AHA Scientific Statement

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

Endorsed by the American Academy of Pediatrics

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Background—Kawasaki disease is an acute self-limited vasculitis of childhood that is characterized by fever, bilateral nonexudative conjunctivitis, erythema of the lips and oral mucosa, changes in the extremities, rash, and cervical lymphadenopathy. Coronary artery aneurysms or ectasia develop in ≈15% to 25% of untreated children and may lead to ischemic heart disease or sudden death.

Methods and Results—A multidisciplinary committee of experts was convened to revise the American Heart Association recommendations for diagnosis, treatment, and long-term management of Kawasaki disease. The writing group proposes a new algorithm to aid clinicians in deciding which children with fever for ≥5 days and ≤4 classic criteria should undergo echocardiography, receive intravenous gamma globulin (IVIG) treatment, or both for Kawasaki disease. The writing group reviews the available data regarding the initial treatment for children with acute Kawasaki disease, as well for those who have persistent or recrudescent fever despite initial therapy with IVIG, including IVIG retreatment and treatment with corticosteroids, tumor necrosis factor-α antagonists, and abciximab. Long-term management of patients with Kawasaki disease is tailored to the degree of coronary involvement; recommendations regarding antiplatelet and anticoagulant therapy, physical activity, follow-up assessment, and the appropriate diagnostic procedures to evaluate cardiac disease are classified according to risk strata.

Conclusions—Recommendations for the initial evaluation, treatment in the acute phase, and long-term management of patients with Kawasaki disease are intended to assist physicians in understanding the range of acceptable approaches for caring for patients with Kawasaki disease. The ultimate decisions for case management must be made by physicians in light of the particular conditions presented by individual patients. **(*Circulation.* 2004;110:2747-2771.)**

Key Words: AHA Scientific Statements ■ vasculitis ■ aneurysm ■ diagnosis ■ therapy

Kawasaki disease is an acute, self-limited vasculitis of unknown etiology that occurs predominantly in infants and young children. First described in Japan in l967 by Tomisaku Kawasaki, the disease is now known to occur in both endemic and community-wide epidemic forms in the Americas, Europe, and Asia in children of all races.[1] Kawasaki disease is characterized by fever, bilateral nonexudative conjunctivitis, erythema of the lips and oral mucosa, changes in the extremities, rash, and cervical lymphadenopathy. Coronary artery aneurysms or ectasia develop in ≈15% to 25% of untreated children with the disease and may lead to myocardial infarction (MI), sudden death, or ischemic heart

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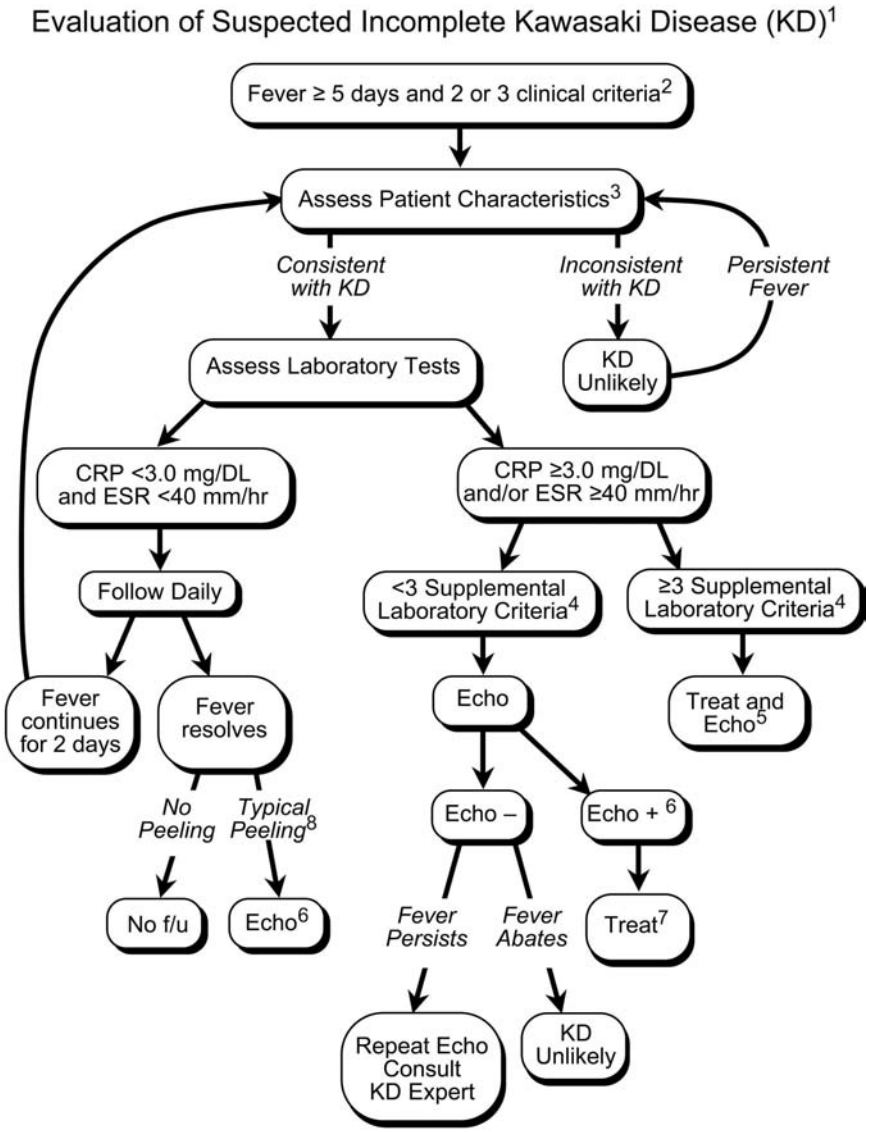

Figure 1. Evaluation of suspected incomplete Kawasaki disease. (1) In the absence of gold standard for diagnosis, this algorithm cannot be evidence based but rather represents the informed opinion of the expert committee. Consultation with an expert should be sought anytime assistance is needed. (2) Infants ≤6 months old on day ≥7 of fever without other explanation should undergo laboratory testing and, if evidence of systemic inflammation is found, an echocardiogram, even if the infants have no clinical criteria. (3) Patient characteristics suggesting Kawasaki disease are listed in Table 1. Characteristics suggesting disease other than Kawasaki disease 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 d ≥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 echocardiogram. (6) Echocardiogram 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 LV function, mitral regurgitation, pericardial effusion, or *z* scores in LAD or RCA of 2–2.5. (7) If the echocardiogram is positive, treatment should be given to children within 10 d 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.

disease.[2,3] In the United States, Kawasaki disease has surpassed acute rheumatic fever as the leading cause of acquired heart disease in children.[4] Treatment of Kawasaki disease in the acute phase is directed at reducing inflammation in the coronary artery wall and preventing coronary thrombosis, whereas long-term therapy in individuals who develop coronary aneurysms is aimed at preventing myocardial ischemia or infarction.

A new feature of these recommendations is an algorithm for the evaluation and treatment of patients in whom incomplete or atypical Kawasaki disease is suspected (refer to Criteria for Treatment of Kawasaki Disease later in this statement and Figure 1). We attempt to summarize the current state of knowledge of the management of patients with Kawasaki disease. The recommendations are evidence based and derived from published data wherever possible. The levels of evidence on which recommendations are based are classified as follows: level A (highest), multiple randomized clinical trials; level B (intermediate), limited number of randomized trials, nonrandomized studies, and observational registries; and level C (lowest), primarily expert consensus.

Recommendations for initial evaluation, treatment in the acute phase, and long-term management of patients with Kawasaki disease are intended to assist physicians in understanding the range of acceptable approaches for caring for patients with Kawasaki disease. Where published data do not define well the best medical practices, our report provides practical interim recommendations. Ultimately, management decisions must be individualized to a patient's specific circumstances.

Epidemiology

In the past, Kawasaki disease may have masqueraded as other illnesses, and old reports on infantile polyarteritis nodosa describe pathological findings that are identical to those of fatal Kawasaki disease.[5–8] Kawasaki disease is markedly more prevalent in Japan and in children of Japanese ancestry, with an annual incidence of ≈112 cases per 100 000 children <5 years old.[9] In the United States, the incidence of Kawasaki disease has been best estimated from hospital discharge data.[10,11] An estimated 4248 hospitalizations associated with Kawasaki disease occurred in the United States in

2000, with a median age of 2 years.[10] Race-specific incidence rates derived from administrative data indicate that Kawasaki disease is most common among Americans of Asian and Pacific Island descent (32.5/100 000 children <5 years old), intermediate in non-Hispanic African Americans (16.9/100 000 children <5 years old) and Hispanics (11.1/100 000 children <5 years old), and lowest in whites (9.1/100 000 children <5 years old).[10] These estimates are similar to those reported in smaller studies.[12,13] Recent reports have emphasized the occurrence of Kawasaki disease in older children, who may have a higher prevalence of cardiovascular complications related to late diagnosis.[14–16]

Rates of recurrence and familial occurrence of Kawasaki disease are best documented in the literature from Japan; these rates may be lower in other races and ethnicities. In Japan, the recurrence rate of Kawasaki disease has been reported to be ≈3%.[17] The proportion of cases with a positive family history is ≈1%.[17,18] Within 1 year after onset of the first case in a family, the rate in a sibling is 2.1%, which is a relative risk of ≈10-fold as compared with the unaffected Japanese population; ≈50% of the second cases develop within 10 days of the first case.[19] The risk of occurrence in twins is ≈13%.[19,20] Higher rates of Kawasaki disease in the siblings of index cases and twins suggest a possible role for genetic predisposition that interacts with exposure to the etiologic agent or agents in the environment.[19–22] The reported occurrence of Kawasaki disease in children of parents who themselves had the illness in childhood also supports the contribution of genetic factors.[23–26]

In the United States, Kawasaki disease is more common during the winter and early spring months; boys outnumber girls by ≈1.5 to 1.7:1; and 76% of children are <5 years old.[10,11] Reported associations of Kawasaki disease with antecedent respiratory illness and exposure to carpet-cleaning fluids have not been consistently confirmed.[12,13,27–30] Other factors that are reportedly associated with Kawasaki disease include having preexisting eczema,[31] using a humidifier,[30] and living near a standing body of water.[32]

The case fatality rate in Kawasaki disease in Japan is 0.08%.[17] The standardized mortality ratio (the observed number of deaths divided by the expected number of deaths based on vital statistics in Japan) in patients diagnosed between 1982 and 1992 was 1.25 (95% CI, 0.84 to 1.85) overall and 2.35 (95% CI, 0.96 to 5.19) for boys with cardiac sequelae.[33] In the United States, the in-hospital mortality rate is ≈0.17% (the investigators used administrative data that may include readmissions for coronary disease).[15] Virtually all deaths in patients with Kawasaki disease result from its cardiac sequelae.[34] The peak mortality occurs 15 to 45 days after the onset of fever; during this time well-established coronary vasculitis occurs concomitantly with a marked elevation of the platelet count and a hypercoagulable state.[35] However, sudden death from MI may occur many years later in individuals who as children had coronary artery aneurysms and stenoses. Many cases of fatal and nonfatal MI in young adults have been attributed to "missed" Kawasaki disease in childhood.[36]

Etiology and Pathogenesis

The etiology of Kawasaki disease remains unknown, although clinical and epidemiological features strongly suggest an infectious cause. A self-limited, generally nonrecurring illness that manifests itself by fever, rash, enanthem, conjunctival injection, and cervical adenopathy fits well with an infectious etiology or trigger. The epidemiological features noted above, including age distribution, winter–spring seasonality, occurrence of community outbreaks with wave-like geographic spread, and apparent epidemic cycles, are suggestive of a transmissible childhood disease. The laboratory features also suggest infection. However, efforts to identify an infectious agent in Kawasaki disease with conventional bacterial and viral cultures and serological methods, as well as with animal inoculation, have failed to identify an infectious cause.

An attractive hypothesis is that Kawasaki disease is caused by a ubiquitous infectious agent that produces clinically apparent disease only in certain genetically predisposed individuals, particularly Asians. Its rarity in the first few months of life and in adults suggests an agent to which the latter are immune and from which very young infants are protected by passive maternal antibodies. Because little evidence exists of person-to-person transmission, this hypothesis assumes that most infected children experience asymptomatic infection with only a small fraction developing overt clinical features of Kawasaki disease. The genetic basis of susceptibility is currently unknown.

The hypothesis that Kawasaki disease is related to a bacterial superantigenic toxin has been suggested because of the reported selective expansion of Vβ2 and Vβ8 T-cell receptor families, but this theory remains controversial.[37–40] A recent prospective multicenter study failed to show a significant difference in the prevalence of toxin-producing strains between patients with Kawasaki disease and febrile controls.[41] Recent investigations support an alternative hypothesis: The immune response in Kawasaki disease is oligoclonal (antigen driven, ie, similar to a response to a conventional antigen) rather than polyclonal (as found typically in superantigen-driven responses), and immunoglobulin A (IgA) plasma cells play a central role.[42–44]

It also is possible that Kawasaki disease results from an immunologic response that is triggered by any of several different microbial agents. Support for this hypothesis includes documented infection by different microorganisms in different individual cases, failure to detect a single microbiological or environmental agent after almost 3 decades of study, and analogies to other syndromes caused by multiple agents (eg, aseptic meningitis). This hypothesis is somewhat difficult to reconcile with the distinctive clinical/laboratory picture of Kawasaki disease and with its epidemiological features, however.

Efforts to associate Kawasaki disease with exposure to drugs or to such environmental pollutants as toxins, pesticides, chemicals, and heavy metals have failed, although clinical similarities between Kawasaki disease and acrodynia (mercury hypersensitivity) are notable.

Striking immune perturbations occur in acute Kawasaki disease, including marked cytokine cascade stimulation and

endothelial cell activation. The key steps leading to coronary arteritis are still being clarified, but endothelial cell activation, $CD68^+$ monocyte/macrophages, $CD8^+$ (cytotoxic) lymphocytes, and oligoclonal IgA plasma cells appear to be involved.[43,45] The prominence of IgA plasma cells in the respiratory tract, which is similar to findings in fatal viral respiratory infections, suggests a respiratory portal of entry of an etiologic agent or agents.[44] Enzymes including matrix metalloproteinases that are capable of damaging arterial wall integrity may be important in the development of aneurysmal dilatation.[46] Vascular endothelial growth factor (VEGF), monocyte chemotactic and activating factor (MCAF or MCP-1), tumor necrosis factor-α (TNF-α), and various interleukins also appear to play important roles in the vasculitic process.[47–54]

Pathology

Although the coronary arteries virtually always are involved in autopsy cases, Kawasaki disease is a generalized systemic vasculitis involving blood vessels throughout the body. Aneurysms may occur in other extraparenchymal muscular arteries, such as the celiac, mesenteric, femoral, iliac, renal, axillary, and brachial arteries.[55] The early stages in the formation and development of arteritis in Kawasaki disease have been well studied morphologically in relatively large muscular arteries.[55] The media of affected vessels demonstrate edematous dissociation of the smooth muscle cells, which is most obvious toward the exterior. Endothelial cell swelling and subendothelial edema are seen, but the internal elastic lamina remains intact. An influx of neutrophils is found in the early stages (7 to 9 days after onset), with a rapid transition to large mononuclear cells in concert with lymphocytes (predominantly $CD8^+$ T cells) and IgA plasma cells.[42–45] Destruction of the internal elastic lamina and eventually fibroblastic proliferation occur at this stage. Matrix metalloproteinases are prominent in the remodeling process.[56] Active inflammation is replaced over several weeks to months by progressive fibrosis, with scar formation.

Arterial remodeling or revascularization may occur in Kawasaki disease with coronary arteritis. Progressive stenosis in the disease results from active remodeling with intimal proliferation and neoangiogenesis; the intima is markedly thickened and consists of linearly arranged microvessels, a layer that is rich in smooth muscle cells, and fibrous layers. Several growth factors are prominently expressed at the inlet and outlet of aneurysms, where they are activated by high shear stress.[57]

During the clinical course of Kawasaki disease, vomiting and abdominal pain are seen often. Kurashige and colleagues described the intestinal tract in 31 fatal cases, but in only 3 patients was mesenteric arteritis found.[58] Using biopsy specimens of the jejunal mucosa, Nagata et al studied cell surface phenotypes of mononuclear cells and enterocytes.[59] Both $HLA\text{-}DR^+CD3^+$ (activated T cells) and DR^+CD4^+ cells (activated helper T cells) were significantly increased in the lamina propria of patients with acute Kawasaki disease as compared with controls. In contrast, $CD8^+$ cells (suppressor/cytotoxic T cells) were significantly reduced in both the epithelium and the lamina propria of individuals with Kawasaki disease as compared with controls. During the convalescent phase of the disease, these cell patterns returned to normal.[59] Hydrops of the gallbladder may be clinically apparent in patients with Kawasaki disease. A study of surgically removed gallbladders revealed a nonspecific severe perivascular inflammatory cell infiltration[60]; distinct arteritis in the gallbladder wall has not been well documented.

Lymphadenopathy, an early finding in patients with Kawasaki disease, usually disappears by autopsy. Pathological findings in lymph nodes include thrombotic arteriolitis and severe lymphadenitis with necrosis.[55] Lymph node biopsies performed in the first week of the illness revealed abnormal hyperplasia of the endothelium of the postcapillary venule and hyperplasia of reticular cells around the postcapillary venule.[1]

Diagnosis

In the absence of a specific diagnostic test or pathognomonic clinical feature, clinical criteria have been established to assist physicians in diagnosing Kawasaki disease. Other clinical and laboratory findings observed in patients with this disease are frequently helpful in diagnosis. Table 1 describes the clinical and laboratory features of Kawasaki disease according to the epidemiological case definition.

Principal Clinical Findings

The classic diagnosis of Kawasaki disease has been based on the presence of $\geq$5 days of fever and $\geq$4 of the 5 principal clinical features (see Table 1).[3] Typically, all of the clinical features are not present at a single point in time, and watchful waiting is sometimes necessary before a diagnosis can be made. Patients with fever for $\geq$5 days and $<$4 principal features can be diagnosed as having Kawasaki disease when coronary artery disease is detected by 2D echocardiography (2DE) or coronary angiography. In the presence of $\geq$4 principal criteria, the diagnosis of Kawasaki disease can be made on day 4 of illness. Kawasaki disease should be considered in the differential diagnosis of a young child with unexplained fever for $\geq$5 days that is associated with any of the principal clinical features of this disease.

The fever typically is high spiking and remittent, with peak temperatures generally $>$39°C (102°F) and in many cases $>$40°C (104°F). In the absence of appropriate therapy, fever persists for a mean of 11 days, but it may continue for 3 to 4 weeks and, rarely, even longer. With appropriate therapy, the fever usually resolves within 2 days.

Changes in the extremities are distinctive. Erythema of the palms and soles or firm, sometimes painful induration of the hands or feet, or both erythema and induration often occur in the acute phase of the disease. Desquamation of the fingers and toes 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. Approximately 1 to 2 months after the onset of fever, deep transverse grooves across the nails (Beau's lines) may appear.

An erythematous rash usually appears within 5 days of the onset of fever. The rash may take various forms; the most common is a nonspecific, diffuse maculopapular eruption. Occasionally seen are an urticarial exanthem, a scarlatiniform

TABLE 1. Clinical and Laboratory Features of Kawasaki Disease

Epidemiological case definition (classic clinical criteria)*
Fever persisting at least 5 d†
Presence of at least 4 principal features:
Changes in extremities
Acute: Erythema of palms, soles; edema of hands, feet
Subacute: Periungual peeling of fingers, toes in weeks 2 and 3
Polymorphous exanthem
Bilateral bulbar conjunctival injection without exudate
Changes in lips and oral cavity: Erythema, lips cracking, strawberry tongue, diffuse injection of oral and pharyngeal mucosae
Cervical lymphadenopathy (>1.5-cm diameter), usually unilateral
Exclusion of other diseases with similar findings‡
Other clinical and laboratory findings
Cardiovascular findings
Congestive heart failure, myocarditis, pericarditis, valvular regurgitation
Coronary artery abnormalities
Aneurysms of medium-size noncoronary arteries
Raynaud's phenomenon
Peripheral gangrene
Musculoskeletal system
Arthritis, arthralgia
Gastrointestinal tract
Diarrhea, vomiting, abdominal pain
Hepatic dysfunction
Hydrops of gallbladder
Central nervous system
Extreme irritability
Aseptic meningitis
Sensorineural hearing loss
Genitourinary system
Urethritis/meatitis
Other findings
Erythema, induration at Bacille Calmette-Guérin (BCG) inoculation site
Anterior uveitis (mild)
Desquamating rash in groin
Laboratory findings in acute Kawasaki disease
Leukocytosis with neutrophilia and immature forms
Elevated erythrocyte sedimentation rate
Elevated C-reactive protein
Anemia
Abnormal plasma lipids
Hypoalbuminemia
Hyponatremia
Thrombocytosis after week 1§
Sterile pyuria
Elevated serum transaminases
Elevated serum gamma glutamyl transpeptidase
Pleocytosis of cerebrospinal fluid
Leukocytosis in synovial fluid

*Patients with fever at least 5 d and <4 principal criteria can be diagnosed with Kawasaki disease when coronary artery abnormalities detected by 2-D echocardiography or angiography.

†In presence of ≥4 principal criteria, Kawasaki disease diagnosis can be made on day 4 of illness. Experienced clinicians who have treated many Kawasaki disease patients may establish diagnosis before day 4.

‡See Table 2.

§Some infants present with thrombocytopenia and disseminated intravascular coagulation.

TABLE 2. Differential Diagnosis of Kawasaki Disease: Diseases and Disorders With Similar Clinical Findings

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

rash, an erythroderma, an erythema-multiforme–like rash, or, rarely, a fine micropustular eruption. Bullous and vesicular eruptions have not been described. The rash usually is extensive, with involvement of the trunk and extremities and accentuation in the perineal region, where early desquamation may occur.

Bilateral conjunctival injection usually begins shortly after the onset of fever. It typically involves the bulbar conjunctivae (sparing the limbus, an avascular zone around the iris) much more often than the palpebral or tarsal conjunctivae; is not associated with an exudate, conjunctival edema or corneal ulceration; and usually is painless. Mild acute iridocyclitis or anterior uveitis may be noted by slit lamp; it resolves rapidly and rarely is associated with photophobia or eye pain.

Changes of the lips and oral cavity include (1) erythema, dryness, fissuring, peeling, cracking, and bleeding of the lips; (2) a "strawberry tongue" that is indistinguishable from that associated with streptococcal scarlet fever, with erythema and prominent fungiform papillae; and (3) diffuse erythema of the oropharyngeal mucosae. Oral ulcerations and pharyngeal exudates are not seen.

Cervical lymphadenopathy is the least common of the principal clinical features. It is usually unilateral and confined to the anterior cervical triangle, and its classic criteria include ≥1 lymph node that is >1.5 cm in diameter. Imaging studies frequently demonstrate multiple enlarged nodes without suppuration.[61] The lymph nodes often are firm and nonfluctuant, are not associated with marked erythema of the overlying skin, and are nontender or only slightly tender. Occasionally, the lymph node swelling of Kawasaki disease can be confused with bacterial adenitis.

Because the principal clinical findings that fulfill the diagnostic criteria are not specific, other diseases with similar clinical features should be excluded (Table 2).

Other Clinical and Laboratory Findings

Cardiac Findings

Cardiovascular manifestations can be prominent in the acute phase of Kawasaki disease and are the leading cause of long-term morbidity and mortality. During this phase, the pericardium, myocardium, endocardium, valves, and coronary arteries all may be involved. Cardiac auscultation of the

infant or child with Kawasaki disease in the acute phase often reveals a hyperdynamic precordium, tachycardia, a gallop rhythm, and an innocent flow murmur in the setting of anemia, fever, and depressed myocardial contractility secondary to myocarditis. Children with significant mitral regurgitation may have a pansystolic regurgitant murmur that is typical of this condition. Occasionally, patients with Kawasaki disease and poor myocardial function may present with low cardiac output syndrome or shock. Electrocardiography may show arrhythmia, prolonged PR interval, or nonspecific ST and T wave changes.

Noncardiac Findings

Multiple noncardiac clinical findings may be observed in patients with Kawasaki disease. Arthritis or arthralgia can occur in the first week of the illness and tends to involve multiple joints, including the small interphalangeal joints as well as large weight-bearing joints. Arthritis or arthralgia developing after the 10th day of illness favors large weight-bearing joints, especially the knees and ankles.

Children with Kawasaki disease often are more irritable than are children with other febrile illnesses. Transient unilateral peripheral facial nerve palsy occurs rarely. Transient high-frequency sensorineural hearing loss (20 to 35 dB) can occur during acute Kawasaki disease,[62,63] but persistent sensorineural hearing loss is rare.[64] Gastrointestinal complaints, including diarrhea, vomiting, and abdominal pain, occur in approximately one third of patients. Rarely, Kawasaki disease can present as an acute surgical abdomen.[65] Hepatic enlargement and jaundice can occur. Acute acalculous distention of the gallbladder (hydrops) occurs in ≈15% of patients during the first 2 weeks of the illness and can be identified by abdominal ultrasound.[60] Erythema and induration at the site of a previous vaccination with Bacille Calmette-Guérin (BCG) is common in Japan, where BCG is used widely.[66] Rare findings include testicular swelling, pulmonary nodules[50] and infiltrates,[67] pleural effusions, and hemophagocytic syndrome.[68]

Laboratory Findings

Leukocytosis is typical during the acute stage of Kawasaki disease, with a predominance of immature and mature granulocytes. Approximately 50% of patients have white blood cell counts >15 000/mm^3. Leukopenia is rare. Anemia may develop, usually with normal red blood cell indexes, particularly with more prolonged duration of active inflammation. Severe hemolytic anemia requiring transfusions is rare and may be related to intravenous immunoglobulin (IVIG) infusion.[69–72] Elevation of acute phase reactants, such as erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP), is nearly universal in Kawasaki disease, usually returning to normal by 6 to 10 weeks after onset of the illness. Because the degree of elevation of ESR and CRP may show a discrepancy in some patients at the time of presentation, both should be measured.[73] Furthermore, elevation of ESR (but not of CRP) can be caused by IVIG therapy per se; therefore, ESR should not be used as the sole determinant of the degree of inflammatory activity in IVIG–treated patients.

A characteristic feature of the later phases of the illness is thrombocytosis, with platelet counts ranging from 500 000 to >1 million/mm^3. Thrombocytosis rarely is present in the first week of the illness, usually appears in the second week, and peaks in the third week with a gradual return to normal by 4 to 8 weeks after onset in uncomplicated cases. The mean peak platelet count is ≈700 000/mm^3. Thrombocytopenia is seen rarely in the acute stage and may be a sign of disseminated intravascular coagulation. A low platelet count at illness presentation is a risk factor for coronary aneurysms (see Risk Scores for Predicting Aneurysms). In patients with arthritis, arthrocentesis typically yields purulent-appearing fluid with a white blood cell count of 125 000 to 300 000/mm^3, a normal glucose level, and negative Gram stain and cultures.[74] Plasma lipids are markedly altered in acute Kawasaki disease, with depressed plasma cholesterol, high-density lipoprotein (HDL), and apolipoprotein AI.[75–78]

Mild to moderate elevations in serum transaminases occur in ≤40% of patients and mild hyperbilirubinemia in ≈10%.[79] Plasma gammaglutamyl transpeptidase is elevated in ≈67% of patients.[80] Hypoalbuminemia is common and is associated with more severe and more prolonged acute disease. Urinalysis reveals intermittent mild to moderate sterile pyuria in ≈33% of patients, although suprapubic urine generally does not show pyuria, which suggests urethritis. In children who undergo lumbar puncture, ≈50% demonstrate evidence of aseptic meningitis with a predominance of mononuclear cells, as well as normal glucose and protein levels.[81]

Elevation of serum cardiac troponin I, a marker that is specific for myocardial damage, has been reported in acute Kawasaki disease, which is consistent with myocardial cell injury in the early phase of the disease.[82,83] Such elevation was not confirmed in another study.[84] Troponin assays do not play a role in the routine management of children with Kawasaki disease.

Laboratory tests, even though they are nonspecific, can provide diagnostic support in patients with clinical features that are suggestive but not diagnostic of Kawasaki disease. A moderately to markedly elevated CRP or ESR, which is almost universally seen in children with Kawasaki disease, is uncommon in viral infections. Platelet counts usually are >450 000/mm^3 in patients evaluated after day 7 of illness. Clinical experience suggests that Kawasaki disease is unlikely if platelet counts and acute-phase inflammatory reactants (ie, ESR and CRP) are normal after day 7 of illness. In addition, low white blood cell count, lymphocyte predominance, and low platelet count in the absence of disseminated intravascular coagulation suggest a viral etiology.

Incomplete (Atypical) Kawasaki Disease

Some patients who do not fulfill the criteria outlined in Table 1 have been diagnosed as having "incomplete" or "atypical" Kawasaki disease, a diagnosis that often is based on echocardiographic findings of coronary artery abnormalities. The term "incomplete" may be preferable to "atypical" because these patients lack sufficient clinical signs of the disease to fulfill the classic criteria; they do not demonstrate atypical clinical features. The phrase "atypical Kawasaki disease" should be reserved for patients who have a problem, such as renal impairment, that generally is not seen in Kawasaki disease. The conventional diagnostic criteria should be

viewed as guidelines that are particularly useful in preventing overdiagnosis but may result in failure to recognize incomplete forms of illness. Incomplete Kawasaki disease is more common in young infants than in older children, making accurate diagnosis and timely treatment especially important in these young patients who are at substantial risk of developing coronary abnormalities.[85] The laboratory findings of incomplete cases appear to be similar to those of classic cases. Therefore, although laboratory findings in Kawasaki disease are nondiagnostic, they may prove useful in heightening or reducing the suspicion of incomplete Kawasaki disease.

Echocardiography also may be useful in evaluating children with protracted fever and some features of Kawasaki disease. Although aneurysms rarely form before day 10 of illness, perivascular brightness, ectasia, and lack of tapering of the coronary arteries in the acute stage of Kawasaki disease may represent coronary arteritis before the formation of aneurysms. Decreased left ventricular (LV) contractility, mild valvular regurgitation (most commonly mitral regurgitation), and pericardial effusion also may be seen in an echocardiogram of a person with acute Kawasaki disease.

Incomplete Kawasaki disease should be considered in all children with unexplained fever for ≥5 days associated with 2 or 3 of the principal clinical features of Kawasaki disease (see Criteria for Treatment of Kawasaki Disease and Figure 1). Because young infants may present with fever and few, if any, principal clinical features, echocardiography should be considered in any infant aged <6 months with fever of ≥7 days' duration, laboratory evidence of systemic inflammation, and no other explanation for the febrile illness.

Common Pitfalls in Diagnosis

Certain common pitfalls in the diagnosis of Kawasaki disease should be noted. Children may present with only fever and a unilateral enlarged cervical lymph node. The rash and mucosal changes that follow often are mistaken for a reaction to antibiotics that are administered for presumed bacterial lymphadenitis. Sterile pyuria may be mistaken for a partially treated urinary tract infection with sterile urine cultures. The young infant may present with fever, rash, and cerebrospinal fluid pleocytosis and be misdiagnosed with viral meningitis. Occasionally, a child may present with an acute abdomen and be admitted to a surgical service. Kawasaki disease should be considered in the differential diagnosis of every child with fever of at least several days' duration, rash, and nonpurulent conjunctivitis, especially in children <1 year old and in adolescents, in whom the diagnosis is frequently missed.

Risk Scores for Predicting Aneurysms

Several scoring systems have been developed to identify children at highest risk for coronary artery abnormalities.[86–89] Duration of fever, presumably reflecting the severity of ongoing vasculitis, has been confirmed as a powerful predictor of coronary artery aneurysms in various studies.[87–89] Harada et al[90,91] developed a risk score to use at the time a child presents with Kawasaki disease to determine the risk of future coronary aneurysms. At some centers in Japan, the Harada score is used to determine whether IVIG treatment will be used. Intravenous gamma globulin is given to children who fulfill 4 of the following criteria, assessed within 9 days of onset of illness: (1) white blood cell count >12 000/mm^3; (2) platelet count <350 000/mm^3; (3) CRP >3+; (4) hematocrit <35%; (5) albumin <3.5 g/dL; (6) age ≤12 months; and (7) male sex. For children with <4 risk factors but continuing acute symptoms, the risk score is reassessed daily. In North America, where IVIG is recommended for all children with Kawasaki disease, Beiser et al[92] constructed a predictive instrument for the development of coronary artery lesions among patients treated with high-dose IVIG within the first 10 days of the onset of illness using data from a US multicenter database of patients with acute Kawasaki disease. The risk factors that Beiser and associates used in the sequential classification instrument included baseline neutrophil and band counts, hemoglobin concentration, platelet count, and temperature on the day after IVIG infusion. This instrument allowed the clinician to identify within 1 day of treatment the low-risk children in whom extensive and frequent cardiac testing may be unnecessary. Its positive predictive value was less satisfactory, however; the frequencies of the development of coronary artery abnormalities in boys and girls who were classified as high risk were only 13.8% and 5.5%, respectively. Because of the imperfect performance of scoring systems, all patients who are diagnosed with Kawasaki disease should be treated with IVIG.

Criteria for Treatment of Kawasaki Disease

The original guidelines for the diagnosis of Kawasaki disease were created by a committee that was appointed by the Japanese Ministry of Health in 1970. At that time, the coronary artery complications of Kawasaki disease were not yet appreciated. In addition, neither effective treatment nor a noninvasive method of assessing coronary artery abnormalities existed. The case definition was created, therefore, for epidemiological surveillance and to establish the extent of the clinical syndrome now known as Kawasaki disease in Japan. The case definition intentionally was made restrictive to exclude patients with rheumatic fever and Stevens-Johnson syndrome.

More than 3 decades later, the clinical landscape has changed dramatically. Echocardiographic screening for coronary enlargement has shown that a substantial number of children with Kawasaki disease and coronary artery abnormalities are not identified by the classic case definition.[93–95] Thus, although the present case definition provides a specific tool for epidemiological surveillance, it may not be the optimal method for aiding clinicians in the recognition of children with a systemic vasculitis that requires prompt treatment. Given the potential seriousness of the complications, together with the efficacy and safety of early treatment, high sensitivity of the treatment criteria is more important than is high specificity. We have therefore devised an algorithm to aid clinicians in deciding whether a child with signs and symptoms suggestive of Kawasaki disease should be treated with IVIG. To strive for the greatest sensitivity while maintaining sufficient specificity to prevent widescale overuse of IVIG, we have attempted to base our recommendations on laboratory and echocardiographic data derived

from the population of patients with Kawasaki disease who meet the classic epidemiological case definition.

The 1993 American Heart Association guidelines on Kawasaki disease suggested that the diagnosis could be made on day 4 of fever, with day 1 by convention being the first day of fever.[3] In the presence of 4 of 5 classic criteria (Table 1), US and Japanese experts agree that only 4 days of fever are necessary before initiating treatment.

It is also broadly agreed that Kawasaki disease can be diagnosed in the absence of full criteria when coronary abnormalities are present. The definition of coronary artery abnormalities has changed since the original Japanese Ministry of Health criteria were devised. In particular, coronary artery dimensions, adjusted for body surface area, provide a more accurate assessment of the size of the proximal right coronary artery (RCA) or left anterior descending coronary artery (LAD) as compared with expected population norms.[96,97] A z score $\geq$2.5 (ie, a coronary dimension that is $\geq$2.5 SDs above the mean for body surface area) in 1 of these arterial segments would be expected to occur in $\approx$0.6% of the population without Kawasaki disease, and a z score $\geq$3.0 in 1 of these segments would be expected to occur in $\approx$0.1% of the population without Kawasaki disease. Having a coronary artery z score $\geq$2.5 in both the proximal RCA and LAD would be uncommon in the general population. Because of anatomic variation in the left main coronary artery (LMCA), its z score must be interpreted with caution. Occasional cases of coronary prominence in patients with other disorders have been noted. Clinical experience, however, suggests that coronary enlargement in other febrile illnesses is rare, whereas coronary enlargement in Kawasaki disease is relatively common. Thus, coronary artery z scores should be incorporated into the recommendations for the evaluation and treatment of Kawasaki disease.

The present writing group proposes a scheme to aid the clinician in deciding which patients with fever and $<$4 classic criteria should undergo echocardiography or receive IVIG treatment or both for Kawasaki disease (Figure 1). In the absence of a gold standard for diagnosis, this algorithm cannot be evidence based but rather represents the informed opinion of a committee of experts (evidence level C). We offer this opinion as guidance to clinicians until an evidence-based algorithm or a specific diagnostic test for Kawasaki disease becomes available.

Cardiac Findings

Coronary Aneurysms

Echocardiography

The major sequelae of Kawasaki disease are related to the cardiovascular and, more specifically, the coronary arterial system, so cardiac imaging is a critical part of the evaluation of all patients with suspected Kawasaki disease. Because it is noninvasive and has a high sensitivity and specificity for the detection of abnormalities of the proximal LMCA and RCA, echocardiography is the ideal imaging modality for cardiac assessment (evidence level C). Evaluation of the cardiovascular sequelae of Kawasaki disease requires serial cardiac ultrasound studies and should be performed using equipment with appropriate transducers and supervised by an experienced echocardiographer. The initial echocardiogram should be performed as soon as the diagnosis is suspected, but initiation of treatment should not be delayed by the timing of the study (ie, waiting for sedation). This initial study establishes a baseline for longitudinal follow-up of coronary artery morphology, LV and left valvular function, and the evolution and resolution of pericardial effusion when present. Because detailed echocardiographic imaging is compromised if a child is uncooperative, sedation often is required for younger children (eg, chloral hydrate 65 to 100 mg/kg, maximum 1000 mg, or other short-acting sedative or hypnotic agents).

TABLE 3. Echocardiographic Views of Coronary Arteries in Patients With Kawasaki Disease

Left main coronary artery: Precordial short axis at level of aortic valve; precordial long axis of left ventricle (superior tangential); subcostal left ventricular long axis
Left anterior descending coronary artery: Precordial short axis at level of aortic valve; precordial superior tangential long axis of left ventricle; precordial short axis of left ventricle
Left circumflex: Precordial short axis at level of aortic valve; apical 4-chamber
Right coronary artery, proximal segment: Precordial short axis at level of aortic valve; precordial long axis (inferior tangential) of left ventricle; subcostal coronal projection of right ventricular outflow tract; subcostal short axis at level of atrioventricular groove
Right coronary artery, middle segment: Precordial long axis of left ventricle (inferior tangential); apical 4-chamber; subcostal left ventricular long axis; subcostal short axis at level of atrioventricular groove
Right coronary artery, distal segment: Apical 4-chamber (inferior); subcostal atrial long axis (inferior)
Posterior descending coronary artery: Apical 4-chamber (inferior); subcostal atrial long axis (inferior); precordial long axis (inferior tangential) imaging posterior interventricular groove

The 2D imaging should be performed with the highest frequency transducer possible. Imaging with high-frequency transducers should be attempted even in older children, as these probes allow for higher-resolution, detailed evaluation of the coronary arteries. Studies should be recorded in a dynamic video or digital cine format because the normal translational movement of the heart facilitates the display of the coronary artery anatomy. Such recordings will allow future review and comparison with subsequent studies. In addition to standard imaging from parasternal, apical, subcostal, and suprasternal notch windows, 2DE evaluation of patients with suspected Kawasaki disease should focus on imaging the LMCA, LAD, left circumflex coronary artery (LCX), RCA (proximal, middle, and distal segments), and posterior descending coronary arteries. Multiple imaging planes and transducer positions are required for the optimal visualization of all major coronary segments (Table 3, Figure 2). Maximal efforts should be made to visualize all major coronary segments. In order of highest to lowest frequency, 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 posterior descending coronary artery.

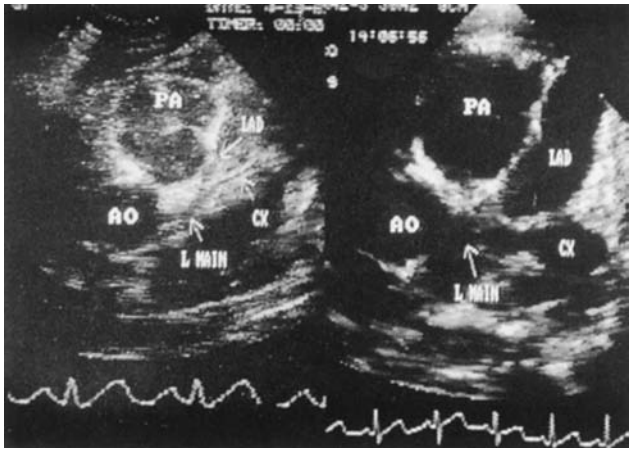

Figure 2. 2D echocardiogram. AO indicates aorta; PA, pulmonary artery; LAD, left anterior descending coronary artery; CX, circumflex coronary artery; and L MAIN, left main coronary artery.

Evaluation of the coronary arteries should include quantitative assessment of the internal vessel diameters. Measurements should be made from inner edge to inner edge and should exclude points of branching, which may have normal focal dilation. The number and location of aneurysms and the presence or absence of intraluminal thrombi also should be assessed. Aneurysms are classified as saccular if axial and lateral diameters are nearly equal or as fusiform if symmetric dilatation with gradual proximal and distal tapering is seen. When a coronary artery is larger than normal (dilated) without a segmental aneurysm, the vessel is considered ectatic. Care must be taken in making the diagnosis of ectasia because of considerable normal variation in coronary artery distribution and dominance. In the last American Heart Association statement,[3,98] aneurysms were classified as small (<5 mm internal diameter), medium (5 to 8 mm internal diameter), or giant (>8 mm internal diameter). The Japanese Ministry of Health criteria classify coronary arteries as abnormal if the internal lumen diameter is >3 mm in children <5 years old or >4 mm in children ≥5 years old; if the internal diameter of a segment measures ≥1.5 times that of an adjacent segment; or if the coronary lumen is clearly irregular.[99] Current statistics on the prevalence of coronary artery abnormalities secondary to Kawasaki disease are based on these criteria. Although the Japanese Ministry of Health criteria are not based on an individual patient's body size, coronary artery dimensions in children without Kawasaki disease have been shown to increase with indexes of body size, such as body surface area or body length.

More recently, de Zorzi and colleagues showed that the body surface area–adjusted coronary dimensions of some people with Kawasaki disease whose coronary arteries were considered "normal" are larger than expected in the acute, convalescent, and late phases when compared with references established for body size.[96] Figure 3 shows coronary internal diameters according to body surface area in the population without Kawasaki disease. Because use of the Japanese Ministry of Health criteria may result in both underdiagnosis and underestimation of the true prevalence of coronary

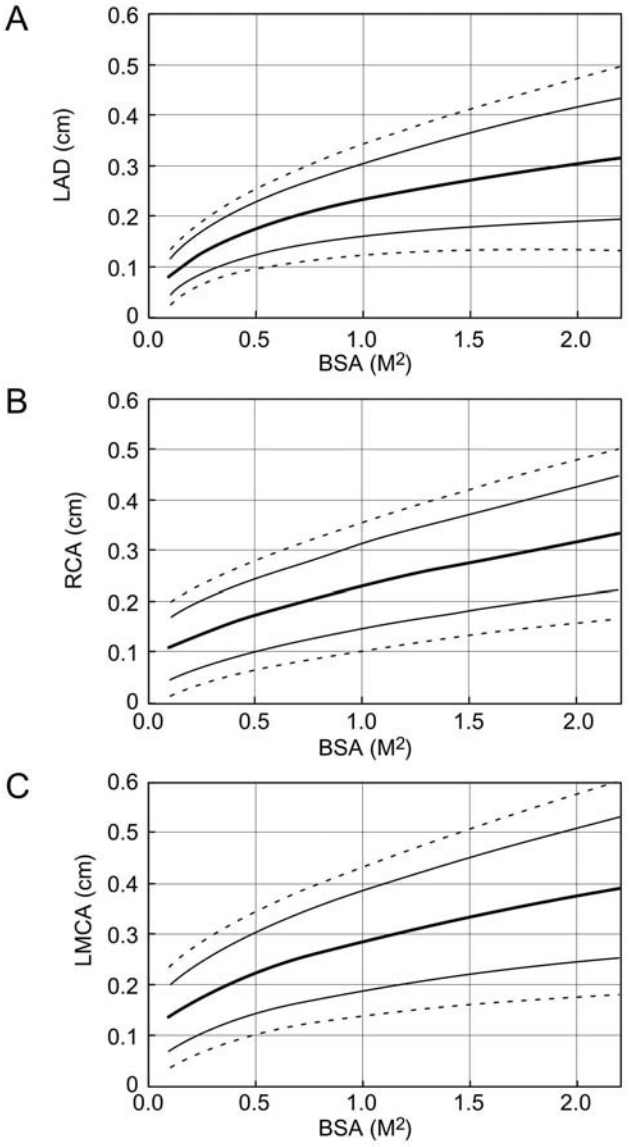

Figure 3. Mean and prediction limits for 2 and 3 SDs for size of (A) LAD, (B) proximal RCA, and (C) LMCA according to body surface area for children <18 years old. LMCA *z* scores should not be based on dimension at orifice and immediate vicinity; enlargement of LMCA secondary to Kawasaki disease usually is associated with ectasia of LAD, LCX, or both.

dilation, coronary vessel measurements adjusted for body surface area should be compared with those of the population without Kawasaki disease. Of note, *z* scores are available for only the LMCA, proximal LAD, and proximal RCA, so that the Japanese Ministry of Health criterion of "size 1.5 times that of the surrounding segment" is still useful for diagnosing aneurysms in peripheral sites. Enlargement of the LMCA caused by Kawasaki disease does not involve the orifice and rarely occurs without associated ectasia of the LAD, LCX, or both arteries. In addition to measuring coronary artery dimensions, imaging the coronary arteries also may reveal the lack of normal tapering and perivascular echogenicity or "brightness."[23]

Although the echocardiographic examination of patients with Kawasaki disease is focused on the coronary arteries,

other information can and should be obtained. Histological evidence suggests that myocarditis is universal in acute Kawasaki disease, and other studies have shown depressed ventricular contractility to be common early in the course of Kawasaki disease. Therefore, assessment of LV function should be a part of the echocardiographic evaluation of all patients with suspected Kawasaki disease. LV end-diastolic and end-systolic dimensions and a shortening fraction should be measured from standard M-mode tracings. Apical imaging allows the estimation of LV end-diastolic and end-systolic volumes and an ejection fraction. Although loading conditions influence these measurements, they are more readily measured than are complex indexes of contractility and are adequate for routine clinical follow-up. Evaluating regional wall motion may be useful, especially in children with coronary artery abnormalities. The aortic root also should be imaged, measured, and compared with references for body surface area because evidence exists that mild aortic root dilation is common among patients with Kawasaki disease.[100] Because pericarditis may be associated with the vasculitis and myocarditis seen in patients with Kawasaki disease, the presence or absence of a pericardial effusion should be noted.

Standard pulsed and color flow Doppler interrogation should be performed to assess the presence and degree of valvular regurgitation (in particular for mitral and aortic valves). Color flow Doppler with a low Nyquist limit setting from a favorable angle of view may allow coronary flow to be demonstrated and may be useful in positively identifying coronary artery lumens.

It is important to recognize the limitations of echocardiography in the evaluation and follow-up of patients with Kawasaki disease. Although echocardiographic detection of thrombi and coronary artery stenosis has been reported, the sensitivity and specificity of echocardiography for identifying these abnormalities is unclear. In addition, the visualization of coronary arteries becomes progressively more difficult as a child grows and body size increases. Angiography, intravascular ultrasound (IVUS), transesophageal echocardiography, and other modalities including magnetic resonance angiography (MRA) and ultrafast computed tomography (CT) may be of value in the assessment of selected patients (see below).

For uncomplicated cases, echocardiographic evaluation should be performed at the time of diagnosis, at 2 weeks, and at 6 to 8 weeks after onset of the disease. More frequent echocardiographic evaluation is needed to guide management in children at higher risk (eg, those who are persistently febrile or who exhibit coronary abnormalities, ventricular dysfunction, pericardial effusion, or valvular regurgitation). Recent studies have shown that repeat echocardiography performed 1 year after the onset of the illness is unlikely to reveal coronary artery enlargement in patients whose echocardiographic findings were normal at 4 to 8 weeks.[101,102] Because abnormalities in coronary artery function,[103–105] coronary flow reserve,[106] and aortic root dilation[100] remain potential concerns even among patients in whom coronary dilatation was never detected, repeat echocardiography beyond 8 weeks in patients with previously normal findings should be considered optional. Follow-up echocardiograms should identify the progression or regression of coronary abnormalities, evaluate ventricular and valvular function, and assess the presence or evolution of pericardial effusions.

Other Noninvasive Tests

Magnetic resonance imaging (MRI) and MRA may delineate coronary artery aneurysms in the proximal coronary artery segments and provide data regarding flow profile (evidence level C).[107–109] A recent small series in patients with Kawasaki disease demonstrated that coronary MRA accurately diagnosed all coronary artery aneurysms, coronary occlusions, and coronary stenoses present on x-ray angiography.[110] MRI and MRA may be used to image peripheral artery aneurysms. Ultrafast CT also has been used to assess coronary aneurysms.[111,112] Further larger studies in patients with Kawasaki disease are needed to establish the reliability of MRA and ultrafast CT for the detection of coronary artery aneurysms and stenoses in distal segments, as well as for the presence of collateral circulation.

Cardiac stress testing for reversible ischemia is indicated to assess the existence and functional consequences of coronary artery abnormalities in children with Kawasaki disease and coronary aneurysms (evidence level A). The types of stress tests reported in children with Kawasaki disease include nuclear perfusion scans with exercise,[113,114] exercise echocardiography,[115,116] and stress echocardiography with pharmacological agents such as dobutamine,[117,118] dipyridamole, or adenosine.[119] More recently, MRI stress imaging with quantification of regional perfusion has detected significant coronary stenoses.[120] Myocardial perfusion also can be assessed by myocardial contrast echocardiography, taking gas-filled microbubbles to measure the microcirculatory flow and hence capillary density in different myocardial regions.[121] With stress, the myocardial blood volume fraction decreases distal to a stenosis, causing a perfusion defect on myocardial contrast echocardiography.[122,123]

The predictive value of stress tests for coronary artery disease requiring intervention is a function of the probability of significant disease in the population tested (Bayes' theorem). For example, false-positive tests are more likely in patients with a previously low probability of coronary disease. Used appropriately, stress test results may guide a clinician's decision to refer a patient for invasive evaluation (ie, cardiac catheterization), as well as for catheter or surgical intervention. The choice of stress modality should be guided by institutional expertise with particular techniques, as well as by the age of the child (eg, pharmacological stress should be used in young children in whom traditional exercise protocols are not feasible).

Cardiac Catheterization and Angiography

Coronary angiography offers a more detailed definition of coronary artery anatomy than does cardiac ultrasound, making it possible to detect coronary artery stenosis or thrombotic occlusion and to determine the extent of collateral artery formation in patients with Kawasaki disease (Figure 4). Before recommending coronary angiography to a patient, a physician must compare the potential benefits of the procedure with its risks and cost. In patients with mild ectasia or small fusiform aneurysms demonstrated by echocardiogra-

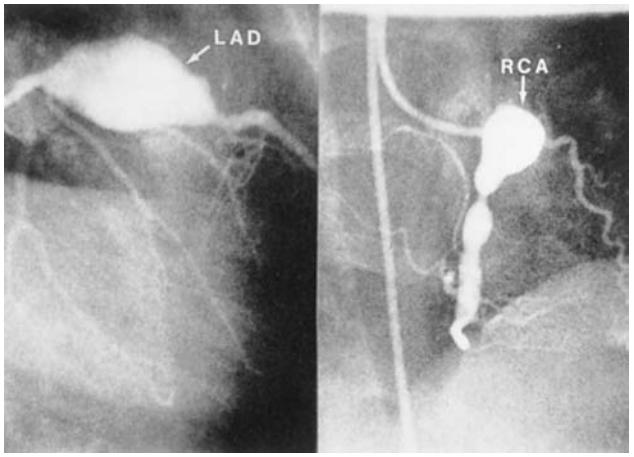

Figure 4. Coronary angiogram demonstrating giant aneurysm of the LAD with obstruction and giant aneurysm of the RCA with area of severe narrowing in 6-year-old boy.

phy, coronary angiography is unlikely to provide any further useful information and is not recommended (evidence level C). Patients with more complex coronary artery lesions may benefit from coronary angiography after the acute inflammatory process has resolved. Practices regarding the timing of cardiac catheterization for such patients vary greatly from center to center; coronary angiography is generally recommended 6 to 12 months after the onset of illness or sooner if indicated clinically (evidence level C). In long-term follow-up, the decision to perform angiography may be guided by echocardiographic imaging of coronary arteries, ventricular regional wall motion abnormalities, and clinical signs or noninvasive studies indicating myocardial ischemia. The failure to image distal coronary arteries in a patient in whom large proximal aneurysms have regressed may be an indication for another imaging modality, including cardiac angiography, to guide the appropriate use of antithrombotic agents (evidence level C). Patients who have undergone surgical revascularization or catheter intervention may have a repeat cardiac catheterization so that the efficacy of the treatment can be evaluated (evidence level C).

Additional techniques used during cardiac catheterization may detect structural or functional changes in the coronary artery wall. Patients with angiographically documented regression of coronary artery aneurysms have shown abnormal thickening of the intima-media complex by IVUS[124] and abnormal vasoreactivity in response to various vasodilators.[125,126] The long-term clinical implications of these anatomical and functional changes are unknown at this time.

Aneurysms can occur in arteries outside the coronary system, most commonly the subclavian, brachial, axillary, iliac, or femoral vessels, and occasionally in the abdominal aorta and renal arteries.[127] For this reason, abdominal aortography and subclavian arteriography are recommended in patients with Kawasaki disease undergoing coronary arteriography for the first time (evidence level C).

Myocarditis

Myocarditis has been demonstrated in autopsy and myocardial biopsy studies to be a common feature of early Kawasaki disease.[34,128] Myocardial inflammation has been documented in 50% to 70% of patients using ^{67}Ga citrate scans (planar or single photon emission CT)[129] and ^{99m}Tc-labeled white blood cell scans.[130–132] The severity of myocarditis does not appear to be associated with the risk of coronary artery aneurysms, however.[133,134]

Although the majority of patients with Kawasaki disease has abnormal myocardial contractility by echocardiographic assessment at presentation, myocardial mechanics improve rapidly after IVIG therapy, with a high concordance between the clinical and myocardial responses to therapy.[135] The speed of recovery suggests that depressed contractility in patients with Kawasaki disease is caused by rapidly reversible mechanisms such as those involving circulating toxins or activated cytokines. It is also possible that the inflammatory infiltrate found between the muscle fibers on postmortem examination in early Kawasaki disease may resolve quickly.

The occurrence of myocarditis during the acute phase of Kawasaki disease has fostered concern about the potential long-term effects of the disease on myocardial function. Biopsy of the right ventricular myocardium was performed in 201 patients with Kawasaki disease to assess the evolution and course of myocardial change.[136] The interval between onset of the disease and myocardial biopsy ranged from 2 months to 11 years. Myocardial abnormalities, including fibrosis and cellular disarrangement, as well as abnormal branching and hypertrophy of myocytes, were detected at all time periods after onset of the disease; their severity was unrelated to the presence of coronary artery abnormalities. In addition, electron microscopic examination of endomyocardial biopsies has demonstrated ultrastructural abnormalities late after Kawasaki disease.[137]

Despite the concerns raised about histopathologic abnormalities on myocardial biopsy, long-term myocardial contractility and function measured by echocardiography appear to be normal, except among patients with ischemic heart disease.[135] Assessment of the full impact of Kawasaki disease on heart function must await follow-up studies of these children into adulthood.

Valvular Regurgitation

Mitral regurgitation may result from transient papillary muscle dysfunction, MI, or valvulitis. The appearance of mitral regurgitation after the acute stage usually is secondary to myocardial ischemia, although late-onset valvulitis unrelated to ischemia has been documented.[138] Kato et al[2] reported 6 patients (1.0% of their series) with mitral regurgitation in the acute or subacute stage of Kawasaki disease, with resolution in 3 patients, death from MI in 2, and persistence from papillary muscle dysfunction in 1.

Aortic regurgitation has been documented angiographically by Nakano and colleagues[139] in ≈5% of children with Kawasaki disease and was attributed to valvulitis. Other investigators have observed a much lower incidence of aortic regurgitation in the acute phase,[2] but late-onset aortic regurgitation has been reported as an exceedingly rare finding after Kawasaki disease and may be associated with the need for aortic valve replacement.[2,138,140] Approximately 4% of a

consecutive series with Kawasaki disease had mild aortic regurgitation as seen by echocardiogram.[100]

Treatment

Initial Treatment

Aspirin

Aspirin has been used in the treatment of Kawasaki disease for many years. Although aspirin has important anti-inflammatory (at high doses) and antiplatelet (at low doses) activity, it does not appear to lower the frequency of the development of coronary abnormalities.[141] During the acute phase of illness, aspirin is administered at 80 to 100 mg/kg per day in 4 doses with IVIG (see next section). High-dose aspirin and IVIG appear to possess an additive anti-inflammatory effect. Practices regarding the duration of high-dose aspirin administration vary across institutions, and many centers reduce the aspirin dose after the child has been afebrile for 48 to 72 hours. Other clinicians continue high-dose aspirin until day 14 of illness and ≥48 to 72 hours after fever cessation. When high-dose aspirin is discontinued, clinicians begin low-dose aspirin (3 to 5 mg/kg per day) and maintain it until the patient shows no evidence of coronary changes by 6 to 8 weeks after the onset of illness (evidence level C). For children who develop coronary abnormalities, aspirin may be continued indefinitely (evidence level B). Of note, the concomitant use of ibuprofen antagonizes the irreversible platelet inhibition that is induced by aspirin[142]; thus, in general, ibuprofen should be avoided in children with coronary aneurysms taking aspirin for its antiplatelet effects (evidence level B).

Reye syndrome is a risk in children who take salicylates while they are experiencing active infection with varicella or influenza, and has been reported in patients taking high-dose aspirin for a prolonged period after Kawasaki disease.[143,144] It is unclear whether the low-dose therapy used for antiplatelet effect increases the risk of Reye syndrome. Children who are taking salicylates long-term should receive an annual influenza vaccine.[145] Although vaccine manufacturers recommend that salicylates be avoided for 6 weeks after the administration of varicella vaccine, physicians need to weigh the theoretical risks associated with varicella vaccine against the known risks of wild-type varicella in children receiving long-term salicylate therapy.[145] Some physicians substitute another antiplatelet medication for aspirin during the 6-week period. Parents of the children receiving salicylates should be instructed to contact their child's physician promptly if the child develops symptoms of or is exposed to either influenza or varicella.

IVIG

The efficacy of IVIG administered in the acute phase of Kawasaki disease in reducing the prevalence of coronary artery abnormalities is well-established.[141,146–148] The mechanism of action of IVIG in treating Kawasaki disease is unknown. IVIG appears to have a generalized anti-inflammatory effect. The possible mechanisms of action include modulation of cytokine production, neutralization of bacterial superantigens or other etiologic agents, augmentation of T-cell suppressor activity, suppression of antibody synthesis, and provision of anti-idiotypic antibodies.

A variety of dose regimens have been used in Japan and the United States. Two meta-analyses have demonstrated a dose-response effect, with higher doses given in a single infusion having the greatest efficacy.[141,148] Furthermore, peak adjusted serum IgG levels are lower among patients who subsequently develop coronary artery abnormalities and are inversely related to fever duration and laboratory indexes of acute inflammation.[147,149] The association of lower peak IgG levels with worse outcomes lends further support to the concept of a relationship between serum IgG concentration and therapeutic effectiveness.

Patients should be treated with IVIG, 2 g/kg in a single infusion (evidence level A), together with aspirin (see previous section).[3] This therapy should be instituted within the first 10 days of illness and, if possible, within 7 days of illness. Treatment of Kawasaki disease before day 5 of illness appears no more likely to prevent cardiac sequelae than does treatment on days 5 to 7, but it may be associated with an increased need for IVIG retreatment.[150,151] IVIG also should be administered to children presenting after the 10th day of illness (ie, children in whom the diagnosis was missed earlier) if they have either persistent fever without other explanation[152] or aneurysms and ongoing systemic inflammation, as manifested by elevated ESR or CRP (evidence level C).

Gamma globulin is a biological product made from pooled donor plasma, and potentially important product-manufacturing differences exist. Perhaps for this reason, adverse effects appear to vary considerably among products.[153–155] The results of clinical studies comparing the efficacy of immune globulin products have conflicted,[156,157] with most studies failing to find a significant difference between brands. Within the US healthcare system, the use of high-dose IVIG is cost-effective.[130] In Japan, however, some centers treat only children who are predicted to be at high risk for developing coronary artery disease,[90] although practices have been changing since 1996 with the approval by the Japanese Ministry of Health of the 2 g/kg regimen.

Measles and varicella immunizations should be deferred for 11 months after a child receives high-dose IVIG.[145] A child in whom the risk of exposure to measles is high, however, may be vaccinated earlier and then be reimmunized ≥11 months after IVIG administration if the child has an inadequate serological response. Even when treated with high-dose IVIG regimens within the first 10 days of illness, ≈5% of children with Kawasaki disease develop at the least transient coronary artery dilation and 1% develop giant aneurysms.[98,141,148] Additional potentially beneficial treatments are discussed below, but the optimal treatment awaits delineation of the specific agent or agents and pathogenetic mechanisms of Kawasaki disease.

Steroids

Although corticosteroids are the treatment of choice in other forms of vasculitis, their use has been limited in children with Kawasaki disease.[158] Corticosteroids were used as the initial therapy for Kawasaki disease long before the first report of IVIG efficacy by Furusho et al in 1984.[146] Although an early

study by Kato et al[159] suggested that steroids exert a detrimental effect when used as the initial therapy for Kawasaki disease, subsequent studies have shown either no ill effects or possible benefit. In a randomized trial of high-dose intravenous methylprednisolone plus heparin as compared with heparin alone, Kijima et al[160] found that steroid therapy was associated with a greater rate of improvement in coronary abnormalities. In a randomized trial in 100 children treated with intravenous prednisolone followed by an oral taper versus low-dose IVIG (300 mg/kg per day for 3 consecutive days), Nonaka and colleagues[161] reported shorter fever duration in the steroid group but no significant difference in the prevalence of coronary aneurysms. In a retrospective review, Shinohara et al[162] found that treatment regimens that included prednisolone were associated with significantly shorter fever duration and a lower prevalence of coronary artery aneurysms. Most recently, a small randomized trial examined whether the addition of 30 mg/kg of intravenous methylprednisolone to conventional therapy with IVIG (2 g/kg) and aspirin improved outcomes.[163] Patients who received steroids had a shorter duration of fever and shorter hospital stays, as well as a lower mean ESR and median CRP 6 weeks after the onset of illness. No differences between treatment groups in coronary outcomes were noted, with limited statistical power. Children to whom corticosteroids and IVIG were administered, compared with those who received IVIG alone, had reduced levels of cytokines, including interleukin-2 (IL-2), IL-6, IL-8, and IL-10 within 24 hours of IVIG administration.[164] At present, the usefulness of steroids in the initial treatment of Kawasaki disease is not well established (evidence level C). A National Heart, Lung, and Blood Institute–funded, multicenter randomized, placebo-blind trial that is in progress will provide more information on the effectiveness of such treatment.

Pentoxifylline

Pentoxifylline is a methyl xanthine compound that specifically inhibits TNF-α messenger RNA transcription. Because TNF-α appears to be important in the inflammatory cascade in Kawasaki disease, pentoxifylline has been assessed as a therapeutic adjunct to standard therapy. In a small clinical trial in which all patients were treated with a low-dose regimen of IVIG plus aspirin, the individuals who received high-dose pentoxifylline appeared to have fewer aneurysms and therapy was well tolerated.[165] A recent study reported the pharmacokinetics of an oral pediatric suspension of pentoxifylline in children with acute Kawasaki disease.[166] The drug was well tolerated and no toxicities were noted. The role of pentoxifylline in the initial treatment of Kawasaki disease is uncertain (evidence level C).

Treatment of Patients Who Failed to Respond to Initial Therapy

IVIG

Approximately ≥10% of patients with Kawasaki disease fail to defervesce with initial IVIG therapy.[156,167,168] Failure to respond usually is defined as persistent or recrudescent fever ≥36 hours after completion of the initial IVIG infusion. Most experts recommend retreatment with IVIG, 2 g/kg (evidence level C). The putative dose-response effect of IVIG forms the theoretical basis for this approach.

Steroids

Corticosteroids also have been used to treat patients who have failed to respond to initial therapy for Kawasaki disease.[158] Several small case series have described children with Kawasaki disease with recrudescent or persistent fever despite IVIG treatment in whom the administration of steroid therapy was associated with an improvement in symptoms and the absence of a significant progression in coronary artery abnormalities or adverse effects.[168–170] In a recent small randomized trial, Hashino et al[171] compared the efficacy and safety of additional IVIG therapy with pulse steroid therapy in patients with IVIG–resistant Kawasaki disease. Seventeen patients who did not respond to an initial infusion of 2 g/kg IVIG plus aspirin followed by an additional IVIG infusion of 1 g/kg were randomized to receive either a single additional dose of IVIG (1 g/kg) or pulse steroid therapy. Patients in the steroid group had a shorter duration of fever and lower medical costs. No significant difference in the incidence of coronary artery aneurysms was noted between the 2 groups, but power to detect a difference was limited.

Studies of steroids in the initial therapy for Kawasaki disease, as well as in therapy for patients with persistent or recrudescent fever despite treatment with IVIG and aspirin, have shown that corticosteroids reduce fever. The effects of steroids on coronary artery abnormalities are still uncertain, however. Until multicenter controlled trials are available, the present writing group recommends that steroid treatment be restricted to children in whom ≥2 infusions of IVIG have been ineffective in alleviating fever and acute inflammation (evidence level C). The most commonly used steroid regimen is intravenous pulse methylprednisolone, 30 mg/kg for 2 to 3 hours, administered once daily for 1 to 3 days.

Other Treatments

Plasma exchange has been reported in an uncontrolled clinical trial to be an effective therapy in patients who are refractory to IVIG and to lower the incidence of coronary artery aneurysms.[172] Of note, treatment assignment was not randomized, and few details about the comparability of treatment groups were provided in this short report. Earlier reports of dramatic response to this mode of treatment consist of small case series.[173,174] Because of its risks, plasma exchange is not in general recommended (evidence level C).

Ulinastatin is a human trypsin inhibitor purified from human urine that has been used in Japan as an adjunctive therapy for acute Kawasaki disease. This 67 000-Da glycoprotein inhibits neutrophil elastase as well as prostaglandin H2 synthase at the messenger RNA level.[175] Ulinastatin has been proposed as useful in IVIG–refractory patients,[175] but its effectiveness is unproven and additional experience with this agent is necessary before it can be recommended (evidence level C).

Abciximab, a platelet glycoprotein IIb/IIIa receptor inhibitor, has been used to treat patients in the acute or subacute phase of Kawasaki disease who have large coronary aneurysms.[176] Patients who received abciximab plus standard therapy as compared with historical controls treated with

standard therapy alone showed a greater regression in maximum aneurysm diameter, suggesting that treatment with abciximab might promote vascular remodeling. Prospective controlled trials are needed, but abciximab therapy may be considered in patients with large aneurysms in the acute or subacute phase (evidence level C).

A new class of agents that may play a role in the treatment of patients with refractory Kawasaki disease is *monoclonal antibodies* to various proinflammatory cytokines.[177] A humanized monoclonal antibody against TNF-α, infliximab, is being studied in a clinical trial of treatment for children who fail to become afebrile after initial IVIG treatment. Although its effectiveness in reducing the prevalence of coronary artery aneurysms is unproven, therapy with infliximab or other agents directed at TNF-α might be considered in patients who are resistant to IVIG and steroids (evidence level C).

Cytotoxic agents such as cyclophosphamide, in conjunction with oral steroids, have been suggested as useful for the treatment of exceptional patients with particularly refractory acute Kawasaki disease.[168] This therapy is used widely to treat other severe vasculitides. Cyclosporin A was reported to be ineffective in halting the progression of obliterative panarteritis in a single case report of fatal Kawasaki disease.[178] Of note, the risks of cytotoxic agents exceed the benefits for the vast majority of patients with Kawasaki disease (evidence level C).

In summary, because controlled data are lacking, the relative roles of repeated doses of IVIG, corticosteroids, TNF-α antagonists, plasma exchange, abciximab, and agents such as cyclophosphamide for patients with refractory Kawasaki disease remain uncertain.

Prevention of Thrombosis in Patients With Coronary Disease

The management of coronary disease in patients with Kawasaki disease depends on the severity and extent of coronary involvement. No prospective data exist to guide clinicians in choosing an optimal regimen, so recommendations are based on known pathophysiology, retrospective case series in children with Kawasaki disease, and extrapolation from experience in adults with coronary disease. Therapeutic regimens used in patients with Kawasaki disease depend on the severity of coronary involvement and include antiplatelet therapy with aspirin, with or without dipyridamole or clopidogrel; anticoagulant therapy with warfarin or low-molecular-weight heparin; or a combination of anticoagulant and antiplatelet therapy, usually warfarin plus aspirin.

Platelet activation is a profound component of the acute illness and persists throughout the convalescent and chronic phases. As a result, antiplatelet agents play a critical role in managing patients at every stage. Low-dose aspirin may be appropriate for asymptomatic patients with mild and stable disease. As the extent and severity of the coronary artery enlargement increase, the combination of aspirin with other antiplatelet agents (eg, clopidogrel, dipyridamole) aimed at antagonizing adenosine-5′diphosphate may be more effective in suppressing platelet activation. Clopidogrel in combination with aspirin has been shown to be more effective than either agent alone in preventing vascular events in both coronary and cerebral territories in adults (the Clopidogrel in Unstable Angina to Prevent Recurrent Events study).[179–182] Most experts believe that a predominantly platelet-directed approach is appropriate in the setting of stable, mild-to-moderate disease (evidence level C).

When a coronary aneurysm expands rapidly, the risk of thrombosis is particularly high. For this reason, the use of heparin with aspirin has been advocated (evidence level C). The goals for treatment in this group include prevention of thrombosis, as well as modification of the evolution of the derangement of the coronary shape and size, which may relate to the remodeling effects of endothelial damage and thrombosis.

The coronary aneurysm presents increasingly abnormal flow conditions, which are unlike other common clinical conditions such as atherosclerosis.[183] Within the aneurysm itself, the vessel dilatation results in low blood flow velocities and relative stasis of flow, which predispose the aneurysm to chronic thrombus formation. Additional severe abnormalities of coronary flow may arise over time secondary to incremental stenoses at the proximal or distal or proximal and distal ends of the aneurysm. This combination of stenosis at the aneurysm inlet, in immediate proximity to a dilated, low-velocity region, is a powerful stimulus to thrombus formation. Platelets are activated by the high shear stress that occurs at the stenosis and then are stimulated further as they decelerate and linger within the turbulent, low-velocity regions distal to the stenosis. The post-stenotic turbulence also is responsible for endothelial activation that results from gradients in the region of shear stress. Thus, progressive stenosis of these chronically hypercoagulable segments augments both the platelet and endothelial mechanisms for thrombosis. Finally, the presence of chronic thrombus in the aneurysm presents fibrin and clotting precursors that can amplify the thrombotic cascade. Patients with giant aneurysms, with or without stenosis, are at the highest risk for coronary thrombosis.

The most common antithrombotic regimen for patients with giant aneurysms is low-dose aspirin together with warfarin, maintaining an international normalized ratio (INR) of 2.0 to 2.5 (evidence level C). Some physicians substitute a therapeutic dose of low-molecular-weight heparin for warfarin, although this therapy requires twice-daily subcutaneous injections.

Treatment of Coronary Thrombosis

Once thrombosis is initiated in proximity to a segment at risk, it may progress rapidly and create a thrombus burden unlike that which occurs in adult atherosclerotic coronary occlusion. Coronary occlusion in adults with atherosclerosis involves plaque rupture or inflammation that exposes lipids and the extracellular matrix to the coagulation system. Kawasaki disease–associated acute thrombosis is not related to this form of plaque instability or rupture. Therefore, established thrombolytic protocols for adults with atherosclerotic coronary disease may not necessarily be optimal for the Kawasaki disease population.

The treatment of acute coronary occlusion in patients with Kawasaki disease should target multiple steps in the coagu-

TABLE 4. Antiplatelet, Anticoagulant, and Thrombolytic Medications

Medication	Route	Dosage
Aspirin	PO	Antiplatelet dose: 3–5 mg/kg qd
Clopidogrel	PO	1 mg/kg per day* to max (adult dose) of 75 mg/d
Dipyridamole	PO	2–6 mg/kg per day in 3 divided doses†
Unfractionated heparin	IV	Load: 50 U/kg Infusion: 20 U/kg per hour Adjust dosage to achieve desired therapeutic level, usually plasma heparin level=0.35–0.7 in antifactor Xa activity or aPTT 60–85 s
Low-molecular-weight heparin	SC	*Infants <12 months* Treatment: 3 mg/kg per day, divided q12h Prophylaxis: 1.5 mg/kg per day, divided q12h *Children/adolescents* Treatment: 2 mg/kg per day, divided q12h Prophylaxis: 1 mg/kg per day, divided q12h Adjust dose to achieve desired therapeutic level, usually antifactor Xa=0.5–1.0 U/mL
Abciximab	IV	Bolus: 0.25 mg/kg Infusion: 0.125 μg/kg per minute for 12 h
Streptokinase	IV	Bolus: 1000–4000 U/kg over 30 min Infusion: 1000–1500 U/kg per hour
Tissue plasminogen activator	IV	Bolus: 1.25 mg/kg Infusion: 0.1–0.5 mg/kg per hour for 6 h, then reassess
Urokinase	IV	Bolus: 4400 U/kg over 10 min Infusion: 4400 U/kg per hour
Warfarin	PO	0.1 mg/kg per day, given qd (0.05–0.34 mg/kg per day; adjust dose to achieve desired INR, usually 2.0–2.5)

*No published studies in children.
†Clopidogrel preferred to dipyridamole based on adult studies.

lation cascade (Table 4). In case reports, streptokinase,[184,185] urokinase,[186–188] and tissue plasminogen activator (tPA)[189,190] each has been administered to infants and children with coronary thrombosis with varying success rates (evidence level C). Because no randomized controlled trials have been performed in children, the treatment of infants and children with coronary thrombosis is derived from studies in adults with acute coronary syndromes. The goals of therapy include reestablishing coronary patency, salvaging the myocardium, and improving survival.[191] In adult trials, treatment with streptokinase has demonstrated a lower incidence of bleeding than have other agents (eg, Gruppo Italiano per lo Studio della Sopravvivenza nell'Infarto [GISSI-1], Second International Study of Infarct Survival [ISIS-2]),[192,193] but potential allergic complications limit its use in patients with a history of streptococcal pharyngitis within the past 6 months. Better coronary patency rates are achieved with tPA than with streptokinase in adults (Global Utilization of Streptokinase and Tissue Plasminogen Activator for Occluded Coronary Arteries [GUSTO-1]).[194–196] Tenecteplase-tPA is 14 times more fibrin specific than is tPA and may be more fibrinolytic at the site of the thrombus. Its longer association with the fibrin-rich clot and higher fibrin specificity may lead to the enhanced dissolution of older clots (>4 hours), with fewer bleeding complications as compared with tPA (Assessment of the Safety and Efficacy of a New Thrombolytic [ASSENT-2]).[197] All thrombolytic regimens include aspirin and either heparin or low-molecular-weight heparin.

The platelet glycoprotein IIb/IIIa receptor participates in the final common pathway for platelet aggregation. Inhibition of this receptor has shown great promise for improving outcomes when administered with aspirin and heparin, both with and without the use of thrombolytics in adults with acute coronary syndromes.[198–200] Reduced-dose thrombolytic therapy in combination with the administration of a glycoprotein IIb/IIIa inhibitor, such as abciximab, restores antegrade flow as effectively as does full-dose thrombolytic therapy, but it is associated with lower rates of reocclusion and reinfarction (evidence level C). Mechanical restoration of coronary blood flow (ie, the use of immediate coronary angioplasty or stent placement) is effective in adults and has been used in a small number of children (evidence level C).[23] The choice of method to reestablish perfusion in children with Kawasaki disease and coronary thrombosis should be based on that which can be administered with the greatest expertise in a timely fashion.

Surgical and Catheter Coronary Interventions

The current recommendations for surgical and catheter interventions summarize the current opinions of experts based on limited data. The present writing group recommends that decisions about intervention in individual patients be made in concert with experienced adult interventional cardiologists and cardiac surgeons.

Surgical Management

Attempts at excision or plication of the coronary artery aneurysm have not been successful and have caused deaths.

Surgical management in Kawasaki disease comprises primarily coronary artery bypass grafts for obstructive lesions.[201–203] The diameter and length of internal mammary grafts increase with the somatic growth of children as compared with the tendency of saphenous vein grafts to shorten somewhat over time. In a recently published series, the patency rates of arterial grafts (primarily the left and right internal mammary arteries) were 94%, 82%, and 78% at 1, 5, and 10 years, respectively, whereas patency rates for venous grafts were 82%, 63%, and 36%, respectively.[202] No early deaths occurred, and only 2 patients died at late follow-up of mean 6.7±4.5 years, 1 with sudden death and the other in a traffic accident. Freedom from cardiac events after bypass was ≈70% at 10 years. Although the results during the first decade after coronary artery bypass surgery in childhood are encouraging, the arterial graft patency rate in later adult life is still unknown.

The indications for coronary bypass graft procedures in children have not been established in clinical trials, but such surgery should be considered when reversible ischemia is present on stress-imaging test results, the myocardium to be perfused through the graft is still viable, and no appreciable lesions are present in the artery distal to the planned graft site (evidence level C). One panel of experts stated that surgical revascularization may be considered under the following conditions: severe occlusion of the main trunk of the LMCA, severe occlusion of >1 major coronary artery, severe occlusion in the proximal segment of the LAD, collateral coronary arteries in jeopardy, or all of the above.[204] Most experts agree that surgery is indicated after recurrent MI because the prognosis is so unfavorable.[205,206]

Interventional Cardiac Catheterization Techniques

Catheter interventions including balloon angioplasty, rotational ablation, and stent placement have been performed in a relatively small number of children with Kawasaki disease. Most of the experience has been accumulated in Japan. In general, balloon angioplasty has not been successful even with high-pressure balloons when it is done >2 years after the acute illness because of dense fibrosis and calcification in the arterial wall.[207,208] The relatively high balloon pressures that are necessary under these circumstances can lead to late neoaneurysm formation.[208] For this reason, if percutaneous transluminal coronary angioplasty cannot be performed with a balloon pressure of <10 atm, then rotational ablation or bypass surgery is advisable as an alternative procedure.[209] IVUS imaging has been found to be a useful tool for evaluating internal vessel morphology before and after percutaneous transluminal coronary angioplasty.[207] Stent placement has been useful in older children with mild calcification and in children with giant aneurysms. Rotational ablation and stent placement have met with a success rate >80% according to a collective experience in Japan.[210]

The recommendations for catheter intervention for patients with Kawasaki disease recently formulated by the Research Committee of the Japanese Ministry of Health, Labor, and Welfare[209] state that catheter intervention should be considered in patients presenting with ischemic symptoms, patients without ischemic symptoms but with reversible ischemia on stress test, and patients without ischemia but with ≥75% stenosis in the LAD (evidence level C). Bypass surgery is preferred in patients with severe LV dysfunction. Catheter intervention is contraindicated for individuals who have vessels with multiple, ostial, or long-segment lesions (evidence level C).

Cardiac Transplantation

A small number of patients with Kawasaki disease have undergone cardiac transplantation for severe myocardial dysfunction, severe ventricular arrhythmias, and severe coronary arterial lesions for which interventional catheterization or coronary artery bypass procedures were not feasible.[211] The timing of transplant has ranged from a few weeks or months to as long as 12 years after acute Kawasaki disease. Almost half of the transplant patients had undergone previous bypass grafting procedures without experiencing improvement in myocardial function. This procedure should be considered only for individuals with severe, irreversible myocardial dysfunction and coronary lesions for which interventional catheterization procedures or coronary artery bypass are not feasible (evidence level C).

Long-Term Follow-Up

Natural History

Regression and Evolution of Coronary Lesions

Coronary artery lesions resulting from Kawasaki disease change dynamically with time. Angiographic resolution 1 to 2 years after onset of the disease has been observed in ≈50% to 67% of vessels with coronary aneurysms.[2,212] The likelihood that an aneurysm will resolve appears to be determined in large measure by its initial size, with smaller aneurysms having a greater likelihood of regression.[213,214] Other factors that are positively associated with the regression of aneurysms include age at onset of Kawasaki disease <1 year, fusiform rather than saccular aneurysm morphology, and aneurysm location in a distal coronary segment.[212] Vessels that do not undergo apparent resolution of abnormalities may demonstrate persistence of aneurysmal morphology, development of stenosis or occlusion, or abnormal tortuosity. Rupture of a coronary aneurysm can occur within the first few months after Kawasaki disease, but this is an exceedingly rare occurrence.

Course of Patients With Persistent Coronary Artery Abnormalities

Whereas aneurysm size tends to diminish with time, stenotic lesions that are secondary to marked myointimal proliferation are frequently progressive.[2,127,215] The prevalence of stenosis continues to rise almost linearly over time.[2,215] The highest rate of progression to stenosis occurs among patients whose aneurysms are large.[215] The worst prognosis occurs in children with so-called giant aneurysms (ie, those with a maximum diameter ≥8 mm).[215–219] In these aneurysms, thrombosis is promoted by the combination of sluggish blood flow within the massively dilated vascular space and the frequent occurrence of stenotic lesions at the proximal or distal end of the aneurysms.

MI caused by thrombotic occlusion in an aneurysmal, a stenotic, or both types of coronary artery is the principal cause of death from Kawasaki disease.[206] The highest risk of MI occurs in the first year after onset of the disease, and most fatal attacks are associated with obstruction in either the LMCA or both the RCA and LAD.[206] Serial stress tests and myocardial imaging are mandatory in the management of patients with Kawasaki disease and significant coronary artery disease so that the need for coronary angiography and for surgical or transcatheter intervention can be determined.

The carotid artery wall in patients with coronary artery lesions 6 to 20 years after the onset of Kawasaki disease has been found to be less distensible and thicker than that in control patients.[220] These changes of arterial properties in patients with Kawasaki disease are not associated with major alterations of the lipid profile and are postulated to be secondary to the changes in arterial walls after a diffuse vasculitis. Extrapolation from these findings in carotid arteries suggests that the coronary arteries may be predisposed to accelerated atherosclerosis in patients with Kawasaki disease and coronary artery lesions. A similar study has not yet been performed in children with Kawasaki disease who did not develop coronary abnormalities.

Late cardiac sequelae of Kawasaki disease may first manifest in adulthood.[221,222] A history of a Kawasaki disease–like illness in childhood should be sought in patients who present with coronary aneurysms in the absence of generalized atherosclerotic disease. Some adult patients may be unable to recall an illness that occurred so early in life, however.

Course of Patients With Spontaneous Regression of Aneurysms

Approximately 50% of the vascular segments with coronary artery aneurysms in Kawasaki disease show angiographic regression of aneurysms. This regression usually occurs by myointimal proliferation, although more rarely the mechanism of regression can be organization and recanalization of a thrombus.[34,223,224] Pathological examination reveals fibrous intimal thickening despite a normal coronary artery lumen diameter. Similarly, transluminal (intravascular) ultrasound of regressed coronary aneurysms shows marked symmetrical or asymmetrical myointimal thickening.[124,225,226] Regressed coronary artery aneurysms are not only histopathologically abnormal, but they also show reduced vascular reactivity to isosorbide dinitrate and constriction with acetylcholine, indicating endothelial dysfunction.[104,125,126,226] A recent follow-up study with IVUS suggested a significant correlation between the initial diameters of the coronary arteries and intima-medial thickness >10 years later.[225]

Course After Kawasaki Disease Without Detectable Coronary Lesions

Although coronary artery aneurysms produce the most serious sequelae of Kawasaki disease, vascular inflammation during the acute stage of the illness is diffuse. Generalized endothelial dysfunction has been suggested by the observation that plasma 6-keto-prostaglandin F1 remains generally undetectable during the 8 weeks after the onset of Kawasaki disease.[227] In addition, Kawasaki disease produces altered lipid metabolism that persists beyond clinical resolution of the disease.[75,77,228] Children with Kawasaki disease with normal coronary arteries also have been reported to have higher brachial-radial artery mean pulse wave velocity than do children without Kawasaki disease, suggesting increased arterial stiffness.[228] Histological data concerning the long-term status of the coronary arteries in children who never had demonstrable abnormalities are few and difficult to interpret.[223,229]

Some investigators in Japan have studied coronary physiology in the population without aneurysms. Among children with a history of Kawasaki disease but with normal epicardial coronary arteries, lower myocardial flow reserve and higher total coronary resistance compared with normal controls were found by Muzik et al.[106] Children without a history of coronary aneurysms after Kawasaki disease also have been reported to have abnormal endothelium-dependent brachial artery reactivity.[103] The data conflict regarding the impairment of long-term endothelium-dependent relaxation of the epicardial coronary arteries among children in whom coronary artery dilation was never detected.[105,230]

From a purely clinical perspective, children without known cardiac sequelae during the first month of Kawasaki disease appear to return to their previous (usually excellent) state of health, without signs or symptoms of cardiac impairment.[2] Meaningful knowledge about long-term myocardial function, late-onset valvar regurgitation, and coronary artery status in this population must await their careful surveillance in future decades.

Risk Stratification

Clinical experience with Kawasaki disease permits the stratification of patients according to their relative risk of myocardial ischemia. Risk-level categories are listed below and are summarized in Table 5. This stratification allows for patient management to be individualized with respect to medical therapy to reduce the risk of thrombosis, physical activity, frequency of clinical follow-up and diagnostic testing, and indications for cardiac catheterization and coronary angiography. With careful clinical follow-up 10 to 20 years after the onset of Kawasaki disease, patients with no coronary artery changes on echocardiography at any stage of the illness seem to demonstrate a risk for clinical cardiac events that is similar to that in the population without Kawasaki disease,[2] but research studies suggest subclinical abnormalities of endothelial function and myocardial flow reserve.[103,231–233] Furthermore, patients with Kawasaki disease seem to have a more adverse cardiovascular risk profile, with higher blood pressure and greater adiposity, as compared with control children.[234] The risk level for a given patient with coronary artery involvement may change over time because of the changes in coronary artery morphology. For example, the development of thrombosis or stenosis associated with an aneurysm increases the risk for myocardial ischemia. Aneurysms also may regress to normal internal lumen diameter over time; optimal management of patients with regressed aneurysms is controversial because structural and functional coronary artery abnormalities persist.[57,126,226,235,236] The fol-

TABLE 5. Risk Stratification

Risk Level	Pharmacological Therapy	Physical Activity	Follow-Up and Diagnostic Testing	Invasive Testing
I (no coronary artery changes at any stage of illness)	None beyond 1st 6–8 weeks	No restrictions beyond 1st 6–8 weeks	Cardiovascular risk assessment, counseling at 5-y intervals	None recommended
II (transient coronary artery ectasia disappears within 1st 6–8 weeks)	None beyond 1st 6–8 weeks	No restrictions beyond 1st 6–8 weeks	Cardiovascular risk assessment, counseling at 3- to 5-y intervals	None recommended
III (1 small–medium coronary artery aneurysm/major coronary artery)	Low-dose aspirin (3–5 mg/kg aspirin/d), at least until aneurysm regression documented	For patients <11 y old, no restriction beyond 1st 6–8 weeks; patients 11–20 y 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 with echocardiogram + 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, or multiple or complex aneurysms in same coronary artery, without obstruction)	Long-term antiplatelet therapy and warfarin (target INR 2.0–2.5) or low-molecular-weight heparin (target: antifactor Xa level 0.5–1.0 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 outcome	Biannual follow-up with echocardiogram + ECG; annual stress test/evaluation of myocardial perfusion scan	1st angiography at 6–12 mo or sooner if clinically indicated; repeated angiography if noninvasive test, clinical, or laboratory findings suggest ischemia; elective repeat angiography under some circumstances (see text)
V (coronary artery obstruction)	Long-term low-dose aspirin; warfarin or low-molecular-weight heparin if giant aneurysm persists; consider use of β-blockers to reduce myocardial O_2 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 outcome	Biannual follow-up with echocardiogram and ECG; annual stress test/evaluation of myocardial perfusion scan	Angiography recommended to address therapeutic options

lowing suggestions for long-term management are based on a consensus of experts and serve as a guide to clinicians until long-term studies and prospective trials facilitate evidence-based practice (evidence level C).

Risk Levels

Risk Level I—Patients with no coronary artery changes on echocardiography at any stage of the illness

- No antiplatelet therapy is needed beyond the initial 6 to 8 weeks after the onset of illness.
- No restriction of physical activity is necessary after 6 to 8 weeks.
- Because the degree of future risk for ischemic heart disease in this category of patients is still undetermined, periodic assessment and counseling about known cardiovascular risk factors every 5 years is suggested.
- Coronary angiography is not recommended.

Risk Level II—Patients with transient coronary artery ectasia or dilatation (disappearing within the initial 6 to 8 weeks after the onset of illness)

- No antiplatelet therapy is needed beyond the initial 6 to 8 weeks after the onset of illness.
- No restriction of physical activity is necessary after 6 to 8 weeks.
- Risk assessment and counseling is recommended at 3- to 5-year intervals.
- Coronary angiography is not recommended.

Risk Level III—Patients with isolated (solitary) small to medium (>3 mm but <6 mm, or z score between 3 and 7) coronary artery aneurysm in ≥1 coronary arteries on echocardiography or angiography

- Long-term antiplatelet therapy with aspirin should be administered, at least until the aneurysms regress.
- Physical activity without restriction in infants and children in the first decade of life is permitted after the initial 6 to 8 weeks. Stress tests with myocardial perfusion evaluation may be useful in the second decade to guide recommendations for physical activity. Participation in competitive collision or high-impact sports is discouraged in children receiving antiplatelet therapy.
- Annual follow-up by a pediatric cardiologist with echocardiogram and ECG is recommended. Stress tests with myocardial perfusion imaging is recommended every 2 years in patients >10 years old.
- Coronary angiography is indicated if myocardial ischemia is demonstrated by stress tests with imaging.

Risk Level IV—Patients with ≥1 large coronary artery aneurysm (≥6 mm), including giant aneurysms, and patients

in whom a coronary artery contains multiple (segmented) or complex aneurysms without obstruction

- Long-term antiplatelet therapy is recommended. Adjunctive therapy with warfarin with a target INR of 2.0:2.5 is recommended for patients with giant aneurysms. Daily subcutaneous injections of low-molecular-weight heparin merits consideration as an alternative to warfarin for infants and toddlers, in whom blood drawing for INR testing is difficult. Low-molecular-weight heparin also may be used as a bridge during the initial phase of warfarin therapy or during the reintroduction of warfarin after the interruption of therapy for the purpose of elective surgery; therapeutic levels are assessed by measuring antifactor Xa levels. Some experts recommend a combination of aspirin and clopidogrel for patients with multiple or complex aneurysms.
- Recommendations about physical activity should be guided by annual stress tests with myocardial perfusion evaluation. Collision or high-impact sports should be discouraged because of the risk of bleeding. Participation in noncontact dynamic or recreational sports is encouraged if no evidence exists of stress-induced myocardial ischemia.
- Cardiology evaluation with echocardiogram and ECG should be done at 6-month intervals. Stress tests with myocardial perfusion evaluation should be performed annually. The patient should be monitored for known risk factors of atherosclerosis and his or her family should be counseled accordingly.
- Cardiac catheterization with selective coronary angiography should be performed 6 to 12 months after recovery from the acute illness, or sooner if clinically indicated, to delineate the complex coronary artery anatomy. Follow-up angiography may be indicated if noninvasive studies suggest myocardial ischemia. In addition, elective cardiac catheterization in the absence of noninvasive evidence of myocardial ischemia may be useful to rule out subclinical major coronary artery obstructions in some situations, such as when the patient experiences atypical chest pain, the ability to perform dynamic stress testing is limited by age, unique activity restrictions or insurability recommendations are needed, or the anatomy or size of the aneurysm cannot be clearly defined by echocardiography for decisions regarding anticoagulation.
- For females of childbearing age, reproductive counseling is strongly recommended.

Risk Level V—Patients with coronary artery obstruction confirmed by angiography

- Long-term antiplatelet therapy with or without adjunctive therapy with warfarin anticoagulation is recommended (see Risk Level IV)
- β-Adrenergic–blocking drugs should be considered to reduce myocardial oxygen consumption.
- Recommendations about dynamic physical activities should be based on the patient's response to stress testing. Collision or high-impact sports should be discouraged because of the risk of bleeding. Patients should avoid a sedentary lifestyle.
- Cardiology evaluation with an echocardiogram and ECG should be obtained at 6-month intervals. Stress tests with myocardial perfusion evaluation should be performed annually. The patient should be monitored for known risk factors of atherosclerosis and his or her family should be counseled accordingly.
- Cardiac catheterization with selective coronary angiography is recommended to address the therapeutic options of bypass grafting or catheter intervention and to identify the extent of collateral perfusion. Repeat cardiac catheterization may be indicated when new onset or worsening myocardial ischemia is suggested by noninvasive diagnostic testing or clinical presentation. If the patient has undergone surgical revascularization or a catheter intervention, then repeat cardiac catheterization may be indicated to evaluate the efficacy of the treatment.
- For females of childbearing age, reproductive counseling is strongly recommended.

Summary

Kawasaki disease is the leading cause of acquired heart disease in children in the United States. Coronary artery aneurysms or ectasia develop in ≈15% to 25% of untreated children; treatment with IVIG in the acute phase of the disease reduces this risk to <5%. Treatment with high-dose IVIG is recommended for children with fever of 4 days' duration and 4 of 5 classic clinical criteria, as well as for those with fewer clinical criteria in whom coronary abnormalities are noted by echocardiogram. This scientific statement proposes a new algorithm to aid clinicians in deciding which children with fever for ≥5 days and <4 classic criteria should undergo echocardiography, receive IVIG treatment, or both for Kawasaki disease. For patients with persistent or recurrent fever after initial IVIG infusion, IVIG retreatment may be useful. We reviewed the available data regarding other therapies for children with IVIG–resistant Kawasaki disease, including treatment with corticosteroids, TNF-α antagonists, and abciximab. Angiographic resolution occurs in ≈50% of aneurysmal arterial segments, but these segments show persistent histological and functional abnormalities. The remainder may continue to be aneurysmal, often with the development of progressive stenosis or occlusion. The long-term management of patients with Kawasaki disease should be tailored to the degree of coronary involvement. The present writing group made recommendations for each risk level regarding antiplatelet and anticoagulant therapies, physical activity, follow-up assessment, and the appropriate diagnostic procedures that may be performed to evaluate cardiac disease. The risk level for a given patient with coronary arterial involvement may change over time because of the changes in coronary artery morphology. Our statement on the initial evaluation, treatment in the acute phase, and long-term management of patients with Kawasaki disease is intended to provide practical interim recommendations until evidence-based data are available to define best medical practices.

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Writing Group Member Name	Research Grant	Speakers Bureau/Honoraria	Stock Ownership	Consultant/Advisory Board	Other
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