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 \( \approx 15\% \) 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 \( \geq 5 \) days and \( \leq 4 \) 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-\( \alpha \) 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 1967 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 \( \approx 15\% \) to 25\% of untreated children with the disease and may lead to myocardial infarction (MI), sudden death, or ischemic heart...
disease. In the United States, Kawasaki disease has surpassed acute rheumatic fever as the leading cause of acquired heart disease in children. 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. Kawasaki disease is markedly more prevalent in Japan and in children of Japanese ancestry, with an annual incidence of about 112 cases per 100,000 children <5 years old. In the United States, the incidence of Kawasaki disease has been best estimated from hospital discharge data. An estimated 4248 hospitalizations associated with Kawasaki disease occurred in the United States in
2000, with a median age of 2 years. Race-specific incidence rates derived from administrative data indicate that Kawasaki disease is most common among Asians of American 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). These estimates are similar to those reported in smaller studies. 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.

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%. The proportion of cases with a positive family history is ≈1%. 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. The risk of occurrence in twins is ≈13%. 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. The reported occurrence of Kawasaki disease in children of parents who themselves had the illness in childhood also supports the contribution of genetic factors.

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. Reported associations of Kawasaki disease with antecedent respiratory illness and exposure to carpet-cleaning fluids have not been consistently confirmed. Other factors that are reportedly associated with Kawasaki disease include having preexisting eczema, using a humidifier, and living near a standing body of water.

The case fatality rate in Kawasaki disease in Japan is 0.08%. 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. In the United States, the in-hospital mortality rate is ≈0.17% (the investigators used administrative data that may include readmissions for coronary disease). Virtually all deaths in patients with Kawasaki disease result from its cardiac sequelae. 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. 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.

### 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 \( V_{\beta}2 \) and \( V_{\beta}8 \) T-cell receptor families, but this theory remains controversial. 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. 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.

It is also 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 remodelling 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 neangiogenesis; 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-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 ≥5 days of fever and ≥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 ≥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 ≥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 ≥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

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

*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.
‡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 (acrodyinia) |

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 mucosa. 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. The lymph nodes often are firm and nonfluctuant, are not associated with marked erythema of the overlying skin, and are not tender 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, but persistent sensorineural hearing loss is rare. 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. Hepatic enlargement and jaundice can occur. Acute acalculous distention of the gallbladder (hydrops) occurs in patients during the first 2 weeks of the illness and can be identified by abdominal ultrasound. Erythema and induration at the site of a previous vaccination with Bacille Calmette-Guérin (BCG) is common in Japan, where BCG is used widely. Rare findings include testicular swelling, pulmonary nodules, and infiltrates; pleural effusions, and hemophagocytic syndrome.

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 $>15,000/\text{mm}^3$. 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 intravascular immunoglobulin (IVIG) infusion. 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. 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 50,000 to $>1$ million/\text{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 $700,000/\text{mm}^3$. 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/\text{mm}^3, a normal glucose level, and negative Gram stain and cultures. Plasma lipids are markedly altered in acute Kawasaki disease, with depressed plasma cholesterol, high-density lipoprotein (HDL), and apolipoprotein AI.

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

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. Such elevation was not confirmed in another study. 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 $450,000/\text{mm}^3$ 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.\textsuperscript{86} 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.\textsuperscript{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.\textsuperscript{87–89} Harada et al\textsuperscript{80,91} 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\textsuperscript{3}; (2) platelet count <350 000/mm\textsuperscript{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\textsuperscript{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.\textsuperscript{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 widespread 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. 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. 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 uncommom 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).

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.

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

<table>
<thead>
<tr>
<th>Artery</th>
<th>Imaging Plan</th>
</tr>
</thead>
<tbody>
<tr>
<td>Left main coronary artery</td>
<td>Precordial short axis at level of aortic valve;</td>
</tr>
<tr>
<td></td>
<td>precordial long axis of left ventricle (superior tangential);</td>
</tr>
<tr>
<td></td>
<td>subcostal left ventricular long axis</td>
</tr>
<tr>
<td>Left anterior descending coronary artery</td>
<td>Precordial short axis at level of aortic valve;</td>
</tr>
<tr>
<td></td>
<td>precordial superior tangential long axis of left ventricle;</td>
</tr>
<tr>
<td></td>
<td>precordial short axis of left ventricle</td>
</tr>
<tr>
<td>Left circumflex</td>
<td>Precordial short axis at level of aortic valve;</td>
</tr>
<tr>
<td></td>
<td>apical 4-chamber</td>
</tr>
<tr>
<td>Right coronary artery, proximal segment</td>
<td>Precordial short axis at level of aortic valve;</td>
</tr>
<tr>
<td></td>
<td>precordial long axis (inferior tangential) of left ventricle;</td>
</tr>
<tr>
<td></td>
<td>subcostal coronal projection of right ventricular outflow tract;</td>
</tr>
<tr>
<td></td>
<td>subcostal short axis at level of atrioventricular groove</td>
</tr>
<tr>
<td>Right coronary artery, middle segment</td>
<td>Precordial long axis of left ventricle (inferior tangential); apical 4-chamber;</td>
</tr>
<tr>
<td></td>
<td>subcostal left ventricular long axis</td>
</tr>
<tr>
<td></td>
<td>subcostal short axis at level of atrioventricular groove</td>
</tr>
<tr>
<td>Right coronary artery, distal segment</td>
<td>Apical 4-chamber (inferior); subcostal atrial long axis (inferior)</td>
</tr>
<tr>
<td></td>
<td>Posterior descending coronary artery (apical 4-chamber (inferior);</td>
</tr>
<tr>
<td></td>
<td>subcostal atrial long axis (inferior)</td>
</tr>
<tr>
<td></td>
<td>Imaging posterior interventricular groove</td>
</tr>
</tbody>
</table>

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.
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,\textsuperscript{3,98} aneurysms were classified as small (\(\leq 5\) 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 \(\geq5\) years old; if the internal diameter of a segment measures \(\geq1.5\) times that of an adjacent segment; or if the coronary lumen is clearly irregular.\textsuperscript{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.\textsuperscript{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 dilatation, 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 secondary to Kawasaki disease usually is associated with ectasia of LAD, LCX, or both. Although the echocardiographic examination of patients with Kawasaki disease is focused on the coronary arteries,
should be considered optional. Follow-up echocardiograms beyond 8 weeks in patients with previously normal findings dilatation was never detected, repeat echocardiography be-

potential concerns even among patients in whom coronary flow reserve,106 and aortic root dilation100 remain performed 1 year after the onset of the illness is unlikely to

Recent studies have shown that repeat echocardiography at 6 to 8 weeks after onset of the disease. More frequent

angiography (MRA) and ultrafast computed tomography

phy, and other modalities including magnetic resonance

vascular ultrasound (IVUS), transesophageal echocardiogra-

these abnormalities is unclear. In addition, the visualization sensitivity and specificity of echocardiography for identifying

demonstrated and may be useful in positively identifying coronary artery lumens.

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 echocardiog-

rapy 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, intra-

vascular ultrasound (IVUS), transesophageal echocardiogra-

phy, 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 dilatation100 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 pharmaco-

logical 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’ theo-

rem). For example, false-positive tests are more likely in patients with a previously low probability of coronary dis-

ease. 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-
Myocarditis

Myocarditis has been demonstrated in autopsy and myocardial biopsy studies to be a common feature of early Kawasaki disease. Myocardial inflammation has been documented in 50% to 70% of patients using 67Ga citrate scans (planar or single photon emission CT) and 99mTc-labeled white blood cell scans. The severity of myocarditis does not appear to be associated with the risk of coronary artery aneurysms, however.

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. 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. 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.

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. Assessment of the full impact of Kawasaki disease on heart function must wait 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. Kato et al reported 6 patients (1.0% of their series) with mitral regurgitation in the acute phase, but late-onset aortic 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 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, 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.
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; 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).1 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 explanation152 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.150 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\textsuperscript{190} 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\textsuperscript{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 in the steroid group but no significant difference in the prevalence of coronary aneurysms. In a retrospective review, Shinohara et al\textsuperscript{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.\textsuperscript{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.\textsuperscript{164} At present, the usefulness of steroids in the initial treatment of Kawasaki disease is not well established (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.\textsuperscript{158} Several small case series have described children with Kawasaki disease with recrudescence 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.\textsuperscript{168–170} In a recent small randomized trial, Hashino et al\textsuperscript{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.\textsuperscript{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.\textsuperscript{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.\textsuperscript{175} Ulinastatin has been proposed as useful in IVIG–refractory patients,\textsuperscript{176} 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.\textsuperscript{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. 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. This therapy is used widely to treat other severe vasculitides. Cyclosporin A was reported to be ineffective in halting the progression of obliterator panarteritis in a single case report of fatal Kawasaki disease. 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). 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. 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-
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 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 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 thrombolitics 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.

---

**TABLE 4. Antiplatelet, Anticoagulant, and Thrombolytic Medications**

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

*No published studies in children.
†Clopidogrel preferred to dipyridamole based on adult studies.
Surgical management in Kawasaki disease comprises primarily coronary artery bypass grafts for obstructive lesions.\textsuperscript{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.\textsuperscript{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.\textsuperscript{204} Most experts agree that surgery is indicated after recurrent MI because the prognosis is so unfavorable.\textsuperscript{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.\textsuperscript{207,208} The relatively high balloon pressures that are necessary under these circumstances can lead to late neointimal formation.\textsuperscript{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.\textsuperscript{209} IVUS imaging has been found to be a useful tool for evaluating internal vessel morphology before and after percutaneous transluminal coronary angioplasty.\textsuperscript{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.\textsuperscript{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\textsuperscript{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.\textsuperscript{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.\textsuperscript{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.\textsuperscript{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.\textsuperscript{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.\textsuperscript{2,127–125} The prevalence of stenosis continues to rise almost linearly over time.\textsuperscript{2,215} The highest rate of progression to stenosis occurs among patients whose aneurysms are large.\textsuperscript{215} The worst prognosis occurs in children with so-called giant aneurysms (ie, those with a maximum diameter ≥8 mm).\textsuperscript{2,125–129} 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, transhuminal (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

<table>
<thead>
<tr>
<th>Risk Level</th>
<th>Pharmacological Therapy</th>
<th>Physical Activity</th>
<th>Follow-Up and Diagnostic Testing</th>
<th>Invasive Testing</th>
</tr>
</thead>
<tbody>
<tr>
<td>I (no coronary artery changes at any stage of illness)</td>
<td>None beyond 1st 6–8 weeks</td>
<td>No restrictions beyond 1st 6–8 weeks</td>
<td>Cardiovascular risk assessment, counseling at 5-y intervals</td>
<td>None recommended</td>
</tr>
<tr>
<td>II (transient coronary artery ectasia disappears within 1st 6–8 weeks)</td>
<td>None beyond 1st 6–8 weeks</td>
<td>No restrictions beyond 1st 6–8 weeks</td>
<td>Cardiovascular risk assessment, counseling at 3- to 5-y intervals</td>
<td>None recommended</td>
</tr>
<tr>
<td>III (1 small–medium coronary artery aneurysm/major coronary artery)</td>
<td>Low-dose aspirin (3–5 mg/kg aspirin/d), at least until aneurysm regression documented</td>
<td>For patients &lt;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</td>
<td>Annual cardiology follow-up with echocardiogram + ECG, combined with cardiovascular risk assessment, counseling; biennial stress test/evaluation of myocardial perfusion scan</td>
<td>Angiography, if noninvasive test suggests ischemia</td>
</tr>
<tr>
<td>IV (≥1 large or giant coronary artery aneurysm, or multiple or complex aneurysms in same coronary artery, without obstruction)</td>
<td>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</td>
<td>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</td>
<td>Biannual follow-up with echocardiogram and ECG; annual stress test/evaluation of myocardial perfusion scan</td>
<td>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)</td>
</tr>
<tr>
<td>V (coronary artery obstruction)</td>
<td>Long-term low-dose aspirin; warfarin or low-molecular-weight heparin if giant aneurysm persists; consider use of β-blockers to reduce myocardial O₂ consumption</td>
<td>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</td>
<td>Biannual follow-up with echocardiogram and ECG; annual stress test/evaluation of myocardial perfusion scan</td>
<td>Angiography recommended to address therapeutic options</td>
</tr>
</tbody>
</table>

Suggested 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.
Disclosure

<table>
<thead>
<tr>
<th>Writing Group Member Name</th>
<th>Research Grant</th>
<th>Speakers Bureau/Honoraria</th>
<th>Stock Ownership</th>
<th>Consultant/Advisory Board</th>
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This table represents the relationships of writing group members that may be perceived as actual or reasonably perceived conflicts of interest as reported on the Disclosure Questionnaire, which all members of the writing group are required to complete and submit.

References


Kawasaki disease (KD) is a vasculitis of unknown etiology with a predilection for the coronary arteries, which has become the leading cause of acquired structural heart disease. Peak prevalence is winter/spring, with 75% of affected children <5 years old. Coronary artery aneurysms/ectasia develop in 15-25% of untreated children with KD.

**Criteria for diagnosis:**
Fever ≥ 5 days (generally ≥ 102 F), with ≥ 4 physical findings:
1. Bilateral conjunctival injection (non-exudative, with limbic sparing)
2. Erythema of lips/oral mucosa
3. Extremity changes (swelling, redness, etc.)
4. Rash (any form except vesicular has been described)
5. Cervical adenopathy (usually unilateral, > 1.5cm)

Terminology: Patients deemed to have KD without meeting all the criteria have “Incomplete KD;” the phrase “Atypical KD” is reserved for those patients having unusual signs/symptoms.

**Diagnostic pitfalls:**
- Rash and mucosal changes may be blamed on a drug reaction
- Sterile pyuria may be treated as a UTI
- Fever and irritability may be treated as meningitis
- Older children (>8 yrs)/adolescents and infants (< 1 yr old) may be overlooked (consider Infectious Disease or rheumatology consult)

Diagnosis is clinical, but the following evaluation is suggested to establish severity and exclude other causes:
- Bloodwork – CBC w/diff, ESR, CRP, blood culture, CMP, GGT, Monospot (only in kids ≥ 4 yrs old), adenovirus IgM, EBV antibodies (Viral Capsid Antigen IgM and IgG, Early Antigen IgG, Nuclear Antigen IgG), CMV antibodies (IgM/IgG), Enterovirus PCR (May-November only)
- Other body sites – Urine for U/A, culture, and CMV PCR; throat swab for rapid strep and culture, nasal/rectal swabs for Staph aureus detection, viral swab of conjunctivae for adenovirus DFA (need good swab with cells for adequate DFA!)
- Consider obtaining and storing 5-10 mL of whole blood prior to IVIG infusion for future serologic testing. Place PPD prior to steroid pulses.
- Cardiology consult for ECG and echocardiogram during acute phase, and 6-week follow-up
- Consider rheumatology or ID consultation for atypical or incomplete KD, children < 1 or ≥ 8 years of age, children with persistent inflammation of undetermined etiology, and children failing initial treatment

**Treatment:** IVIG (2g/kg) and high-dose aspirin (80-100mg/kg) are currently the first-line therapies:
- Treatment with IVIG should begin within the 1st 10 days of fever (ideally, within 7 days) to minimize the risk of coronary artery aneurysms, but treatment rarely needs to begin emergently (obtain labs, review with team, ensure adequate hydration first).
Use the pre-printed IVIG infusion order form and infuse over 8-12 hrs to minimize side effects. Risks of IVIG include anaphylaxis, acute renal dysfunction, pulmonary edema, thrombosis, and aseptic meningitis. Though IVIG is plasma-derived, risk of viral transmission is exceedingly rare due to fractionation and viral inactivation procedures used in its production. IVIG “failure” means recurrent fever ≥ 36 hrs after completion of IVIG infusion. High-dose aspirin is continued ~3-7 days (at least until patient is afebrile ≥ 48 hrs). If treatment failure occurs: repeat IVIG treatment and request rheumatology consultation.

Did you know?

The diagnostic evaluation outlined above comes to $5000-$6000 in hospital charges… one dose of IVIG runs $5000-$13,000 depending on the size of the patient.

Discharge planning:

- Give an inactivated (killed) influenza vaccine to children on aspirin therapy to prevent Reye’s syndrome.
- Children who have received IVIG may not respond appropriately to live vaccines given within 11 months of (either before or after) IVIG dose — your patient may need a doctor’s note to repeat or delay MMR/Varicella/rotavirus vaccines.
- Children with KD should be discharged on low-dose ASA (3-5mg/kg, try to round to a baby aspirin: 81 mg daily) with instructions that aspirin should be discontinued if/when subsequent echocardiogram is normal as per their cardiologist.
- Contact the PCP prior to discharge to review the case and ensure that he/she will be able to provide appropriate follow-up. If there is any concern, an in-house ID or Rheumatology consult may be warranted to ensure adequate outpatient monitoring of the disease condition.

Relevant Literature:

1. 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, Newburger et al, Pediatrics, Dec 2004; 114: 1708 - 1733.
4. Initial Intravenous Gammaglobulin Treatment Failure in Kawasaki Disease, Wallace et al, Pediatrics, Jun 2000; 105: e78
8. Lexicomp online (IVIG)
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Last updated 3.2012
Incomplete Kawasaki disease in patients younger than 1 year of age: a possible inherent risk factor

Yunku Yeo · TaeYeon Kim · KeeSoo Ha · GiYoung Jang · JungHwa Lee · KwangChul Lee · ChangSung Son · Joo Won Lee

Abstract Kawasaki disease (KD) patients younger than 1 year of age are at especially high risk of developing coronary artery abnormalities (CAA). To define the clinical characteristics of this group, as well as the risk factors predisposing them to CAA, we reviewed the medical records of 136 KD patients younger than 1 year of age who were treated at the Korea University Medical Center from January 2001 to July 2006. Of these patients, 16 developed CAA (11.8%). The CAA(+) group had a longer duration of total fever than the CAA(−) group (9.1±3.7 days vs. 6.3±2.0 days, \( p = 0.011 \)), but did not differ in the duration of pre- and post-intravenous gamma-globulin (IVGG) fever. The CAA(+) group had fewer diagnostic symptoms than the CAA(−) group (2.7±1.1 vs. 4.3±1.2, \( p < 0.001 \)). Of the hematological findings, the CAA(+) group only differed from the CAA(−) group in having significantly higher total white blood cell (19.2±6.0 vs. 14.7±4.7 K/mm\(^3\), \( p = 0.007 \)) and platelet (462.9±101.0 vs. 383.6±121.1 K/mm\(^3\), \( p = 0.014 \)) levels. Multivariable logistic regression analysis showed that the only factors which were significantly associated with the development of CAA in KD patients younger than 1 year of age. Therefore, these patients should be monitored for incomplete KD, especially if unexplained fever continues, and treatment to shorten the duration of total fever should be initiated.

Keywords Kawasaki disease · Infants · Coronary abnormalities · Incomplete manifestation

Abbreviations
KD Kawasaki disease
IVGG Intravenous gamma-globulin
CAA Coronary artery abnormalities
CRP C-reactive protein
ESR Erythrocyte sedimentation rate
BNP B-type natriuretic peptide

Introduction
Kawasaki disease (KD) is an acute febrile disease characterized by systemic vasculitis in young children. Exaggerated inflammatory responses to certain microorganisms in genetically susceptible individuals seem to contribute to the development of this clinical syndrome [4, 15]. Treatment with high-dose intravenous gamma-globulin (IVGG) in combination with aspirin reduces the incidence of coronary artery abnormalities (CAA) in these patients, which include coronary artery dilatation and/or aneurysms, from over 20% to around 5% [4, 8, 15]. KD is currently recognized as a leading cause of acquired heart diseases in children worldwide. This is due, in part, to the increased annual incidence of KD [21] and, in part, to the increased recognition of CAA through measurements of the body surface area-adjusted coronary artery diameters [7].
While the causes of KD are not yet clear, efforts have been directed toward decreasing the development of CAA. KD patients younger than 1 year of age are reported to have a higher incidence of CAA [1, 3, 9, 11, 17, 19, 20]. The diagnosis of KD in infants is often challenging, since they are more likely to have incomplete presentation [5, 19]. This can lead to a delay in the diagnosis and treatment of KD, which has been suggested to be a major contributor to the development of CAA [1, 3]. Therefore, it may be useful to define the clinical characteristics associated with the development of CAA in this age group, as this may reveal the risk factors for CAA. This information could then be used to decrease the incidence of CAA in KD patients.

Materials and methods

We reviewed the medical records of 136 KD patients younger than 1 year of age who were treated at the Korea University Medical Center from January 2001 to July 2006. The diagnoses of KD and CAA were made on the basis of the clinical manifestations and the report of a subcommittee of the Japanese Research committee on Kawasaki disease that sought to standardize the diagnostic criteria of CAA [6, 13]. Five or more typical clinical manifestations, including fever more than 38°C, are needed to diagnose KD. In the cases in which the clinical manifestations did not fulfill the diagnostic criteria and other diagnoses were excluded, symptoms that are frequently associated with KD and elevated inflammatory indices during the acute phase were considered to support the diagnosis of incomplete KD [15]. These incomplete KD cases were included in this analysis only if they showed a typical convalescent finding, such as skin peeling. Since patients with incomplete KD may have delayed treatment, which contributes to the development of CAA, we compared the total duration of fever in the presence or absence of CAA. Febrile days were counted from the onset of fever until IVGG started (pre-IVGG fever) or fever subsided completely (total fever). The days of post-IVGG fever were counted by subtracting the days of pre-IVGG fever from the days of total fever, thereby, including the day that IVGG was administered. All patients were treated with high-dose IVGG (2 g/kg) delivered in a single dose and high-dose aspirin (80–100 mg/kg/day) during the acute stage and, thereafter, with low-dose aspirin (3–5 mg/kg/day) [18]. The development of CAA was evaluated by serial echocardiograms performed at the acute phase of the disease, usually between 7 and 10 days after the onset of fever and, thereafter, at monthly intervals for at least 2 months. During this period, patients exhibiting any CAA, regardless of later resolution, were counted as CAA (+). Variables, including clinical manifestations, laboratory findings during the acute febrile phase before IVGG, and responses to treatment, were analyzed by using SPSS for Windows (SPSS Inc., Chicago, IL). The data were expressed as mean±standard deviation or percentages, where appropriate. Nominal data and continuous data were analyzed using the chi-square test and the unpaired t-test, respectively. Data showing a significant difference were tested again by multivariable logistic regression analysis. A p-value of <0.05 was considered to be statistically significant.

Results

Comparison of variables in CAA(+) and CAA(−) patients

Of the 136 KD patients, 16 patients had complications of CAA (11.8%). Table 1 summarizes the clinical and laboratory findings of the patients. The incidence of CAA did not differ in a gender-specific manner. The CAA(+) group had fewer diagnostic symptoms (which always included fever) than the CAA(−) group (2.7±1.1 vs. 4.3±1.2, p<0.001). Of the 15 CAA(+) patients with incomplete KD, two, five, six, and two patients had one, two, three, and four symptoms, respectively. Of the 62 CAA(−) patients with incomplete KD, three, seven, 19, and 33 patients had one, two, three, and four symptoms, respectively. The symptom that was most frequently absent in the incomplete KD cases was changes in extremities. This was true regardless of whether the patients had CAA or not.

The CAA(+) group had a longer duration of total fever than the CAA(−) group (9.1±3.7 days vs. 6.3±2.0 days, p=0.011) and were more likely to have total fevers lasting eight or more days. The CAA(+) group was also more likely to have pre-IVGG fever lasting for seven or more days than the CAA(−) group (43.6% vs. 12.5%, p=0.005). With regard to the Harada score (which was originally designed to establish the indications for IVGG [10] and whose components are now frequently cited as risk factors for the development of CAA), even the highest Harada scores of 6 or 7 did not predict CAA. Of the hematological findings, the CAA(+) group only differed from the CAA(−) group in having significantly higher total white blood cell (19.2±6.0 K/mm³ vs. 14.7±4.7 K/mm³, p=0.007) and platelet (462.9±101.0 K/mm³ vs. 383.6±121.1 K/mm³, p=0.014) levels. The two groups did not differ in C-reactive protein (CRP) levels, which is not consistent with the observations of two other studies examining general populations of KD patients [12, 14]. While the CAA(+) group tended to have higher levels of B-type natriuretic peptide (BNP), which is a sensitive but unspecific marker of cardiac structural and functional abnormalities [16], this difference did not attain statistical significance (p=0.276). The CAA(+) group showed more myocardial and/or
pericardial involvements than the CAA(−) group (62% vs. 17.5%, p<0.001).

We then examined the incomplete KD patients more closely, and the results are shown in Table 2. Of the 136 patients, 77 (56.6%) showed incomplete clinical manifestation (classified as having four or fewer symptoms). Of these, 15 developed CAA (19.5%). Conversely, complete manifestations (classified as having five or six symptoms) were observed in 59 of the 136 patients (43.3%), of which, only one developed CAA (1.7%). Thus, incomplete clinical manifestation was highly associated with the development of CAA. This was especially true if the patients had three or fewer symptoms, because, of the CAA(+) patients, 81.3% had fewer than four symptoms compared to only 24.7% of the CAA(−) patients (p<0.001). Furthermore, of the 16 CAA cases, 15 (93.7%) showed incomplete KD manifestations.

To determine whether incomplete KD manifestations delayed diagnosis, we compared the pre-IVGG fever durations of the CAA(+) and CAA(−) patients with fewer than four or five symptoms (Table 2). While the CAA(+)
patients with fewer than five symptoms did tend to have pre-IVGG fever for longer than the equivalent CAA(−) group (6.9±4.1 days vs. 4.8±1.5 days), this difference was not significant (\( p=0.068 \)). This was also true for the patients with less than four symptoms, as the CAA(+) patients with fewer than four symptoms had, on average, 6.7±4.2 days of pre-IVGG fever compared to 5.0±1.6 days for the equivalent CAA(−) group (\( p=0.174 \)). Thus, not having all of the symptoms did not significantly delay the diagnosis.

Comparison of the durations of post-IVGG fever revealed no significant difference between the incomplete presenting CAA(+) and CAA(−) patients (Table 2), which indicates that responsiveness to treatment is not responsible for the development of CAA. Consistent with the observations in Table 1, the incomplete presenting CAA(+) patients had a significantly longer duration of total fever than the equivalent CAA(−) patients, which suggests that the total fever duration may be a risk factor for CAA.

Risk factors predicting the development of CAA

Several variables, including those shown in Table 1 to differ significantly between the CAA(+) and CAA(−) groups, were tested with multivariable logistic regression analysis (Table 3). The number of total symptoms showed an odds ratio of 0.493, indicating that having one more symptom decreased the risk of CAA by 0.493-fold. In other words, one less symptom increased the risk by 2.028-fold (95% CI=0.293–0.829, \( p=0.007 \)). The number of days of total fever showed an odds ratio of 1.405, indicating that one more day of fever increased the risk by 1.405-fold (95% CI=1.092–1.808, \( p=0.008 \)). The two groups did not differ significantly in terms of the other variables tested, namely, the Harada score and the levels of white blood cells, platelets, CRP, alanine aminotransferase, and total bilirubin.

### Table 3 Multivariable logistic regression analysis of potential risk factors for developing CAA

<table>
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<tr>
<th>Variables</th>
<th>Odds ratio (CI*)</th>
<th>p-value</th>
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<tr>
<td>Total no. of symptoms</td>
<td>0.493 (0.293–0.829)</td>
<td>0.007</td>
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<td>Days of total fever</td>
<td>1.405 (1.092–1.808)</td>
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<td>Harada score</td>
<td>0.997 (0.369–2.693)</td>
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<td>WBC</td>
<td>1.000 (1.000–1.000)</td>
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<td>Platelet</td>
<td>1.000 (1.000–1.000)</td>
<td>0.856</td>
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<tr>
<td>CRP</td>
<td>1.006 (0.858–1.811)</td>
<td>0.938</td>
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<tr>
<td>ALT</td>
<td>1.007 (1.000–1.015)</td>
<td>0.052</td>
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<tr>
<td>Bilirubin, total</td>
<td>1.199 (0.642–2.241)</td>
<td>0.569</td>
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CI=95% confidence interval
CAA=coronary artery abnormality; WBC=white blood cell; CRP=C-reactive protein; ALT=alanine aminotransferase

**Discussion**

In the majority of KD cases, most or all of the clinical manifestations appear in a tight cluster within the first five days, thereby, enabling complete diagnosis. However, in some cases, incomplete presentation occurs. Sometimes, this is because the clinical manifestations are presented over a prolonged course of time. The intervention with IVGG may also modify the development of additional signs. Incomplete presentation is a major obstacle for the diagnosis of KD and can lead to delays in diagnosis. Such delays in diagnosis and subsequent treatment may be why the development of CAA is associated with incomplete presentation [5,19,20]. However, whether incomplete presentation is a risk factor for CAA in KD has not been assessed, as previous studies have only examined incomplete KD cases when coronary abnormalities were involved [5]. To address this issue, here, we examined a cohort of KD patients that included patients with incomplete and complete KD. We then compared their relative rates of CAA development. The incomplete KD patients were diagnosed on the basis of other supportive laboratory findings and typical convalescent findings. The general prevalence of incomplete KD in a nationwide surveillance in Japan is about 13.8% [2]. In contrast, the prevalence of incomplete KD in our study was 56.6%, which suggests that incomplete presentation occurs much more commonly in infants.

We observed that CAA developed significantly more frequently in cases with incomplete KD. Multivariable analysis of various variables, including the number of total symptoms and the total fever duration, revealed that having one less symptom increased the risk of developing CAA by 2.028-fold (Table 3). It has been suggested previously that the incomplete presentation of KD may be associated with a higher incidence of CAA because it delays treatment [1,3]. However, while the CAA(+) patients had, on average, a ~2-day longer duration of pre-IVGG fever than CAA(−) patients, this difference did not attain statistical significance. This may be because of the relatively small numbers in this study population. It is also possible, although it is less likely, that incomplete manifestation did not consistently delay treatment in our patients. However, if this would be the case, it may suggest that incomplete KD be an independent risk factor for CAA. Since the CAA(+) and CAA(−) groups did not differ in the duration of post-IVGG fever, it appears that the development of CAA by this age group does not depend on the responsiveness to IVGG.

The acute phase in most KD patients is characterized by leukocytosis, especially the dominance of polymorphonuclear leukocytes, which is suggestive of an infectious etiology. In addition, the greater incidence of KD in young children than in older children and adults suggests that KD...
pathogenesis may be the result, at least in part, of an immature or dysfunctional immune response to infections. Since a functional immune system is needed not only to terminate inflammation but also to develop clinical symptoms, the inadequate immune system of young children may explain the high frequency of incomplete presentation that terminates inflammation but also to develop clinical symptoms. Incomplete immune response to infections. The pathogenesis may be the result, at least in part, of an immature or dysfunctional immune response to infections.


In conclusion, incomplete clinical manifestation not only makes the diagnosis of KD difficult, but it may also be an inherent predisposing factor for CAA in KD patients younger than 1 year of age. These results strongly suggest that, in this age group, the diagnostic criteria for KD should be revised such that incomplete manifestation of the diagnostic symptoms of KD should not be a reason for delaying IVGG therapy. Moreover, until a definitive diagnostic test for KD is available, coronary investigation should be performed in patients younger than 1 year old who have presented with an unexplained fever lasting more than fever days and any of the clinical manifestations supporting the diagnosis of KD. Treatment should be initiated appropriately so that the duration of total fever does not exceed eight days.

References


Refractory Kawasaki Disease

Alexandra F. Freeman, MD and Stanford T. Shulman, MD

Key Words: Kawasaki disease, IVGG therapy, refractory.

(Pediatr Infect Dis J 2004;23: 463–464)

Kawasaki disease (KD) is a vasculitis of early childhood with a striking predilection for the coronary arteries. Treatment is directed toward the inflammatory response responsible for clinical and pathologic manifestations. Current treatment reduces risk of coronary sequelae at 1–2 months after disease onset from 20–25% to 2–4%.1 When given within 10 days of onset of fever, intravenous immunoglobulin (IVIG) at 2 g/kg with high dose aspirin (80–100 mg/kg/day) results in rapid defervescence and clinical improvement in ~90% of patients.

Specific guidelines do not exist for the management of patients who do not respond to initial therapy. Several nonresponsive patients are a challenge because the risk for coronary artery sequelae increases with prolonged fever. It is not possible to predict prospectively that a KD patient will not respond to initial therapy; responders and nonresponders have comparable baseline characteristics, such as age, sex and number of diagnostic criteria. Some have identified lab predictors of IVIG nonresponsiveness, such as degree of anemia, height of C-reactive protein and lactate dehydrogenase elevation,2 but others found non significant lab differences between responders and nonresponders.3,4 A retrospective study found that KD patients treated earlier in their illness were more likely to be refractory to therapy3; other studies did not replicate this finding.5

INITIAL APPROACH TO THE REFRACTORY KD PATIENT

Few studies address treatment of IVIG-refractory KD because only 10–15% of patients fail initial therapy, and the disease is self-limited, making it difficult to ascribe benefit to a therapeutic intervention without controlled trials with adequate numbers of patients. Such studies do not exist.

Most centers, including ours, treat the KD patient who remains febrile or has recurrence of fever 48–72 h after initial 2 g/kg IVIG and high dose aspirin with an additional 2 g/kg IVIG.5 In a retrospective study of 179 patients treated with IVIG, 89% responded to the first dose of IVIG, and 67% of nonresponders responded to a second dose of IVIG.3 Thus, only 3–4% of KD patients failed to respond after the second dose of IVIG with aspirin. Although most US centers use a second IVIG dose of 2 g/kg, no controlled trials have compared 1 g/kg to 2 g/kg IVIG for retreatment. The antiinflammatory effect of aspirin also may be optimized by monitoring serum salicylate levels. Judicious adjustment of salicylate dose to 120 mg/kg/day or more, with monitoring of serum salicylate concentration to detect impending toxicity, may be helpful. When treating apparently refractory KD patients, it is also prudent to reconsider the diagnosis, as no diagnostic test exists for KD and other illnesses may mimic its presentation.

There are various approaches to the KD patient who remains febrile and ill after 2 doses of 2 g/kg IVIG, and there are very few data on which to base recommendations. The most common approaches are to treat (1) with a third dose of IVIG (usually 2 g/kg) or (2) with corticosteroids. We most often give a third dose of IVIG, although at least some patients who have failed 2 doses of IVIG also fail the third. In the previously cited study, only 2 of 179 patients received a third dose of IVIG, and both remained febrile.3 An alternative is to treat KD patients who fail 1, 2 or 3 doses of IVIG with corticosteroids as “rescue therapy.”

STEROID USE IN KD

Although KD is a vasculitis and corticosteroids are a mainstay of therapy for vasculitides, KD is unusual in that there is strong evidence of an infectious etiology. Reluctance to use corticosteroids for KD dates to Kato’s study in 1979, in the pre-IVIG era. In this small study KD patients treated with oral prednisolone had a particularly high rate of development of coronary aneurysms (11/17, 65%). None of 7 patients in this study treated with aspirin and prednisolone developed coronary aneurysms. Although this and other early studies led to caution regarding steroids in KD, it was a small, nonrandomized study, and steroids were used as “primary therapy.” Recent reports of corticosteroids as “rescue therapy” in IVIG-refractory KD have not shown an association between corticosteroids and an increase in coronary aneurysms. However, caution must still be exercised, because possible adverse effects of corticosteroids include hypertension and thrombosis.

KD patients refractory to IVIG were reported to improve and to defervesce after steroid therapy in several small series. In 1996 Wright reported 4 children who had failed 2 doses of IVIG (2 g/kg followed by 1 g/kg) and who improved after intravenous 30-mg/kg/day methylprednisolone pulses for 1–3 days.

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days without significant worsening of coronary abnormalities (all had abnormal coronary arteries preceding the steroid doses). In 2000 Dale reported 7 KD patients who remained febrile despite IVIG and aspirin and were then treated with oral prednisolone (2 mg/kg/day) for 2 weeks followed by a 6-week taper. Six of 7 patients became afebrile within 72 h of steroids (5 within 48 h), and in none of these 6 patients did coronary disease progress. One patient remained febrile for 10 days despite steroids, with progression of coronary abnormalities. In a small study Hashino treated 17 patients who were febrile despite aspirin and 2 IVIG courses (2 g/kg followed by 1 g/kg), with either pulsed steroids (9) or additional IVIG (8). The 9 who received steroids improved; however, immediate but transient coronary dilatation was noted in 3/9 after steroid therapy. These reports suggest that corticosteroids often hasten defervescence in IVIG-refractory patients. However, a multicenter trial clearly is needed to assess the relative risks and benefits of steroids, especially on coronary abnormalities, and to determine the most appropriate route of administration and dose.

OTHER THERAPIES

Even less published experience exists in IVIG-refractory KD for the use of other therapies typically used to treat other vasculitides. Two KD patients were treated with cyclophosphamide after continued fever and other signs of inflammation despite 2 courses of 2 g/kg of IVIG and 2–4 3-day courses of intravenous methylprednisolone (30 mg/kg/day). Both experienced return of inflammation when corticosteroids were tapered. The addition of cyclophosphamide to prednisone appeared to be associated with resolution of symptoms and lab abnormalities, and both medications were tapered slowly over 1.5 and 7 months.

In a recent Japanese study, 50 refractory KD patients improved after plasma exchange, and coronary abnormalities were detected in 20%; 69 refractory patients were treated with additional IVIG, and coronary abnormalities were detected in 41%. Cyclosporin A was used in a highly refractory patient, who had failed 4 courses of IVIG and 3 days of pulse steroids. The patient finally became afebrile 7 days after addition of cyclosporin A to steroids, although coronary aneurysms remained. Although these therapies apparently have adverse effects, the number of patients treated is extremely limited, and the necessary controlled trials have not been performed. That KD is self-limited compounds the difficulty of reaching conclusions regarding efficacy of a specific therapy without a controlled trial.

Ulinastatin is a neutrophil-elastase inhibitor available in Japan that is purified from human urine and used in Japan for inflammatory conditions such as Stevens-Johnson syndrome and for refractory KD in small uncontrolled trials. Additional studies are needed with appropriate controls.

Recently infliximab (Remicade), a monoclonal antibody against tumor necrosis factor-α (TNF-α), was used in a few IVIG-refractory KD patients. Infliximab is licensed for treatment of rheumatoid arthritis and Crohn’s disease. It is hypothesized to be beneficial in KD because TNF-α may be involved in the inflammatory process in acute KD. Burns et al. reported 7 acute KD patients who were refractory to IVIG and aspirin and then treated with 1 infusion of 5 mg/kg infliximab. These patients had failed to respond to 2 or 3 doses of IVIG, and 3 remained febrile despite 3–5 doses of methylprednisolone. All improved and defervesced after one dose of infliximab with no adverse effects. Coronary aneurysms were noted in all 7 patients before infliximab therapy, with subsequent normalization in 3/7 patients. Our experience with infliximab for refractory KD is limited to 2 patients, one who had an 8-day response but then relapsed and another in whom the response was indeterminant. To address the benefit of infliximab in refractory patients, a multicenter clinical trial is planned.

CONCLUSIONS

Therapy for KD with IVIG and aspirin has reduced the incidence of coronary aneurysms remarkably, from about 20–25% to <3%. However, for nonresponsive patients, limited data are available to guide therapy. Although most opt to treat such patients with additional IVIG, some patients remain refractory to therapy and are treated with corticosteroids and occasionally more experimental therapies such as immunosuppressants (e.g., cyclophosphamide) or infliximab. The relative value of these rescue therapies is difficult to assess due to both the self-limited nature of KD and the limited number of patients. Multicenter trials are necessary to assess clinical response and potential adverse outcomes. Because no diagnostic test exists for KD, one must always remain vigilant for the possibility of an alternative diagnosis in the patient with apparent refractory KD.

REFERENCES


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