlet fever can be evaluated with rapid streptococcal antigen testing; fever caused by group A *Streptococcus* is usually not associated with conjunctivitis and usually improves significantly within 24 hours of initiation of antibiotics. Rocky Mountain spotted fever presenting with fever and rash can appear similar to KD and occurs in specific geographic regions in the United States; treatment for this potentially fatal infection should not be withheld while KD is being considered.

Acrodynia can cause irritability and extremity changes similar to KD; an ingestion history of mercury should be sought if these are prominent manifestations. Children who have systemic-onset juvenile idiopathic arthritis present with fever and rash, and coronary dilation on echocardiography has been described in this population; however, the ocular and oropharyngeal signs of KD are quite unusual in the systemic form of arthritis.

Concomitant infections do not preclude the diagnosis of KD. In one study from Toronto, over 30% of children who had typical KD had laboratory evidence of at least one infection. (11) Patients who have KD have nonspecific symptoms as well, such as headache, abdominal pain, and malaise. Clinicians should not dismiss the diagnosis of KD in children who have symptoms that are attributed commonly to viral illnesses.

Evaluation for Suspected KD

Laboratory Studies

Children who have KD typically have leukocytosis with a predominance of neutrophils and immature forms. Many of these children have a normocytic normochromic anemia, with the average hematocrit at presentation being 2 SDs below the norm for age. A sudden drop in hemoglobin concentration following IVIG may be attributable to hemolytic anemia.

Platelet counts usually are elevated by the end of the first week of illness (450,000/mm^3), and may evolve into significant thrombocytosis, with platelet counts averaging 700,000/mm^3 by the third week. Platelet counts exceeding 1 million/mm^3 are not uncommon. Relatively lower platelet counts at the time of presentation are a risk factor for later development of CAL, likely reflecting greater adherence of platelets to an activated endothelium. Rarely, marked thrombocytopenia at diagnosis may be attributable to diffuse intravascular coagulation.

Inflammatory markers are elevated in nearly all cases of KD. The ESR and CRP should be assessed at diagnosis. The ESR following treatment with IVIG often is high, because the protein load from the infusion elevates the ESR, obscuring the extent of disease activity. Nonetheless, measurements of the ESR can be helpful in assessing the degree of inflammation at diagnosis. CRP levels are unaffected by IVIG and can be used in both the acute and subacute phases to gauge the degree of inflammation.

Transaminases are elevated in approximately 40% of patients with KD, and a mild hyperbilirubinemia can occur. Plasma gammaglutamyl transpeptidase levels are elevated in approximately two thirds of patients who have KD. Sterile pyuria (ie, dipstick negative) of ≥12 white blood cells/μL is present in approximately 80% of patients who have KD. Such pyuria may be found also in children who have other febrile illnesses, but the magnitude is greater in patients who have KD. (12) Other laboratory findings, such as hypoalbuminemia and hyponatremia, reflect more severe illness and can be associated with capillary leak. Lipid panels in patients who have KD are markedly altered, with decreased levels of total cholesterol, as well as apolipoprotein A1 and high-density lipoprotein. Markers of cardiac damage or dysfunction, such as troponins and B-type natriuretic peptide, also may be elevated, but are not obtained routinely.

Although laboratory studies are not a component of the classic criteria for KD, they are included in the algorithm for treatment of suspected incomplete KD, because

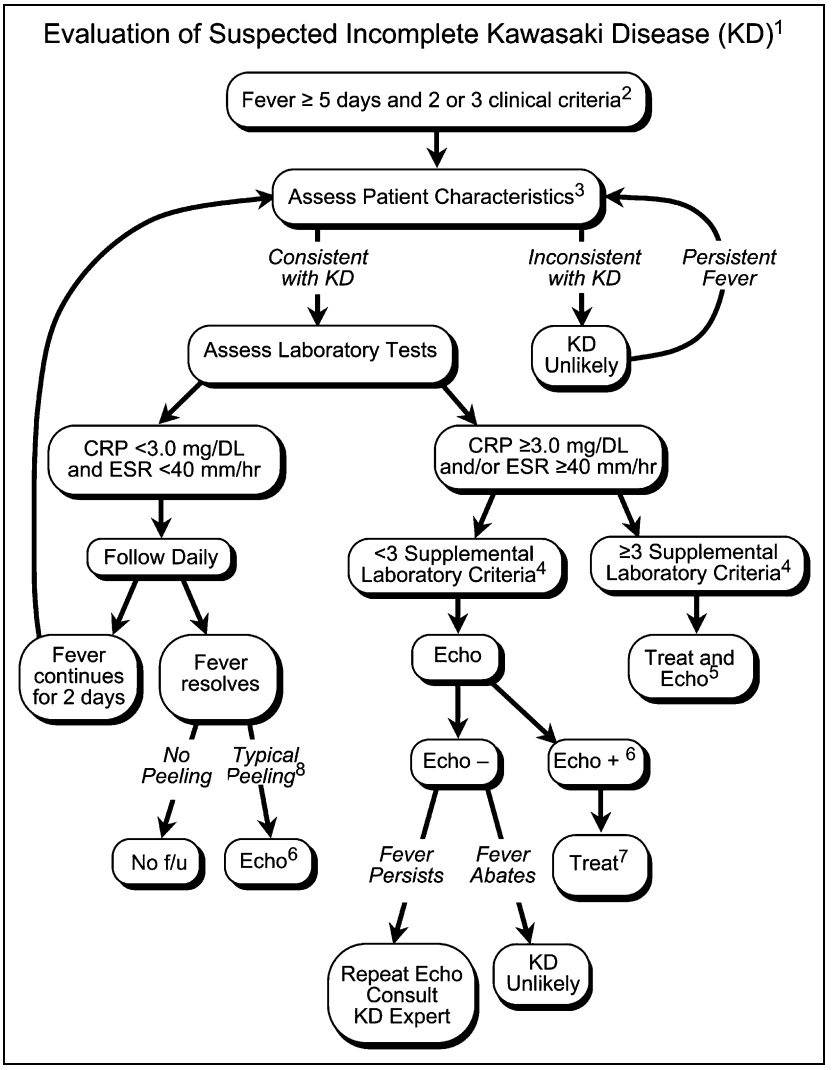

Figure 5. Evaluation of suspected incomplete Kawasaki disease (KD). (1) In the absence of gold standard for diagnosis, this algorithm cannot be evidence-based but rather represents the informed opinion of the expert committee. Consultation with an expert should be sought any time assistance is needed. (2) Infants ≤6 months old on day ≥7 of fever without other explanation should undergo laboratory testing and, if evidence of systemic inflammation is found, echocardiography, even if the infants have no clinical criteria. (3) Patient characteristics suggesting KD are listed in Table 1. Characteristics suggesting disease other than KD include exudative conjunctivitis, exudative pharyngitis, discrete intraoral lesions, bullous or vesicular rash, or generalized adenopathy. Consider alternative diagnoses (see Table 2). (4) Supplemental laboratory criteria include albumin ≤3.0 g/dL, anemia for age, elevation of alanine aminotransferase, platelets after 7 days ≥450,000/mm^3, white blood cell count ≥15,000/mm^3, and urine ≥10 white blood cells/high-power field. (5) Can treat before performing echocardiography. (6) Echocardiography is considered positive for purposes of this algorithm if any of 3 conditions are met: *z* score of LAD or RCA ≥2.5, coronary arteries meet Japanese Ministry of Health criteria for aneurysms, or ≥3 other suggestive features exist, including perivascular brightness, lack of tapering, decreased left ventricular function, mitral regurgitation, pericardial effusion, or *z* scores in LAD or RCA of 2.0 to 2.5. (7) If echocardiography is positive, treatment should be given to children within 10 days of fever onset and those beyond day 10 with clinical and laboratory signs (CRP, ESR) of ongoing inflammation. (8) Typical peeling begins under nail bed of fingers and then toes. Figure and legend reprinted with permission from Newburger JW, Takahashi M, Gerber MA, et al. 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. *Circulation*. 2004;110(17):2748. CRP=C-reactive protein; echo=echocardiography; ESR=erythrocyte sedimentation rate; f/u=follow-up; LAD=left anterior descending artery; RCA=right coronary artery.

Table 2. Differential Diagnosis of Kawasaki Disease

Infections
- Viral
  - Measles
  - Adenovirus
  - Enterovirus
  - Epstein-Barr virus
- Bacterial
  - Scarlet fever
  - Cervical lymphadenitis
  - Rocky Mountain spotted fever
  - Leptospirosis

Toxin-mediated diseases
- Staphlycoccal scalded skin syndrome
- Toxic shock syndrome (associated with *Staphylococcus* or *Streptococcus*)

Hypersensitivity reactions
- Drug hypersensitivity reactions
- Stevens-Johnson syndrome

Other
- Systemic onset juvenile idiopathic arthritis
- Acrodynia (mercury toxicity)

many of the laboratory abnormalities described previously are seen consistently in KD.

The child has echocardiography performed. Her coronary artery dimensions are within normal limits for age, but her left anterior descending artery does not taper normally. Her left ventricular function is normal, and no pericardial effusion is seen.

Cardiac Imaging

Echocardiography is an excellent imaging modality for evaluating coronary artery dimensions, myocardial function, valve regurgitation, and pericardial effusion. The procedure is noninvasive, and in experienced hands has high sensitivity and specificity for dilation in the proximal coronary arteries. Sedation often is required in younger children to obtain optimal images. If the diagnosis is clear, treatment for KD should not be withheld while waiting to schedule or obtain the results of echocardiography. Two-dimensional echocardiography should be performed with the highest-frequency probe available to produce high-resolution images. Standard views for cardiac echocardiography include parasternal, apical, subcostal, and suprasternal notch windows.

Patients who have definite or suspected KD should undergo assessment of each coronary artery, including the left main coronary artery, left anterior descending artery (LAD), left circumflex coronary artery, right coronary artery (RCA), and posterior descending coronary artery. The proximal LAD and RCA are affected most commonly by coronary artery aneurysms.

Coronary arteries should be evaluated with respect to their size and appearance. The size of an artery should be measured from internal edge to internal edge, avoiding areas of branching that can be associated with areas of natural dilation. The widely used Japanese Ministry of Health criteria classify coronary artery sizes according to age, with an internal lumen diameter greater than 3 mm abnormal in children less than age 5 years, and internal lumen diameter greater than 4 mm abnormal in children age ≥5 years. Additionally, artery segments that are ≥1.5 times larger than the adjacent section and those segments having an irregular coronary lumen also are considered abnormal. Because coronary artery dimensions change with the size of the child, body surface area–adjusted coronary dimensions (z scores) also should be obtained for the left main coronary artery, LAD, and RCA. The other coronary arteries do not have established z scores, and as such, the Japanese Ministry of Health criteria may be applied to those segments. Aneurysms can be classified as small (<5 mm internal diameter), medium (5–8 mm internal diameter), and giant (>8 mm internal diameter) when using absolute dimensions.

The appearance of the coronary arteries is informative as well. In most children who have KD, coronary diameters are greatest on the first echocardiography performed early in the disease. (13) Larger baseline measurements predict the development of worsening CALs over the ensuing 4 to 6 weeks in a subset of children. If coronary artery dimensions are normal in the subacute period (up to 6 weeks), it is highly unlikely that the child will develop dilatation of coronary vessels thereafter, unless the disease relapses or recurs.

In addition to documenting findings in the coronary arteries, echocardiography provides assessment of left ventricular and valve function. Left ventricular systolic dysfunction (ie, ejection fraction >2 SDs below normal) occurs in 20% of children who have acute KD. Histologic studies suggest that myocarditis is universal in patients who have KD and can be severe enough to produce a clinical picture consistent with shock. The myocarditis improves rapidly with administration of IVIG. The pericardium should be assessed with echocardiography for evidence of effusion. Last, although mitral regurgitation is seen in 27% of patients early in the course of KD, aortic regurgitation is less common (1%).

Echocardiography should be obtained at diagnosis, 1 to 2 weeks later, and 6 weeks post discharge. Children who have persistent or recrudescent fever or who have

known CALs need more frequent monitoring to inform treatment decisions, and close follow-up with a pediatric cardiologist is essential. AHA recommendations suggest follow-up echocardiography at 1 year in children who never had coronary sequelae; however, echocardiography should be performed more frequently among those who have CALs.

Although echocardiography is the preferred method of visualizing the coronary arteries early after KD, coronary angiography is used in children who have significant coronary artery aneurysms using techniques of computed tomography, magnetic resonance angiography, or cardiac catheterization.

Based on the clinical findings, the child is diagnosed as having KD and is prescribed IVIG at 2 g/kg and aspirin (ASA) 80 to 100 mg/kg per day divided every 6 hours.

Treatment

Once the diagnosis of KD is confirmed, treatment with high-dose IVIG (2 g/kg) and high-dose ASA (80 to 100 mg/kg per day divided into 4 doses) should be instituted promptly. Ideally, treatment is administered within the first 7 days of illness, and by day 10 (as defined by the first day of fever) at the latest. Treatment with IVIG after day 10 of illness is reserved for those with ongoing fever and evidence of systemic inflammation on laboratory studies. To avoid infusion reactions, premedication with standard dosing of diphenhydramine should be considered strongly. Additionally, IVIG should be administered slowly, over 8 to 12 hours, to avoid hemodynamic instability. IVIG can be associated with low-grade fevers within the first 48 hours of its administration. Hemolytic reactions to IVIG are well described.

Approximately 15% of children who have KD will have recurrent or persistent fever after the first dose of IVIG and are considered resistant to IVIG and at higher risk for CALs. The treatment of these children remains an area of controversy, because studies to evaluate treatment strategies for IVIG resistance are limited. Most clinicians administer another dose of IVIG (2 g/kg) 48 hours after the first dose if fever persists or is recrudescent.

Because KD is a vasculitis, corticosteroids have undergone trials in KD. Steroids can be administered as "primary" therapy when given at the time of the first dose of IVIG, or as "secondary" therapy when given for IVIG resistance. Furthermore, corticosteroids can be given in high-"pulse" doses of 30 mg/kg of intravenous methylprednisolone, or in lower doses (0.5 to 2.0 mg/kg per day) of prednisolone orally.

The use of corticosteroids in KD has an interesting history, because an early report raised the possibility of steroids worsening coronary artery disease; however, subsequent studies indicated a likely beneficial effect in children. Most recently, a study by Kobayashi et al (14) involving high-risk Japanese children showed that primary therapy with a combination of corticosteroids (prednisolone 2 mg/kg per day) and IVIG provided protection against poor coronary outcomes. However, this regimen has not been tested in non-Japanese populations, and the protocol involved a prolonged course of intravenous corticosteroid with concomitant hospitalization. The optimal regimen of corticosteroids for IVIG resistance has yet to be determined, and the lack of consensus has fostered considerable practice variation across centers.

Other therapies used in IVIG resistance include infliximab, a tumor necrosis factor inhibitor (5 mg/kg per dose). Retrospective data indicate that infliximab may decrease the number of days of fever, but may not alter coronary artery outcomes. Results of a prospective trial using infliximab as primary therapy are awaited. There are reports from Japan and the United States that calcineurin inhibitors, such as cyclosporine A, may be effective in patients with IVIG resistance.

There are very few indications for ASA in childhood given the risk of Reye syndrome, but KD remains one of them. Studies have shown that use of ASA does not affect the development of CALs (15); however, all of the major clinical trials to study treatment of KD have used ASA. Use of other nonsteroidal anti-inflammatory drugs, such as ibuprofen, has not been studied recently. In treating KD, ASA is given at high (anti-inflammatory) doses of 80 to 100 mg/kg per day, divided into every-6-hour dosing initially, followed by antithrombotic doses of 3 to 5 mg/kg per day in once-daily dosing.

There is practice variation in duration of high-dose ASA administration. Some practitioners give high-dose ASA until patients are afebrile for 48 hours, whereas others continue with high-dose ASA for 2 weeks. Low-dose ASA typically is discontinued if echocardiography findings are normal at the 6-week visit.

Children who have persistent CAL at 6 weeks are continued on low-dose ASA, and yearly influenza vaccinations are strongly recommended in those cases to decrease the risk of Reye syndrome. Patients who are not fully vaccinated should receive immunizations according to the guidelines put forth in the American Academy of Pediatrics' *Red Book*, which state that measles and varicella-containing vaccinations are contraindicated for 11 months after administration of IVIG for KD. (16)

For those patients who have moderate to large aneurysms, a second antiplatelet agent may be added to ASA. Children who have giant aneurysms require anticoagulation with low-molecular-weight heparin or warfarin, in addition to ASA. Such regimens are best implemented

with the collaboration of pediatric hematologists or coagulation services.

The role of 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitors (statins) in children who have KD remains an area of research. Statins have both cholesterol-lowering and immunomodulatory properties. In a small study of 11 children who had KD and CALs, use of a statin for 3 months resulted in improved flow-mediated dilation (an indication of endothelial health) and CRP levels. (17) Although these results are of interest, larger-scale clinical trials are needed before one can recommend use of statins in the earliest phases of KD. However, the threshold for use of statins in children who have aneurysms is lower because of data suggesting susceptibility of these patients to atherosclerosis.

The patient tolerates her IVIG infusion without complication and defervesces within the subsequent 48 hours. Her tachycardia resolves. The conjunctival injection improves significantly, as does the rash. Upon discharge, she is well appearing and prescribed ASA 40.5 mg daily. She is scheduled for an appointment in 2 weeks for echocardiography and laboratory studies.

Prognosis and Long-Term Management

The prognosis of KD relates entirely to the extent and severity of cardiac disease. With timely IVIG treatment, the incidence of CAL in treated children has fallen to less than 5%, and only 1% of children develop giant aneurysms. Coronary aneurysms regress to normal lumen diameter via proliferation of myofibroblasts in more than one half of affected arterial segments. However, endothelial function is impaired in these segments even after regression. Stenoses at the proximal and distal ends of aneurysms can develop over time and increase the risk of myocardial ischemia. Stenotic lesions are more likely to form in giant aneurysms, as compared with smaller lesions.

Management of children who have significant coronary artery disease may require a combination of beta-blockers to decrease oxidative stress, as well as anticoagulation therapy. These children are followed closely with assessment of coronary function (eg, exercise stress echocardiography in children old enough to run on a treadmill, dobutamine cardiac magnetic resonance imaging for younger children) and structure (echocardiography, coronary angiography).

In those who develop symptoms of angina or findings of reversible ischemia on stress testing, percutaneous coronary intervention, for example with coronary stents, and coronary artery bypass surgery may be indicated. A recent report from Japan that followed patients who had giant aneurysms into adulthood found that long-term survival is relatively good among patients with giant aneurysms, despite their need for multiple catheterizations and surgeries. (18)

Mortality from KD is low (<0.5%), with the highest risk occurring in the first year after illness onset because of acute myocardial infarction among patients who have giant aneurysms. Sluggish blood flow through a dilated arterial segment and activation of platelets and endothelium contribute to the risk for myocardial infarction. Children who have myocardial infarction may present with pallor, vomiting, and abdominal pain; older children may complain of chest pain. Rupture of coronary artery aneurysms is very rare, and generally occurs within the first few months of illness. Severe myocarditis leading to hemodynamic compromise or arrhythmias can lead to death in the first week of illness.

Fortunately, most children who have KD do well after a single dose of IVIG, with rapid clinical improvement and reassuring echocardiographic findings. The risk of premature atherosclerosis among patients with always-normal coronary arteries will not be known definitively until large cohorts of middle-aged patients who have KD are assembled. In the interim, all children with a history of KD, even those without apparent coronary artery involvement, should undergo assessment of risk factors, such as hyperlipidemia and hypertension, and be counseled regarding a healthy lifestyle and avoidance of modifiable cardiac risk factors, such as obesity, smoking, and a sedentary lifestyle.

Summary

- Patients who have acute Kawasaki disease (KD) should be treated promptly with intravenous immunoglobulin (IVIG) to prevent coronary artery abnormalities (based on strong research evidence). (19)
- Patients who have persistent or recrudescent fever following primary therapy with IVIG should receive another dose of IVIG at 2 g/kg (based primarily on consensus). (9) Other secondary therapies to consider include corticosteroids (14)(20) and infliximab (21) (based on some research evidence).
- Echocardiography is an excellent modality for assessing coronary artery changes in children who have early KD (based primarily on consensus).
- In patients who have KD and always-normal coronary arteries, preventive cardiology counseling and follow-up are recommended until further studies delineate the long-term consequences on endothelial health (9) (based on some research evidence as well as consensus).
- In patients who have KD and coronary aneurysms, cardiologic follow-up is tailored to the degree of coronary artery involvement and involves assessment of coronary function and structure (based on strong research evidence). (9)

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1. A 3-year-old boy has had an unremitting fever for 4 days. Which of the clinical findings below best supports Kawasaki disease (KD) as the explanation for his fever?
   - A. Bilateral cervical lymph node enlargement
   - B. Bilateral nonexudative conjunctivitis
   - C. Periungual peeling of fingers and toes
   - D. Tonsillar exudate
   - E. Vesicles on the palms and soles

2. You are aware that other conditions can cause a similar clinical pattern. In your evaluation of this child, which of the following conditions is initially most likely to be confused with KD?
   - A. Adenoviral infection
   - B. Pauciarticular juvenile arthritis
   - C. Rubella
   - D. Staphylococcal scarlet fever
   - E. Varicella-zoster

3. You order laboratory tests to add further diagnostic insights. Which of the following findings strengthen your impression that the child has KD?
   - A. Elevated erythrocyte sedimentation rate
   - B. Lymphocytosis
   - C. Microcytic anemia
   - D. Neutropenia
   - E. Thrombocytopenia

4. A 3-year-old girl meets clinical criteria for KD. You realize that the greatest threat to her is coronary artery disease. The best choice for initial imaging of the coronary arteries is
   - A. Cardiac catheterization
   - B. Computed tomography
   - C. Magnetic resonance angiography
   - D. Radionuclide imaging
   - E. Two-dimensional echocardiography

5. Although her echocardiography shows no coronary artery lesions, you realize that the girl is at risk for developing coronary artery disease and requires preventive therapy. The treatment that lowers the incidence of coronary artery disease in KD the most is high-dose
   - A. Aspirin
   - B. Corticosteroids
   - C. Cyclosporine A
   - D. Infliximab
   - E. Intravenous immune globulin

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