Kawasaki Disease

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Education Gap

Kawasaki disease is the leading cause of acquired heart disease in developed countries. A rare disease without pathognomonic findings or a diagnostic test, Kawasaki disease should be considered in the differential diagnosis of a child with prolonged fever.

Objectives

After completing this article, readers should be able to:

1. Recognize the clinical findings associated with Kawasaki disease (KD).
2. Formulate a differential diagnosis for patients with suspected KD.
3. Describe the laboratory values typically seen in KD.
4. Discuss the role of echocardiography in the management of patients with KD and describe the cardiac complications of the disease.
5. Define the primary treatment of KD with intravenous immunoglobulin and oral aspirin.

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ABBREVIATIONS

ASA	aspirin
CAL	coronary artery lesion
CRP	C-reactive protein
ESR	erythrocyte sedimentation rate
IVIG	intravenous immunoglobulin
KD	Kawasaki disease
LAD	left anterior descending artery
RCA	right coronary artery

CASE STUDY

A 3-year-old previously healthy Hispanic girl is brought to her pediatrician's office by her mother with a history of 6 days of fever. The fever has been present daily and 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 she is febrile to 102°F (38.9°C) and tachycardic at 140 beats/min. Her blood pressure while crying is 110/60 mm Hg. Her weight is 32 lb (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 exudates. She does not have substantial cervical chain lymphadenopathy. A polymorphous maculopapular rash covers her torso and extremities. The dorsum of her hands and feet appear swollen.

On laboratory examination she has a total white blood cell count of 15.6/μL (×10⁹/L), her hemoglobin level is 9.8 g/dL (98 g/L), and her platelet count is 669,000×10³/μL (×10⁹/L). The differential count of the white blood cells is 81% neutrophils and 14% lymphocytes. She has mild elevation of her transaminase values, with an alanine aminotransferase level of 68 U/L (1.14 μkat/L) and a normal aspartate aminotransferase level. Her C-reactive protein (CRP) level is 98 mg/L

(933 nmol/L), and her erythrocyte sedimentation rate is 65 mm/hour. There are 25 white blood cells per high-power field on urinalysis.

OVERVIEW

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

In the absence of a diagnostic test, KD remains a diagnosis based on clinical criteria. All signs and symptoms of KD resolve after the acute illness (even in the absence of treatment), but coronary artery lesions (CALs) develop in 3% to 5% of children treated with intravenous immunoglobulin (IVIG) and in up to 25% of untreated children. The prognosis of the disease hinges entirely on the presence and severity of CALs, which can range from mild dilatation to giant aneurysms (Fig 1). It is unclear at this time whether 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 life.

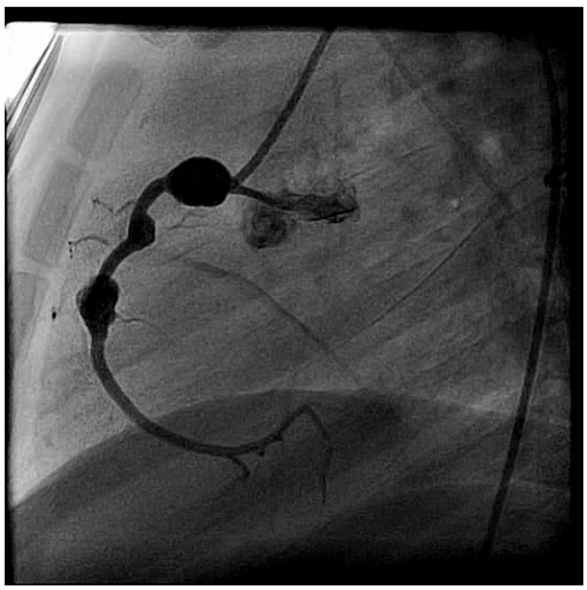

Figure 1. Selective right coronary angiogram demonstrating multiple aneurysms in a child with Kawasaki disease.

EPIDEMIOLOGY

Kawasaki disease was first described in 1967 by a Japanese pediatrician, Dr Tomisaku Kawasaki, as *mucocutaneous lymph node syndrome*. At that time, the cardiac involvement of KD was not apparent, and neither was effective treatment described. Within a few years, autopsy cases of patients with 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, children of Japanese ancestry are at highest risk for KD.

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 as having KD and the incidence rate in Japan have risen rapidly since the 1990s. There have been 3 documented epidemics of KD in Japan, in 1979, 1982, and 1986. In 2012, the incidence rate of KD in Japan was 264.8 per 100,000 children aged 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. Fortunately, the proportion of patients with coronary artery aneurysms and myocardial infarction has decreased from 6% in 1999-2000 to 2.8% in a recent survey. (1) In contrast to Japan, hospitalization rates associated with KD in the United States have been relatively stable for the past decade. The hospitalization rate in 2006 was 20.8 per 100,000 children younger than 5 years, and it was 19 per 100,000 children younger than 5 years in 2009. (2) Most hospitalizations occurred in children younger than 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 further supported by the findings that siblings of children with KD in Japan have a 10-fold increased risk of the disease, and the parents of children with 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 <6 months and >9 years), male sex, Asian and Pacific Islander race, and Hispanic ethnicity have been associated with poor clinical outcomes. Laboratory parameters such as neutrophilia, thrombocytopenia, hyponatremia, elevated CRP level, and elevated transaminase levels have all been associated with poor response to IVIG and/or the development of CALs. (3) Fundamentally,

patients with evidence of substantial and widespread inflammation are at highest risk.

PATHOGENESIS

The etiology of KD 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 in Japan, with an increased incidence in localized areas, suggesting a transmissible vector. Researchers have looked painstakingly and unsuccessfully for an etiologic infectious agent, including Epstein-Barr virus, adenovirus, human coronavirus, human bocavirus, *Yersinia pseudotuberculosis,* herpes viruses, and others.

Toxins, such as those produced by *Staphylococcus aureus* or *Streptococcus pyogenes,* have been postulated as the etiology of KD because the rash can appear similar to an erythroderma, similar to that in toxic shock syndrome or streptococcal toxic shock syndrome. In addition, the efficacy of treatment with IVIG could be explained by immunoglobulin binding of 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 Wegener granulomatosis. Accordingly, 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. A study reported that neutrophils are important actors in the initial attack on coronary artery walls. 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 CALs, establishing a role for the innate immune system. Furthermore, there is evidence that interleukin-1β plays a highly important role in the development of CALs in the murine model of KD. In addition, multiple studies have demonstrated increased expression levels of innate immunity-associated genes and transcriptional profiles during the acute phase of KD. T cells also play an important role in KD. CD8+ T cells have been found in coronary arteries from autopsy specimens. Studies of acute and subacute sera in patients with KD showed a decrease in the population of regulatory T cells in the acute phase, with normalization after treatment with IVIG, indicating that impaired immunoregulation has a possible role in the development of KD.

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 of susceptibility to KD, more severe coronary artery disease, and lack of response to IVIG, termed *IVIG resistance*. (4) *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. The *FCGR2A* locus has also been identified as a susceptibility locus by genome-wide association studies, and a recent study demonstrated that hypomethylation of this locus led to susceptibility to KD and to IVIG resistance.

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 study using the murine model with *L casei* cell wall extract–induced coronary arteritis indicated that B cells are not required for the development of CALs.

CLINICAL ASPECTS

Classical clinical criteria with supportive clinical and laboratory findings are listed in Table 1. (5) Except for fever, the features of KD can fluctuate or accrue over time, and a thorough medical history is required to determine their presence during the course of illness. Children who have at least 4 days of fever and 4 or 5 of the principal criteria meet the case definition of KD. Very early diagnosis, ie, at day 3, can be conferred in rare cases where they child meets at

least 4 of the principal criteria by day 3 of fever, or in the hands of an experienced KD clinician. The case definition also includes children with fewer than 4 criteria if they have coronary artery aneurysms.

The hallmark of KD is fever of abrupt onset, and it is typically greater than 102°F (>39°C) and may not remit with antipyretic medication use. In the absence of treatment, fever typically lasts 11 to 12 days, with rare cases of prolonged fever greater than 3 weeks. Although some children treated with IVIG experience immediate improvement during the infusion, others defervesce 1 to 2 days after IVIG therapy. Approximately 15% of children treated with IVIG have IVIG resistance or persistent or recrudescent fever more than 36 hours after completion of the first IVIG infusion.

More than 90% of children with KD develop bilateral nonexudative conjunctivitis that spares the limbus, ie, with clearing around the iris (Fig 2). In addition, anterior uveitis 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 cracked lips, and a strawberry tongue (Fig 3). Discrete oral ulcers and tonsillar exudates are not typically seen in KD.

The rash of KD usually appears within 5 days of fever and often starts as desquamation in the perineal area that then evolves into a diffuse, erythematous maculopapular rash. Morbilliform rashes, erythema multiforme, and erythroderma can also occur. Bullous or vesicular lesions suggest an alternative diagnosis. Reactivation at the site of bacille Calmette-Guérin vaccination has also been reported in KD.

Children 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 begins 2 to 3 weeks after onset of the fever (Fig 4). Peeling before day 10 of illness (ie, at the time of diagnosis) is not considered consistent with KD and may reflect desquamation seen in streptococcal or viral infections.

Cervical lymph node enlargement is the least common criterion found in patients with KD. It is usually unilateral, located in the anterior cervical chain, nonfluctuant, and nontender. The diameter of the involved node should equal or exceed 1.5 cm. Imaging typically reveals a group of matted nodes without abscess formation.

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

Incomplete KD

A challenging subset of patients who do not meet the classic case definition are said to have incomplete or atypical KD. However, the term *atypical* should be avoided because children with incomplete KD do not have atypical features; rather, they have fever for five or more days and fewer than 4 of the classic features of KD and, thus, do not meet the case definition. Patients with incomplete KD are more likely to be infants and older children and, as such, 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 published an algorithm for the evaluation and treatment of suspected incomplete KD to assist clinicians (Fig 5). (5) The algorithm uses laboratory values and echocardiographic findings in children with only a few clinical features of the disease and also recommends consultation with a KD expert if needed. A multicenter retrospective study of patients with KD with aneurysms presenting before day 21 of illness found that application of the American Heart Association algorithm would have resulted in referral of 97% of patients for IVIG treatment. (6) Of note, infants younger than 6 months are at high risk for the development of CALs yet often have few clinical features to facilitate the diagnosis. For these reasons, it is recommended that infants younger than 6 month with fever for at least 7 days of unclear etiology and elevated inflammatory markers have an echocardiogram.

Differential Diagnosis

Because KD is a self-limited febrile illness, infections dominate the list of differential diagnoses (Table 2). Measles, adenovirus, enterovirus, and Epstein-Barr virus can mimic the clinical presentation of KD. Measles is not typically seen in countries with widespread vaccination; a travel or contact history should be sought in cases in which coryza and cough are conspicuous. Children with adenoviral or enteroviral illnesses are typically less ill compared with children with KD, and laboratory studies may show less evidence of inflammation with lower white blood cell counts and inflammatory markers. In addition, white blood cell indices typically reveal lymphocytosis. Epstein-Barr virus is commonly associated with an exudative pharyngitis and diffuse lymphadenopathy, neither of which is

TABLE 1. Clinical and Laboratory Features of Kawasaki Disease (KD)

Classic KD is diagnosed in the presence of fever for at least 5 d (the day of fever onset is taken to be the first day of fever) together with ≥4 of the 5 following principal clinical features. In the presence of ≥4 principal clinical features, particularly when redness and swelling of the hands and feet are present, the diagnosis of KD can be made with 4 days of fever, although experienced clinicians who have treated many patients with KD may establish the diagnosis with 3 days of fever in rare cases.
1. Erythema and cracking of lips, strawberry tongue, and/or erythema of the oral and pharyngeal mucosa
2. Bilateral bulbar conjunctival injection without exudate
3. Rash: maculopapular diffuse erythroderma or erythema multiforme-like
4. Erythema and edema of hands and feet in the acute phase and/or periungual desquamation in the subacute phase
5. Cervical lymphadenopathy (≥1.5 cm in diameter), usually unilateral
Other clinical and laboratory findings
• **Cardiovascular**
◦ Myocarditis, pericarditis, valvular regurgitation, shock
◦ Coronary artery abnormalities
◦ Aneurysms of medium-sized noncoronary arteries
◦ Aortic root enlargement
◦ Peripheral gangrene
• **Respiratory**
◦ Peribronchial and interstitial infiltrates on chest radiography
◦ Pulmonary nodules
• **Musculoskeletal system**
◦ Arthritis, arthralgia (pleocytosis of synovial fluid)
• **Gastrointestinal tract**
◦ Diarrhea, vomiting, abdominal pain
◦ Hepatitis, jaundice
◦ Hydrops of the gallbladder
◦ Pancreatitis
• **Central nervous system**
◦ Extreme irritability
◦ Aseptic meningitis
◦ Peripheral facial nerve palsy
◦ Sensorineural hearing loss
• **Genitourinary system**
◦ Urethritis/meatitis, hydrocele
• **Other findings**
◦ Desquamating rash in the groin
◦ Retropharyngeal phlegmon
◦ Erythema and induration at the bacille Calmette-Guérin site
◦ Anterior uveitis by slit lamp examination

Continued

TABLE 1. (Continued)

• Laboratory findings in acute KD
◦ Neutrophilia with immature forms
◦ Elevated erythrocyte sedimentation rate
◦ Elevated C-reactive protein level
◦ Elevated serum α1-antitrypsin level
◦ Anemia
◦ Abnormal plasma lipid levels
◦ Hypoalbuminemia
◦ Thrombocytosis after the first week of illness
◦ Sterile pyuria
◦ Elevated serum transaminase levels
◦ Pleocytosis of cerebrospinal fluid
◦ Leukocytosis in synovial fluid

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typically seen 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 the presence of findings of skin pain, skin necrosis, or blisters favors the diagnosis of Stevens-Johnson syndrome. Toxin-mediated syndromes triggered by staphylococcal or streptococcal infections are usually characterized by visceral organ involvement, including renal insufficiency and substantial hepatic dysfunction, which are unusual in KD. Hypotension is also prominent in toxin-mediated illnesses. However, recent reports have documented a KD shock syndrome characterized by substantial hypotension in the acute phase of the disease requiring fluid resuscitation, vasoactive agents, and/or transfer to an ICU setting. Studies to date have been retrospective series but seem to indicate that KD shock syndrome is associated with worse coronary artery outcomes. Scarlet fever can be evaluated with rapid streptococcal antigen testing; fever caused by group A *Streptococcus* is not usually associated with conjunctivitis and usually improves significantly within 24 hours of initiation of antibiotic drug therapy. Rocky Mountain spotted fever presenting with fever and rash

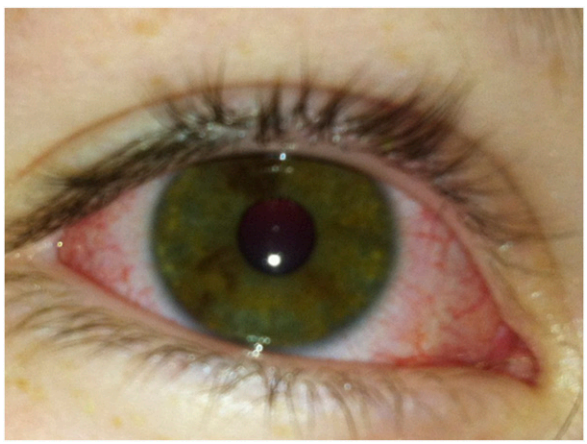

Figure 2. Bilateral nonexudative limbus-sparing conjunctivitis is found in greater than 90% of children with Kawasaki disease.

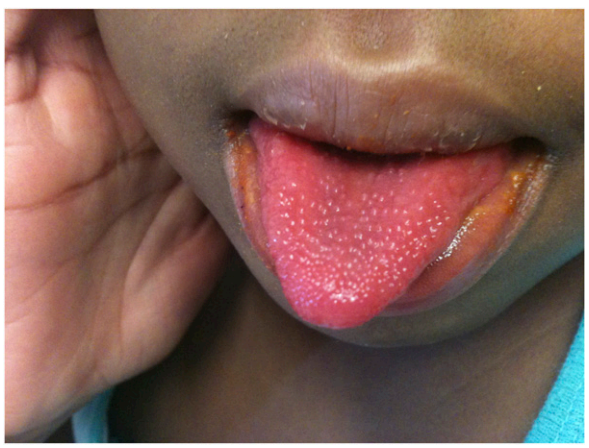

Figure 3. Oropharyngeal changes, including a strawberry tongue as pictured, are common in children with Kawasaki disease.

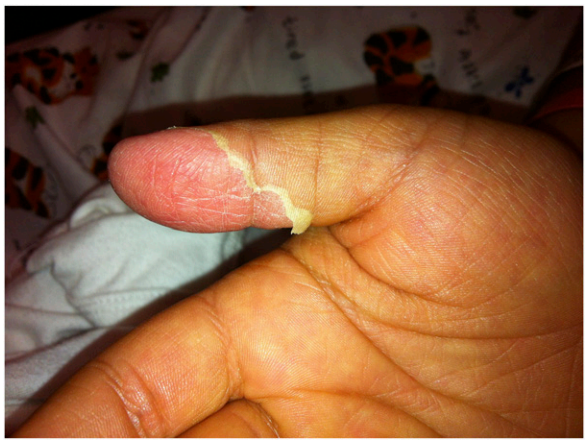

Figure 4. Periungual peeling, first from the finger nail beds and then the toes, is typically seen 2 to 3 weeks after onset of the fever.

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. Kawasaki disease presenting as "lymph node first" can mimic lymphadenitis of the cervical chain, but antibiotic drug therapy does not lead to defervescence, and other KD criteria may evolve with serial examinations. Acrodynia can cause irritability and extremity changes similar to KD; an ingestion history of mercury should be sought if these are prominent manifestations. Last, children with systemic-onset juvenile idiopathic arthritis present with fever and rash, and coronary dilatation 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. Furthermore, children with systemic-onset juvenile idiopathic arthritis tend to have unremitting symptoms until more profound or more targeted immunosuppressive medications are used.

Concomitant infections do not preclude the diagnosis of KD. In a study from Toronto, more than 30% of children with typical KD had laboratory evidence of at least 1 infection. (7) Patients with KD have nonspecific symptoms as well, such as headache, abdominal pain, and malaise. Clinicians should not dismiss the diagnosis of KD in children with symptoms that are commonly attributed to viral illnesses.

EVALUATION OF A PATIENT WITH SUSPECTED KD

Laboratory Studies

Children with KD typically have leukocytosis with a predominance of neutrophils and immature forms. Many

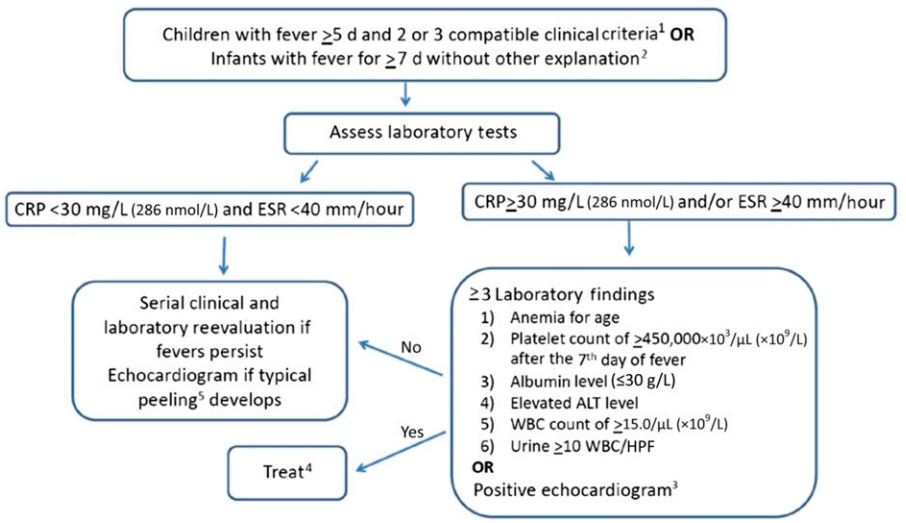

Figure 5. Evaluation of suspected incomplete Kawasaki disease (KD). In the absence of a gold standard for diagnosis, this algorithm cannot be evidence based but rather represents the informed opinion of the expert committee. Consultation with an expert should be sought any time assistance is needed. 1) Clinical findings of KD are listed in Table 1. Characteristics suggesting that another diagnosis should be considered include exudative conjunctivitis, exudative pharyngitis, ulcerative intraoral lesions, bullous or vesicular rash, generalized adenopathy, or splenomegaly. 2) Infants 6 months or younger are the most likely to develop prolonged fever without other clinical criteria for KD; these infants are at particularly high risk for coronary artery abnormalities. 3) Echocardiography is considered positive for the purposes of this algorithm if any of 3 conditions are met: the *Z* score of the left anterior descending coronary artery or right coronary artery is at least 2.5, coronary artery aneurysm is observed, or 3 or more other suggestive features exist, including decreased left ventricular function, mitral regurgitation, pericardial effusion, or *Z* scores in the left anterior descending coronary artery or right coronary artery of 2 to 2.5. 4) If the echocardiographic result is positive, treatment should be given within 10 days of fever onset or after the 10th day of fever in the presence of clinical and laboratory signs (C-reactive protein [CRP], erythrocyte sedimentation rate [ESR]) of ongoing inflammation. 5) Typical peeling begins under the nail beds of the fingers and toes. ALT=alanine aminotransferase; HPF=high-power field; WBC=white blood cell. (Reprinted with permission from McCrindle BW, Rowley AH, Newburger JW, et al. Diagnosis, treatment, and long-term management of Kawasaki disease: a scientific statement for health professionals from the American Heart Association. *Circulation.* 2017;135(17):ee937.)

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
• Staphylococcal 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)

children have a normocytic normochromic anemia, with the average hematocrit level at presentation being 2 standard deviations below the norm for age. A sudden drop in hemoglobin concentration after IVIG therapy may be due to hemolytic anemia. Platelet counts are usually elevated by the end of the first week of illness (450,000/$\times 10^3/\mu$L ($\times 10^9$/L)) and may evolve into major thrombocytosis, with platelet counts averaging 700,000/$\times 10^3/\mu$L ($\times 10^9$/L) by the third week. Platelet counts exceeding 1 million/$\times 10^3/\mu$L ($\times 10^9$/L) are not uncommon. Relatively lower platelet counts at the time of presentation are a risk factor for later development of CALs, likely reflecting greater adherence of platelets to an activated endothelium. Rarely, marked thrombocytopenia at diagnosis may be due to diffuse intravascular coagulation.

Inflammatory markers are elevated in nearly all patients with KD. The erythrocyte sedimentation rate (ESR) and CRP should be assessed at the time of diagnosis. The ESR after treatment with IVIG is often high as the protein load elevates the ESR and obscures the extent of disease activity; therefore, rechecking the ESR after treatment is not informative. Nonetheless, measurements of the ESR can be helpful in assessing the degree of inflammation at diagnosis. Levels of CRP are unaffected by IVIG and can be used in the acute and subacute phases to gauge the degree of inflammation.

Transaminase levels are elevated in approximately 40% of patients with KD, and a mild hyperbilirubinemia can occur. Plasma γ-glutamyl transpeptidase levels are elevated in approximately two-thirds of patients with KD. Sterile pyuria (ie, culture negative) with a white blood cell count of at least 12/μL ($\geq 0.01\times 10^9$/L) is present in approximately 80% of patients with KD. Such pyuria may also be found in children with other febrile illnesses, but the magnitude is greater in patients with KD. Laboratory findings such as hypoalbuminemia and hyponatremia reflect more severe illness and can be associated with capillary leak. Lipid panels in patients with 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, may also be elevated but are not routinely obtained.

Although laboratory studies are not a component of the classical criteria for KD, they are included in the algorithm for treatment of suspected incomplete KD because many of the laboratory abnormalities described previously herein are seen consistently in KD.

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

Cardiac Imaging

Echocardiography is an excellent imaging modality to evaluate coronary artery dimensions in infants and children. In addition, this imaging modality provides evaluation of myocardial function, valve regurgitation, and pericardial effusion. It is noninvasive and in experienced hands has high sensitivity and specificity for dilatation in the proximal coronary arteries. Sedation is often 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 an echocardiogram. Two-dimensional echocardiograms 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 with definite or suspected KD should undergo assessment of each coronary artery, including the left main coronary artery, LAD, left circumflex coronary artery, right coronary artery (RCA), and posterior descending coronary artery. The proximal LAD and RCA are most commonly affected 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 dilatation. 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 younger than 5 years and an internal lumen diameter greater than 4 mm abnormal in children 5 years or older. In addition, artery segments that are 1.5 times or more larger than the adjacent section and segments with an irregular coronary lumen are also considered abnormal. As coronary artery dimensions change with the size of the child, body surface area–adjusted coronary dimensions (*z* scores) should also 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 large (>8-mm internal diameter) when using absolute dimensions.

The appearance of the coronary arteries is also informative. In most children with KD, coronary diameters are greatest at the first echocardiogram performed early in the disease. (8) 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, an ejection fraction more than 2 standard deviations below normal, occurs in 20% of children with acute KD. Histologic studies suggest that myocarditis is universal in patients with KD and can be severe enough to produce a clinical picture consistent with shock. The myocarditis rapidly improves 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 performed at diagnosis, 1 to 2 weeks later, and 5 to 6 weeks after hospital discharge. Importantly, children with persistent or recrudescent fever or with coronary artery dilatation (even mild dilatation at baseline echocardiography) need more frequent monitoring to inform treatment decisions, and close follow-up with a pediatric cardiologist is essential. The frequency of echocardiography in children with CALs should be tailored to the degree of enlargement in the coronary artery, the stability of coronary dimensions (ie, more frequent echoes should be performed when coronary dimensions are enlarging), and the patient's severity of inflammation. Children with giant coronary aneurysms in the acute and subacute phases of illness benefit from frequent (eg, twice weekly) echocardiographic surveillance for thrombus formation. Thrombi that occlude or nearly occlude the vessel lumen require thrombolytic therapy, ideally in the hands of experts in cardiology, hematology, and intensive care.

Although echocardiography is the preferred method of visualizing the coronary arteries early after KD, more comprehensive imaging of coronary arteries in children with significant coronary artery aneurysms is obtained using techniques of computed tomographic angiography, magnetic resonance angiography, or cardiac catheterization.

Based on the clinical findings, the child is diagnosed as having KD and is prescribed IVIG (2 g/kg) and aspirin (ASA) (30–50 mg/kg per day divided every 6 hours).

MANAGEMENT

Once the diagnosis of KD is confirmed, treatment with high-dose IVIG (2 g/kg) and ASA 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, or those with evidence of systemic inflammation on laboratory studies and coronary artery abnormalities. To avoid infusion reactions, premedication with standard dosing of diphenhydramine or another antihistamine should be strongly considered. In addition, IVIG should be administered slowly, over 8 to 12 hours, to avoid hemodynamic instability. Use of IVIG can be associated with low-grade fevers within the first 48 hours of its administration. Hemolytic reactions to IVIG are well described and have become more frequent in recent years, although the reason for the rise in incidence is unclear. The risk of hemolysis is typically dose dependent (ie, patients who received >1 dose of IVIG are at higher risk). Children with non-O blood types are at risk for

hemolysis. Approximately 15% of children with KD will have recurrent or persistent fever after the first dose of IVIG and are 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, there have been trials of corticosteroid therapy in KD. Corticosteroids 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, they can be given in high pulse doses of 30 mg/kg of intravenous methylprednisolone or in lower doses (0.5–2 mg/kg per day) of prednisolone orally. The use of corticosteroids in KD has an interesting history, as an early report raised the possibility of corticosteroids worsening coronary artery disease. However, subsequent studies indicated a likely beneficial effect in children. The RAISE trial (Randomized controlled trial to Assess Immunoglobulin plus Steroid Efficacy in Kawasaki Disease) by Kobayashi et al (9) 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. This study met the primary end point of reduction in coronary artery abnormalities, and all secondary end points, including *z* scores of coronary arteries, duration of fever after enrollment, and need for additional rescue treatment. However, this regimen has not been formally tested in non-Japanese populations, and it involved a prolonged course of intravenous corticosteroids 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 KD include infliximab, a tumor necrosis factor inhibitor (5 mg/kg per dose). Retrospective data indicated that infliximab might decrease the number of days of fever but not alter coronary artery outcomes. Similarly, results of a prospective trial using infliximab as primary therapy did not demonstrate a decrease in CALs at the end of the study period. (10) Last, there are reports from Japan (11) and the United States that calcineurin inhibitors such as cyclosporine may be effective in patients with IVIG resistance; the results of a prospective Japanese trial are awaited.

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 the use of ASA does not impact the development of CALs. 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 recently studied. In KD, ASA is given at medium (30–50 mg/kg per day) to high (80–100 mg/kg per day) divided doses every 6 hours initially, followed by antithrombotic doses of 3 to 5 mg/kg per day in once-daily dosing. Because ASA does not change coronary artery outcomes, it is reasonable to give medium-range doses of ASA and avoid the potential toxicity of high-dose ASA.

There is practice variation in the duration of high-dose ASA administration. Some practitioners give higher doses of ASA until patients are afebrile for 48 hours, and others continue with high-dose ASA for 2 weeks. Low-dose ASA treatment is typically discontinued if the echocardiographic findings are normal at the 6-week visit. Children with persistent CALs at 6 weeks continue taking low-dose ASA, and yearly influenza vaccinations are strongly recommended in those cases to decrease the risk of Reye syndrome. Patients receiving long-term ASA 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. For patients with moderate to large aneurysms, a second antiplatelet agent may be added to ASA. Children with 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 with KD remains an area of research. Statins have both cholesterol-lowering and immunomodulatory properties. In a small study of 11 children with KD and CALs, use of a statin for 3 months resulted in improved flow-mediated dilation (an indication of endothelial health) and CRP levels. 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 with aneurysms is lower because of data suggesting their susceptibility to atherosclerosis.

The patient tolerates her IVIG infusion without complication and defervesces within the subsequent 48 hours. Her tachycardia resolves. On examination, the conjunctival injection significantly improves, as does the rash. On discharge, she is well appearing and prescribed half a baby ASA (40.5 mg) daily. She is scheduled for an appointment with the cardiology department in 1 to 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 CALs 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 half of the 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 compared with smaller lesions.

Management of children with major coronary artery disease may require a combination of β-blockers to decrease oxidative stress and antithrombotic therapy. These children are followed closely with assessment of coronary function (eg, exercise stress echocardiography in children old enough to run on a treadmill and dobutamine stress cardiac MRI for younger children) and structure (eg, echocardiography, coronary angiography by CT, MRI, or cardiac catheterization). In those who develop symptoms of angina or findings of reversible ischemia on stress testing, percutaneous coronary intervention, for example with coronary stents, or coronary artery bypass surgery may be indicated. A report from Japan that followed patients with giant aneurysms into adulthood found that long-term survival is relatively good in patients with giant aneurysms despite their need for multiple catheterizations and surgeries. (12)

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

Fortunately, most children with KD do well after receiving a single dose of IVIG, with rapid clinical improvement and reassuring echocardiographic findings. A study of Californian adults who had developed KD as children (average age at time of analysis was 21 years) revealed a low rate of cardiovascular complications. (13)

The risk of premature atherosclerosis in patients with always-normal coronary arteries will not be known definitively until large cohorts of middle-aged patients with 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 should be counseled regarding a healthy lifestyle and avoidance of modifiable cardiac risk factors, such as obesity, smoking, and a sedentary lifestyle.

Summary

- Patients with acute Kawasaki disease (KD) should be treated promptly with intravenous immunoglobulin (IVIG) to prevent coronary artery abnormalities (based on strong research evidence). (14)
- Patients who have persistent or recrudescent fever after primary therapy with IVIG should receive additional immunomodulatory therapy. The most common practice is administration of a second dose of IVIG at 2 g/kg (based primarily on expert consensus). (15) Other secondary therapies to consider include corticosteroids (16)(17) and infliximab (18) (based on some research evidence).
- Echocardiography is an excellent modality for assessing proximal coronary artery changes in infants and young children with early KD.
- In patients with KD and always-normal coronary arteries, preventive cardiology counseling and follow-up is recommended until further studies delineate the long-term consequences on endothelial health (based on limited research evidence as well as consensus). (15)
- In patients with KD and coronary aneurysms, cardiologic follow-up is tailored to the degree of coronary artery involvement and involves serial assessment of coronary function and structure (based on strong research evidence). (15)

References for this article are at http://pedsinreview.aappublications.org/content/39/2/78.

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1. A 3-year-old Korean boy in your practice was evaluated in the emergency department over the weekend for 5 days of fever, rash, and conjunctivitis. He was admitted to the hospital with the diagnosis of Kawasaki disease (KD). Physical examination on admission was consistent with findings of KD, including fever, a polymorphous nonpruritic rash, conjunctivitis, and mucosal findings. Laboratory studies on admission showed a complete blood cell count with a white blood cell count of 18,000/μL (18×10^9/L) (80% neutrophils) and a platelet count of $600\times10^3/\mu$L (600×10^9/L). A complete metabolic panel was significant for a sodium level of 129 mEq/L (129 mmol/L) and mildly elevated liver enzyme levels. His C-reactive protein level was 88 mg/L (838 nmol/L), and his erythrocyte sedimentation rate was 68 mm/hour. Results of a rapid strep test were negative. A throat culture is pending. He was started on intravenous immunoglobulin (IVIG) per protocol. The parents are concerned about the prognosis and the response to treatment. In assessing his prognostic factors, which of the following factors does not place him at higher risk for a poor outcome?
   A. Age.
   B. Elevated C-reactive protein level.
   C. Sex.
   D. Hyponatremia.
   E. Race.
2. A 5-year-old girl presents to the clinic with 7 days of fever that responds occasionally to acetaminophen. Her physical examination is significant for an erythematous tongue, bilateral conjunctival injection, a maculopapular rash, and cervical lymphadenopathy. She is diagnosed as having KD. Which of the following clinical findings on examination of her hands and feet is most likely to be seen during the acute phase of the disease in this patient?
   A. Bruising of the fingers and toes.
   B. Desquamation of the fingers and toes.
   C. Firm swelling of the palms and soles.
   D. Hemarthrosis of the ankles and wrists.
   E. Lytic lesions in the long bones of the upper and lower extremities.
3. The patient in question 2 is admitted to the hospital for evaluation and management. In determining whether this patient will need to have further infectious evaluation for bacteria and viruses, which of the following represents the percentage of children with KD who might have a coexisting infection?
   A. 10%.
   B. 30%.
   C. 50%.
   D. 70%.
   E. 80%.
4. A 4-year-old Pacific Islander boy is diagnosed as having KD on day 6 of illness. He is admitted to the hospital for further management. Laboratory studies are obtained, and an intravenous peripheral line is placed. Which of the following is the most appropriate initial treatment regimen?
   A. Aspirin (40 mg/kg per day) plus IVIG (2 g/kg per day).
   B. Aspirin (100 mg/kg per day) plus solumedrol (30 mg/kg per day).
   C. Aspirin (80 mg/kg per day) plus solumedrol (2 mg/kg per day).
   D. IVIG (2 g/kg per day) plus cyclosporine (9 mg/kg per day).
   E. IVIG (2 g/kg per day) plus infliximab (5 mg/kg per dose).

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5. A 6-year-old girl is diagnosed as having KD on day 6 of illness and is treated with IVIG (2 g/kg) and aspirin (50 mg/kg per day). She is up to date on her immunizations. Follow-up echocardiography at 6 weeks shows persistent coronary artery lesions, and low-dose aspirin therapy is continued. She comes to her pediatrician for her yearly health supervision visit before starting school in the fall. Which of the following vaccines is recommended during this visit for this patient?

   A. Measles.
   B. Varicella.
   C. Influenza.
   D. Tetanus.
   E. No vaccines are recommended at this point.