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Kawasaki Disease

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Objectives   After completing this article, readers should be able to:

1. Describe the clinical and laboratory manifestations of Kawasaki disease (KD).
2. Describe the features of atypical, or incomplete, KD.
3. Discuss the value of high-dose aspirin and intravenous immune globulin (IVIG) in the treatment of KD and possible therapies for IVIG-refractory KD.
4. Identify the cardiac complications of KD and the importance of evaluation and follow-up.
5. Delineate the prognosis and management of KD.

Introduction

Kawasaki disease (KD) is an acute, self-limited vasculitis of unknown cause that has a striking predilection for the coronary arteries of infants and young children. First described in Japan in 1967 by Tomisaku Kawasaki, the disease now is known to occur in the Americas, Europe, and Asia in children of all races. In retrospect, the entity known as infantile polyarteritis nodosa likely is a part of the continuum of KD, and clinically mild KD probably was confused with diseases such as measles or scarlet fever before the advent of vaccines and antibiotics. In fact, old reports on infantile polyarteritis nodosa describe pathologic findings that are identical to those of fatal KD.

Epidemiology

KD is markedly more prevalent in Japan and in children of Japanese ethnicity, having an annual incidence of 150 cases per 100,000 children younger than 5 years of age, about 10 times the rate in the United States. In the United States, the incidence of KD has been estimated recently by using hospital discharge data. An estimated 4,248 hospitalizations associated with KD occurred in the United States in the year 2000, with a median age of 2 years. The incidence of KD was highest among Asians and Pacific Islanders and lowest in white children. Boys outnumbered girls by 3:2, and 76% of children were younger than age 5 years. In-hospital mortality was 0.17%. Virtually all deaths in patients who have KD result from cardiac sequelae. The peak mortality occurs 15 to 45 days after the onset of fever. However, sudden death from myocardial infarction (MI) may occur many years later in individuals who developed coronary artery aneurysms and stenoses in childhood. Many cases of ischemic heart disease in young adults have been attributed to "missed" KD in childhood.

Recurrence rates and the importance of genetic factors in KD are documented best in Japan, where the recurrence rate is approximately 3%. The proportion of cases that have a positive family history is approximately 1%. The risk of occurrence in twins is approximately 13%. These data suggest that a genetic predisposition interacts with an environmental etiologic agent to cause disease. The occasional occurrence of KD in children of parents who had KD in childhood also supports the contribution of genetic factors. Reported associations of KD with respiratory illnesses and exposure to carpet-cleaning fluids have not been confirmed.

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Causes and Pathogenesis

Although the cause of KD remains elusive, clinical and epidemiologic features strongly suggest an infectious source. A self-limited, generally nonrecurring illness that manifests with fever fits well with an infectious cause or trigger. Laboratory features also suggest an infectious agent as the cause of the inflammation. However, despite extensive efforts to identify an infectious agent in KD with conventional bacterial and viral cultures and serologic methods, researchers have not yet been successful in finding such an agent, although they are making progress. Recent investigations have discovered that the immune response in KD is oligoclonal or antigen-driven (ie, similar to a response to a conventional antigen) rather than polyclonal, and immunoglobulin A (IgA) plasma cells play a central role. The prominence of IgA plasma cells in the respiratory tracts of patients who had fatal acute-stage KD, which is similar to findings in fatal viral respiratory infections, suggests a respiratory pathogen.

KD is a generalized vasculitis affecting all blood vessels throughout the body, but preferentially involving the coronary arteries. The early stages in the development of vasculitis have been well studied in large muscular arteries. An influx of neutrophils is found early after onset, with a rapid transition to large mononuclear cells in concert with lymphocytes and IgA plasma cells. Active inflammation is replaced over several weeks to months by progressive fibrosis, with scar formation.

Diagnosis

Clinical criteria have been established to assist physicians in diagnosing KD because there is no definitive diagnostic test. The classic diagnosis of KD has been based on the presence of five or more days of fever and four or more of the five principal clinical features (Table 1). Those features are 1) changes in the hands and feet (erythema,

edema, peeling), 2) polymorphous exanthema, 3) bilateral bulbar conjunctival injection without exudate, 4) changes in the lips and oral cavity (erythema, strawberry tongue), and 5) cervical lymphadenopathy. Of course, exclusion of other diseases that have similar findings is necessary. Patients who have fever for 5 or more days and only three principal features can be diagnosed as having classic KD when coronary artery disease is detected by two-dimensional echocardiography or coronary angiography. The fever typically is high-spiking and remittent. In the absence of therapy, fever persists for a mean of 11 days. With appropriate therapy, fever usually resolves within 2 days.

Changes in the extremities include erythema of the palms and soles or firm, sometimes painful induration of the hands and feet and later desquamation of the fingers and toes. The desquamation usually begins in the periungual region within 2 to 3 weeks after the onset of fever and may extend to include the palms and soles. In addition, 1 to 2 months after the onset of fever, deep transverse grooves across the nails, known as Beau lines, may appear.

An erythematous rash usually appears within 5 days of the onset of fever. The rash may have various forms, but most common is a nonspecific diffuse rash consisting of scattered macules and erythematous papules. Bullous and vesicular eruptions have not been described in KD; if they are present, the physician should consider other diagnoses. Occasionally seen in KD are urticarial exanthems, a scarlatiniform rash, erythroderma, erythema multiforme, or rarely, a fine micropustular eruption. The rash is accentuated in the perineal region, where early desquamation may begin.

Bilateral painless conjunctival injection usually begins shortly after the onset of fever, typically involving the bulbar conjunctivae and usually not associated with an exudate or conjunctival edema. Changes of the lips and oral cavity are protean and include erythema, dryness, fissuring, peeling, cracking, and bleeding of the lips; a "strawberry tongue" that has erythema and prominent papillae; and diffuse erythema of the oropharyngeal mucosa. Oral ulcers and pharyngeal exudate are not seen.

Cervical lymphadenopathy is the least common of the principal clinical features. It usually is unilateral, is confined to the anterior cervical triangle, and is defined as 1.5 cm or more in diameter. The lymph nodes often are firm and nontender and have no overlying erythema.

Multiple other clinical findings can be seen in patients who have KD. Arthritis or arthralgia can occur in the first week and tends to involve multiple joints. Children who have KD often are more irritable than are children who

Table 1. Diagnostic Criteria for Kawasaki Disease

Fever for at least 5 days and four of the five following criteria:

- Bilateral conjunctival injection
- Changes of the mucous membranes of the upper respiratory tract: injected pharynx; infected, fissured lips; strawberry tongue
- Polymorphous rash
- Changes of the extremities: peripheral edema, peripheral erythema, periungual desquamation
- Cervical adenopathy

have other febrile illnesses. Gastrointestinal complaints, including diarrhea, vomiting, and abdominal pain, occur in approximately one third of patients. Hepatomegaly and jaundice can develop, as can acute acalculous distention of the gallbladder. In addition, up to 15% of affected patients have abnormal findings on chest radiography.

Laboratory Evaluation

Leukocytosis is typical during the acute stage of the illness, with a predominance of immature and mature granulocytes. About 50% of patients who have KD have white blood cell counts greater than 15.0×10^3/mcL (15.0×10^9/L). Anemia may develop, especially with a prolonged duration of active inflammation. Elevated values for the acute-phase reactants, such as erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP), are nearly universal in KD. Both the ESR and CRP should be measured, if possible, because of the potential for discordance of the values. For patients who already have been treated with intravenous immune globulin (IVIG), ESR is not useful as a marker of inflammation because an elevation can be the result of the IVIG therapy.

Thrombocytosis is a characteristic in the subacute stage of illness, with platelet counts ranging from 500.0 to $1,000.0\times10^3$/mcL (500.0 to $1,000.0\times10^9$/L) or more. Thrombocytosis peaks in the third week and gradually returns to normal by 4 to 8 weeks after onset of illness. Mild-to-moderate elevations in serum transaminases occur in 40% or fewer of patients, and mild hyperbilirubinemia is seen in approximately 10%. Hypoalbuminemia is common and is associated with more severe and more prolonged acute disease. Urinalysis reveals mild-to-moderate sterile pyuria in about one third of patients. If those who have KD undergo lumbar puncture, approximately 50% have evidence of aseptic meningitis, with a predominance of mononuclear cells, as well as normal glucose and protein concentrations.

Laboratory tests can provide diagnostic support for patients whose clinical presentations are suggestive but not diagnostic of KD. A moderately-to-markedly elevated CRP (≥30.0 mg/L [3.0 mg/dL]) or ESR (>40 mm/hr), for example, is nonspecific but nearly universal in KD, while unlikely in viral infections. Past experience suggests that KD is unlikely if platelet counts and acute-phase reactant values are normal after the seventh day of fever.

Incomplete or Atypical KD

Some patients do not fulfill the clinical criteria for KD and are diagnosed based on echocardiographic findings of coronary artery abnormalities. Therefore, the conven-

tional diagnostic criteria should be viewed as guidelines to prevent overdiagnosis, but strict adherence to the criteria may result in failure to recognize incomplete forms of KD. Incomplete, or atypical, KD is more common in young infants than in older children, making accurate diagnosis especially important because these patients are at higher risk for developing coronary abnormalities. Echocardiography is useful in diagnosing KD among patients who have only some of the classic features. Although aneurysms rarely form before day 10 of illness, some evidence of arteritis can be present in the acute stage of KD before the formation of aneurysms.

Incomplete KD should be considered in all infants and children who have unexplained fever for 5 or more days associated with two or three of the principal clinical features of KD. In addition, supplemental laboratory criteria, including albumin, hemoglobin, and transaminase measurements as well as urinalysis, can be used to support the diagnosis. Because young infants may present with fever and little else, echocardiography should be considered in any infant younger than 6 months who has fever lasting 7 days or more, laboratory evidence of systemic inflammation, and no other explanation for the febrile illness. An algorithm for the evaluation of children suspected of having incomplete KD is presented in the Figure.

Differential Diagnosis

Other febrile illnesses of childhood can mimic KD (Table 2). Measles, group A streptococcal or staphylococcal infections, and drug hypersensitivity reactions are the illnesses that resemble KD most closely. In addition, the differential diagnosis includes Stevens-Johnson syndrome, adenovirus infection, Rocky Mountain spotted fever, and Epstein-Barr virus infection. However, certain clinical features strongly suggest KD. Conjunctival injection in KD primarily is bulbar and usually is not accompanied by exudate. Lip redness and swelling can be severe enough to cause cracking and bleeding, and "strawberry tongue" is characteristic. Oral ulcers and exudative pharyngitis are not features of the illness. Tense swelling of the hands and feet is distinctive and rarely seen in other childhood febrile illnesses. Perineal accentuation of the rash is common in KD but not in other disorders. Vesicles, bullae, petechiae, and purpura are not seen. KD should be considered in the differential diagnosis of every child who has fever of at least several days' duration, rash, and nonpurulent conjunctivitis, especially in children younger than 1 year of age and in adolescents, in whom the diagnosis frequently is missed and treatment delayed.
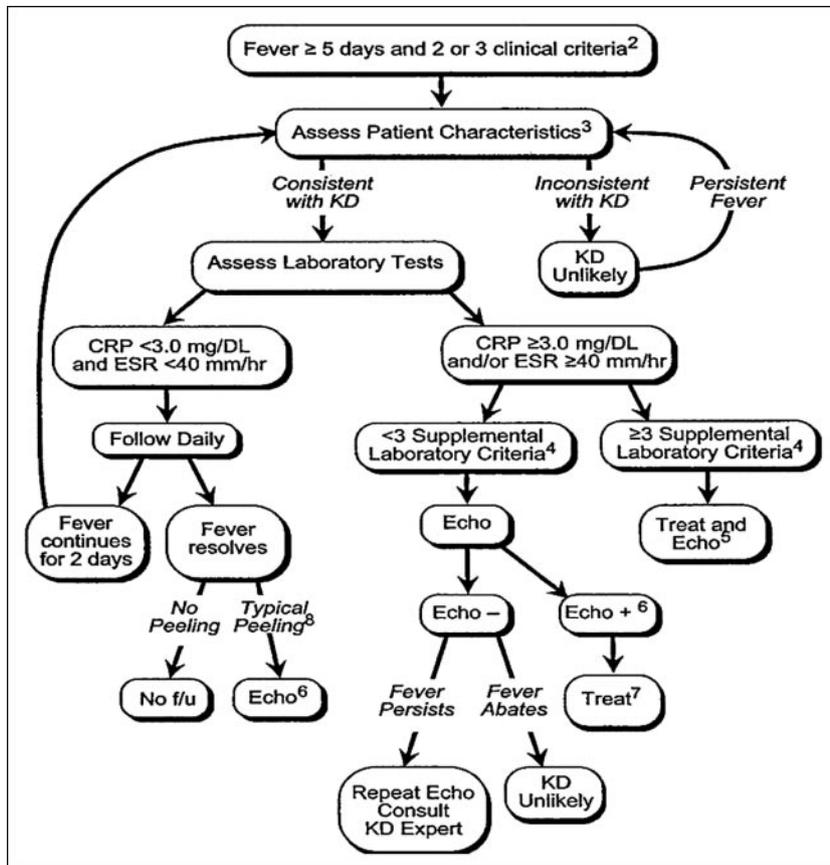
Figure. Evaluation of suspected incomplete Kawasaki disease (KD). 1) In the absence of a gold standard for diagnosis, this algorithm cannot be evidence–based but rather represents the informed opinion of the Expert Committee. Consultation with an expert should be sought anytime assistance is needed. 2) Infants 6 months old on day 7 of fever with no other explanation should undergo laboratory testing and, if evidence of systemic inflammation is found, echocardiography, even if the infants have no clinical criteria. 3) Characteristics suggesting KD are listed in Table 1. Character–istics 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 value of 3.0 g/dL (30.0 g/L), anemia for age, elevation of alanine aminotransferase, platelet count of more than 450.0×10^3/mcL (450.0×10^9/L) after 7 days, white blood cell count 15.0×10^3/mcL (15.0×10^9/L), and 10 white blood cells/high–power field in the urine. 5) Can treat before performing echocardiography (Echo). 6) Echocardiography is considered positive for purposes of this algorithm if any of three conditions are met: z score for left anterior descending or right coronary artery of 2.5; coronary arteries meet Japanese Ministry of Health criteria for aneurysms; or three other suggestive features exist, including perivascular brightness, lack of tapering, decreased left ventricular function, mitral regurgitation, pericardial effusion, or z scores in left anterior descending or right coronary artery of 2 to 2.5. 7) If echocardiography is positive, children should be treated within 10 days of fever onset and those beyond day 10 with clinical and laboratory signs (C–reactive protein, erythrocyte sedimentation rate) of ongoing inflammation. 8) Typical peeling begins under nail bed of fingers and then toes. CRP=C–reactive protein, ESR=erythrocyte sedimentation rate. 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. *Pediatrics*. 2004;114:1708–1733.

Cardiac Imaging

Cardiac imaging is critical in the evaluation of all patients who are suspected of having KD, and echocardiography has been determined to be the ideal imaging modality for cardiac assessment. Initial echocardiography should be performed as soon as the diagnosis is suspected, but treatment should not be delayed by the timing of the study. Cardiac evaluation of patients suspected of having KD should focus on maximal efforts to see all major coronary segments: the left main coronary artery (LMCA), left anterior descending artery (LAD), left circumflex coronary artery (LCX), right coronary artery (RCA), and the posterior descending coronary arteries. The most common sites of coronary aneurysms include the proximal LAD and proximal RCA, followed by the LMCA, then LCX, and finally the distal RCA and the junction between the RCA and the posterior descending coronary artery. In addition, assessment of left ventricular function should be a part of the echocardiographic evaluation of all patients in whom KD is suspected because some degree of myocarditis is almost universal. Myocarditis may manifest as chest pain or tachycardia that can occur out of proportion to the degree of fever, valvular dysfunction, and electrocardiographic changes. The presence of any pericardial effusion also should be noted on echocardiography.

Treatment

The current standard therapy for KD is a combination of aspirin and IVIG. In 1983, Japanese investigators reported that children treated with IVIG had faster resolving fever and developed fewer coronary artery abnormalities than did "historic" controls. A multicenter ran-

Table 2. Differential Diagnosis of Kawasaki Disease

- Viral infections (eg, measles, adenovirus, enterovirus, Epstein–Barr virus)
- Scarlet fever
- Staphylococcal scalded skin syndrome
- Toxic shock syndrome
- Bacterial cervical lymphadenitis
- Drug hypersensitivity
- Stevens–Johnson syndrome
- Juvenile idiopathic arthritis
- Leptospirosis
- Mercury hypersensitivity reaction (acrodynia)

domized trial in the United States showed that children treated with IVIG and high-dose aspirin had significantly faster resolution of fever and other inflammatory markers than did children treated with high-dose aspirin alone and confirmed that coronary artery abnormalities were reduced by about 85%. Subsequent studies have confirmed that initial therapy with IVIG and high-dose aspirin should be the standard therapy for KD.

During the acute phase of illness, aspirin is administered at 80 to 100 mg/kg per day in four doses along with IVIG. High-dose aspirin and IVIG appear to have an additive anti-inflammatory effect. Most clinicians continue high-dose aspirin until day 14 of illness if the child remains afebrile. When high-dose aspirin is discontinued, therapy is continued with low-dose aspirin at 3 to 5 mg/kg per day until the patient shows no evidence of coronary changes by 6 to 8 weeks after the onset of illness. This regimen applies to children who have no coronary abnormalities on initial echocardiography.

For children who develop coronary abnormalities, aspirin may be continued indefinitely. Aspirin has anti-inflammatory properties at high doses and antiplatelet activity at low doses but alone does not appear to lower the frequency of the development of coronary abnormalities. Because Reye syndrome is a risk in children who take salicylates while they are infected with varicella or influenza, parents should be instructed to contact their child's physician immediately if the child develops symptoms of or is exposed to influenza or varicella. Children on aspirin therapy should receive influenza immunizations routinely.

The efficacy of IVIG in reducing the prevalence of coronary artery abnormalities in KD is well established, despite the mechanism of action being unknown. IVIG appears to have a generalized anti-inflammatory effect.

Patients who have KD should be treated with IVIG (2 g/kg in a single infusion) together with high-dose aspirin. Whenever possible, this therapy should be started within the first 10 days of illness, with the first day of fever considered the first day of illness. IVIG also should be administered to children presenting with KD after the 10th day of illness if they have persistent fever with no other explanation or evidence of ongoing inflammation such as an elevated ESR or CRP, with or without coronary abnormalities. Measles and varicella immunizations should be deferred for 11 months after a child receives IVIG. Even when treated appropriately within the first 10 days of illness, approximately 5% of children who have KD develop some coronary artery dilation, and 1% develop giant aneurysms, defined as a greater than 8 mm internal diameter.

Despite steroids being highly effective in treating other forms of vasculitis, their use in KD has been limited. Steroids were the initial therapy for KD before the discovery of the efficacy of IVIG. Although early studies may have shown a detrimental effect of steroids, subsequent studies have shown neither benefit nor ill effects. A recent investigation examined the effect on coronary artery outcomes of pairing the initial dose of IVIG with a dose of intravenous methylprednisolone. The results did not support the addition of a single pulsed dose of steroids to conventional therapy because no significant effect was seen on the development of coronary artery abnormalities. However, there was a potential benefit in the subset of patients who required retreatment with IVIG because of persistent or recurrent fever and, therefore, were at greater risk for coronary abnormalities. More studies will need to be performed to delineate this effect further.

Approximately 10% of patients who have KD fail to respond to initial IVIG therapy. Failure to respond usually is defined as persistent or recrudescent fever 36 hours or more after completion of the initial IVIG infusion. Most experts recommend retreatment with IVIG at the same dose. Treatment of patients who have true IVIG-refractory KD, defined as persistent fevers or elevated inflammatory markers despite having received two courses of IVIG, is controversial. There is no universally accepted "next step" in therapy. Some clinicians use a third dose of IVIG. Steroids also have been used to treat patients whose disease is refractory to IVIG. Steroids have been shown to reduce fever, but the steroid effect on coronary abnormalities remains uncertain. The steroid regimen used most commonly is intravenous pulse methylprednisolone, 30 mg/kg for 2 to 3 hours, administered once daily for 3 days.

A class of agents that may play a role in the treatment of patients who have refractory KD is monoclonal antibodies to proinflammatory cytokines. A monoclonal antibody against tumor necrosis factor-alpha, infliximab, is being studied for treatment of children who fail to become afebrile after initial IVIG treatment. Although its effectiveness in reducing the prevalence of coronary artery aneurysms remains unproven, therapy with infliximab or other agents directed at tumor necrosis factor-alpha might be considered for patients who are refractory to IVIG.

Cytotoxic agents such as cyclophosphamide and methotrexate have been suggested as being useful for the treatment of refractory KD because they are used widely to treat other severe vasculitides. However, the risk of using cytotoxic agents may exceed the benefits for most patients, and they are not recommended routinely at this point. Because controlled data are lacking, the roles for these adjunctive therapies for IVIG-refractory patients remain uncertain. Ongoing research into various treatments is needed to guide clinicians in treating IVIG-refractory patients.

Long-term Follow-up and Outcome

The following features of the natural history of KD have been established, based on large series of patients from Japan and North America. Coronary artery aneurysms occur in 20% to 25% of untreated children. Other cardiovascular complications include myocarditis, pericarditis with effusion, and valvulitis, the latter occurring in about 1% of patients, most commonly involving the mitral valve. Resolution of aneurysms 1 to 2 years after disease onset has been observed in approximately 50% of vessels that have coronary aneurysms. The likelihood that an aneurysm will resolve is determined, in large part, by its initial size, with smaller aneurysms having a greater likelihood of regression. Vessels in which resolution does not occur are at risk for developing stenosis or occlusion by thrombus or myointimal proliferation. A coronary aneurysm can rupture within the first few months after KD, but this complication is exceedingly rare. The worst prognosis is noted in children who have giant aneurysms, where thrombosis is promoted by the sluggish and turbulent blood flow within the dilated vascular space and by the frequent occurrence of stenotic lesions at the proximal or distal end of the aneurysms.

MI caused by thrombotic occlusion of an abnormal coronary artery is the principal cause of death from KD. The greatest risk of MI occurs in the first year after disease onset. The general belief is that if coronary aneurysms are not identified by complete and adequate echocardiography in the first 1 to 2 months after diagnosis, the development of new aneurysms is unlikely. Children who have no known cardiac sequelae during the first month of KD appear to return to their previous state of health without signs or symptoms of cardiac impairment. However, limited evidence suggests possible long-term endothelial dysfunction in children who have no obvious coronary involvement, the significance of which is unknown.

Echocardiography should be performed at the time of diagnosis and subsequently usually at 2 and 6 weeks after disease onset. Children are stratified according to their relative risk of myocardial ischemia. Treatment can be individualized according to risk level, as recommended by the American Heart Association (Table 3). For children at higher risk, such as those who have persistent fever or coronary abnormalities, more frequent imaging may be necessary to guide management. Patients who have no coronary artery changes on echocardiography at any stage of the illness still should be counseled periodically about cardiovascular risk factors (eg, hypertension, diet, exercise) because the future risk for ischemic heart disease in this category of patients remains undetermined.

Patients who have small solitary aneurysms should take long-term aspirin therapy until the aneurysms regress and be followed by a pediatric cardiologist or other physician experienced in the management of KD. Patients who have giant aneurysms or multiple complex aneurysms should be considered candidates for long-term antiplatelet therapy and anticoagulation therapy. The choice of regimen depends on the degree of coronary enlargement. Regimens include combinations of aspirin, clopidogrel, heparin, and warfarin. Treatment with aspirin usually is sufficient for aneurysms that have a maximum diameter of 5 mm, whereas patients who have giant aneurysms generally are treated with a combination of aspirin and warfarin, aiming for an International Normalized Ratio of 2.0 to 2.5. Such severely affected patients should be followed by a cardiologist and have echocardiography, electrocardiography, and stress tests performed at regular intervals.

Other noninvasive tests may be used widely in the future to assess coronary stenoses, aneurysms, and occlusions. Multislice spiral computed tomography scan (MSCT) has been used successfully to "image" the distal segments of coronary arteries in adolescents and young adults to identify small areas of stenosis and aneurysm. Coronary magnetic resonance angiography (CMRA) also has been shown to define coronary artery aneurysms accurately as well as thickened vessel walls in free-breathing sedated children. In the future, MSCT and CMRA may be useful noninvasive alternatives for children who otherwise would need frequent catheterizations as they grow older.

Table 3. **Management of Kawasaki Disease**

Risk Level	Pharmacologic Therapy	Physical Activity	Follow-up and Diagnostic Testing	Invasive Testing
I (no coronary artery changes at any stage of illness)	None beyond first 6 to 8 weeks	No restrictions beyond first 6 to 8 weeks	Cardiovascular risk assessment, counseling at 5-year intervals	None recommended
II (transient coronary artery ectasia disappears within first 6 to 8 weeks)	None beyond first 6 to 8 weeks	No restrictions beyond first 6 to 8 weeks	Cardiovascular risk assessment, counseling at 3- to 5-year intervals	None recommended
III (1 small-to-medium coronary artery aneurysm/major coronary artery)	Low-dose aspirin (3 to 5 mg/kg per day), at least until aneurysm regression documented	For patients <11 years old, no restriction; patients 11 to 20 years old, physical activity guided by biennial stress test, evaluation of myocardial perfusion scan; contact or high-impact sports discouraged for patients taking antiplatelet agents	Annual cardiology follow-up of echocardiography+ECG combined with cardiovascular risk assessment, counseling; biennial stress test/evaluation of myocardial perfusion scan	Angiography, if noninvasive test suggests ischemia
IV (≥1 large or giant coronary artery aneurysm, multiple, or complex aneurysms in same coronary artery without obstruction)	Long-term antiplatelet therapy and warfarin (target International Normalized Ratio 2.0 to 2.5) or low-molecular-weight heparin (target antifactor Xa level 0.5 to 1.0 U/mL) should be combined in giant aneurysms	Contact or high-impact sports should be avoided because of risk of bleeding; other physical activity recommendations guided by stress test/ evaluation of myocardial perfusion scan	Biannual follow-up with echocardiography+ECG; annual stress test/evaluation of myocardial perfusion scan	First angiography at 6 to 12 months or sooner if clinically indicated; repeat angiography if noninvasive test, clinical, or laboratory findings suggest ischemia; elective repeat angiography under some circumstances
V (coronary artery obstruction)	Long-term low-dose aspirin; warfarin or low-molecular-weight heparin if giant aneurysm persists; consider use of beta blockers to reduce myocardial oxygen consumption	Contact or high-impact sports should be avoided because of risk of bleeding; other physical activity recommendations guided by stress test/ myocardial perfusion scan	Biannual follow-up with echocardiography+ECG; annual stress test/evaluation of myocardial perfusion scan	Angiography recommended to address therapeutic options

ECG=electrocardiography. Adapted 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. *Pediatrics.* 2004; 114:1708–1733.

Attempts at excising coronary artery aneurysms have been unsuccessful and have caused deaths. The primary surgical management of KD is coronary artery bypass grafts for obstructive lesions. Catheter interventions such as balloon angioplasty, rotational ablation, and stent placement have been performed in a relatively small number of children who have KD. Catheter intervention for patients who have KD should be considered when ischemic symptoms are present and in patients who have 75% or more stenosis with or without ischemia in the LAD. Approximately 20 patients who have KD have undergone cardiac transplantation for severe myocardial dysfunction, severe ventricular arrhythmias, and severe coronary arterial lesions. Cardiac transplantation should be considered for individuals who have severe, irreversible myocardial dysfunction and coronary lesions for which interventional catheterization procedures or coronary bypass are not feasible.

Conclusion

Although great progress has been made in the treatment of KD, much is left to learn about the cause of the illness. Until an etiologic agent is identified and a definitive diagnostic test devised, children who have KD still will be misdiagnosed (under- and overdiagnosed), and some who have KD will be untreated, suffering potentially serious morbidity or even mortality. Priorities for research are developing a diagnostic test, identifying genetic markers for susceptibility to KD, identifying prog- nostic factors, developing improved therapies, and discovering the cause of KD. The ultimate goal of KD research is to prevent the grave cardiac consequences of the disease, and critical to this goal is elucidation of the causative agent.

Suggested Reading

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PIR Quiz
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6. A 2-year-old child comes to the emergency department because of 6 days of fever (temperature to 102.0°F [38.9°C]), "pinkeye," red lips, and swollen hands and feet. His mother reports a rash today. You suspect Kawasaki disease but think the rash looks a bit atypical. Which of the following skin findings is the *most* suggestive of a diagnosis other than Kawasaki disease?

    A. Bullae on the hands and feet.
    B. Desquamation of the fingers and toes.
    C. Macules and papules over the trunk.
    D. Scarlatiniform rash over the back and chest.
    E. Urticaria over the back and chest.

7. Which of the following is the *most* typical physical examination finding in patients who have Kawasaki disease?

    A. Aphthous oral ulcers.
    B. Diffuse lymphadenopathy.
    C. Exudative conjunctivitis.
    D. Periungual desquamation.
    E. Purulent tonsillar exudates.

8. You are seeing an 18-month-old boy who has had 8 days of a temperature to 101.5°F (38.6°C), diffuse maculopapular rash, and erythematous and cracked lips. His eyes, hands, and feet appear normal, and he has no lymphadenopathy. You suspect incomplete Kawasaki disease and measure C-reactive protein and erythrocyte sedimentation rate, which are 50.0 mg/L (5.0 mg/dL) and 85 mm/hr, respectively. You order echocardiography for the next day. The following laboratory finding that is *most* suggestive of the need to treat Kawasaki disease at this time is:

   A. Elevated amylase concentration.
   B. Leukopenia.
   C. Metabolic acidosis.
   D. Polycythemia.
   E. Thrombocytosis.

9. A 3-year-old-girl who had typical features of Kawasaki disease was admitted to the hospital. Findings on echocardiography were normal. She was given 2 g/kg of intravenous immune globulin (IVIG) and 100 mg/kg of aspirin on admission. Two days after her treatment was initiated, she continues to have a temperature to 102.0°F (38.9°C) and her C-reactive protein concentration remains high, but her rash, conjunctivitis, and swollen hands and feet have improved. In addition to continuing high-dose aspirin therapy, which of the following is the *best* course of treatment at this time?

   A. Administer a 30-mg/kg dose of methylprednisolone.
   B. Discharge from the hospital with cardiology follow-up.
   C. Initiate treatment with cyclophosphamide.
   D. Reconsider the diagnosis and obtain viral titers and blood cultures.
   E. Repeat the 2-g/kg dose of IVIG.

10. You are evaluating a 5-year-old boy who had typical Kawasaki disease 8 weeks ago. He received one dose of IVIG and high-dose aspirin for 2 weeks, followed by low-dose aspirin, which he still is taking. He is asymptomatic and doing very well on restricted activity. Initial echocardiography showed mild coronary artery ectasia, but repeat imaging today shows completely normal findings. Of the following, the *most* appropriate management for this patient at this time is to:

   A. Add low-molecular-weight heparin, continue activity restriction, and repeat echocardiography in 2 months.
   B. Continue aspirin, continue activity restriction, and repeat echocardiography in 2 months.
   C. Discontinue aspirin, discontinue activity restriction, and initiate a cardiology follow-up in 3 years.
   D. Discontinue aspirin, continue activity restriction, and repeat echocardiography in 6 months.
   E. Discontinue aspirin, continue activity restriction, and initiate a cardiology follow-up in 1 year.

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