Guidelines for Long-term Management of Patients With Kawasaki Disease

Report From the Committee on Rheumatic Fever, Endocarditis, and Kawasaki Disease, Council on Cardiovascular Disease in the Young, American Heart Association

Adnan S. Dajani, MD (Chair); Kathryn A. Taubert, PhD; Masato Takahashi, MD; Fred Z. Bierman, MD; Michael D. Freed, MD; Patricia Ferrieri, MD; Michael Gerber, MD; Stanford T. Shulman, MD; Adolf W. Karchmer, MD; Walter Wilson, MD; Georges Peter, MD (Liaison, American Academy of Pediatrics); David T. Durack, MD, DPhil (Liaison, Infectious Diseases Society of America); Shahbudin H. Rahimtoola, MD; (Liaison, Council on Clinical Cardiology)

Kawasaki disease, a generalized vasculitis of unknown etiology, is a leading cause of acquired heart disease in children in the United States. During the acute phase, Kawasaki disease may cause medium- and large-vessel arteritis, arterial aneurysms, valvulitis, and myocarditis. Of particular concern are coronary artery aneurysms, which may precipitate thrombosis or evolve into segmental stenoses in the chronic phase. This committee's previously published articles on diagnostic criteria and therapeutic recommendations for acute Kawasaki disease defined the clinical and laboratory features of Kawasaki disease, made recommendations about the use of aspirin and intravenous gamma globulin, and discussed unresolved therapeutic issues. In this report, guidelines for the long-term follow-up and management of patients with Kawasaki disease are addressed.

Intravenous gamma globulin therapy instituted before the 10th day of illness has reduced both the morbidity of Kawasaki disease and the apparent incidence of coronary artery abnormalities from approximately 20% to 25% to less than 5% at 6 to 8 weeks after initiation of therapy. In most patients coronary ectasia or aneurysms regress within 1 to 2 years. Approximately 1% of patients who recover from acute Kawasaki disease will develop giant coronary artery aneurysms or coronary artery obstruction due to thrombosis or stenosis. The wide spectrum of clinical outcomes, ranging from no sequelae in the majority of patients to life-threatening coronary artery abnormalities in a few, necessitates various management options. Frequency of clinical evaluation and diagnostic testing, as well as long-term medical therapy, should reflect the natural history of Kawasaki disease and its psychosocial and economic impact. In the absence of prospective or retrospective long-term follow-up data, the recommendations presented here are practical interim guidelines.

Assessment of Coronary Artery Anatomy and Myocardial Perfusion

The initial assessment begins in the early phase of the disease.

Echocardiography

Echocardiography is the primary tool for evaluation and follow-up of coronary artery abnormalities. However, for patients with persistent large coronary aneurysms after the first year of follow-up, echocardiography has serious limitations, including its inability to distinguish intimal surface from highly echoreflective adventitial layer or to detect thrombosis or stenosis with accuracy. Also, visualization of coronary arteries becomes progressively more difficult as a child grows and body size increases. Intravascular imaging of the coronary arteries may allow more detailed visualization of coronary wall morphology and the healing process.

Documentation and follow-up of the cardiovascular, and especially the coronary, sequelae of Kawasaki disease require serial cardiac ultrasound studies, which should be supervised or performed by an experienced pediatric echocardiographer. The initial echocardiogram should be obtained as soon as the diagnosis of Kawasaki disease is suspected. This preliminary examination establishes a baseline for longitudinal follow-up of coronary artery morphology, cardiac valvar function, left ventricular function, and evolution and resolution of pericardial effusion when present.
Detailed echocardiographic examination of cardiovascular anatomy is often compromised if an infant is febrile, agitated, and uncooperative. Cardiac ultrasound studies in this population often require that the patient be sedated with high-dose chloral hydrate (65 to 100 mg/kg, maximum dose 1000 mg) or other short-acting sedative or hypnotic agents.

Two-dimensional echocardiographic examination includes display of the left main, anterior descending, and left circumflex coronary arteries as well as the proximal, middle, and distal segments of the right coronary artery and the posterior descending coronary artery. These vessels are visualized in multiple planes using a combination of parasternal long-axis and short-axis and apical four-chamber and two-chamber views, as well as subcostal long and short axis projections (Table 1 and Figure). The diagnosis of normal coronary artery anatomy should not be made until all major coronary artery segments have been visualized and judged to be normal.

The cardiac ultrasound examination should be performed using transducers with the highest frequency possible. This typically requires a 7.5-MHz probe in infants, a 5.0-MHz probe in toddlers, and a 3.5-MHz or 5-MHz probe in older children. Display of coronary artery anatomy is facilitated by the normal translational movement of the heart. Therefore, studies should be recorded in a dynamic video format. This also provides for future review.

Evaluation of coronary artery morphology should include quantitative or qualitative assessment of the inner diameters of the vessels. This may be expressed in millimeters or as percent enlargement relative to an adjacent normal segment. Measurements should exclude points of branching, which may have normal focal dilation. Configuration and number of aneurysms and the presence or absence of intraluminal or mural thrombi should also be assessed. Aneurysms are identified as saccular (nearly equal axial and lateral diameters) or fusiform (symmetric segmental dilatation with gradual proximal and distal tapering). When the coronary artery diameter is larger than normal but a segmental aneurysm is not apparent, the vessel is described as ectatic. Care must be taken in making the diagnosis of ectasia because of considerable normal variation in coronary artery distribution and dominance.6 Aneurysms are classified as small (less than 5 mm in internal diameter), medium (5 to 8 mm in internal diameter), or giant (more than 8 mm in internal diameter).

Left ventricular function is assessed by end-systolic and end-diastolic dimensions and shortening fraction (percent change in cross-sectional diameter). These basic parameters of function, although influenced by loading conditions, are more readily measured than complex indexes of contractility and are adequate for routine clinical follow-up of the patient.

The presence and degree of valvar regurgitation is assessed by standard color flow mapping and pulsed Doppler techniques. Color flow Doppler with a low Nyquist limit setting may be useful in positively identifying coronary artery lumens when the angle of view is favorable.

**Electrocardiogram**

A standard 12-lead electrocardiogram is recommended. Sinus tachycardia, reduction in QRS amplitude, flattening of T waves, prolongation of rate-adjusted PR and QT intervals, and occasional dysrhythmias may occur. During long-term follow-up, the electrocardiogram may indicate ischemia or infarction.

**Stress Testing**

Exercise stress testing may be carried out, with either a treadmill ergometer or a bicycle ergometer, as part of long-term follow-up of patients with documented or suspected coronary artery disease. For patients too young or unable to perform an exercise test, pharmacologic stress testing may be done with intravenous infusion of diprydamole, adenosine, or dobutamine. A stress test with electocardiographic monitoring alone as a method of ischemia detection appears to have low sensitivity and specificity; radioisotope myocardial perfusion scan or regional wall motion assessment by echocardiography in combination with stress testing appears to have a higher sensitivity. However, these modalities of stress testing are still undergoing evaluation at various centers.

**Coronary Angiography**

Before recommending that a patient undergo angiography, the physician must compare the potential benefit of the procedure with the risks and cost.

Coronary angiography offers more detailed definition of coronary artery anatomy than cardiac ultrasound, making it possible to detect coronary artery stenosis or thrombotic occlusion and determine the extent of collateral artery formation. The decision to use it may be guided by echocardiographic imaging of coronary arteries, ventricular wall motion abnormalities, or clinical and electrocardiographic signs or radioisotope perfusion studies indicating myocardial ischemia.

### Table 1: Echocardiographic Views of Coronary Arteries in Patients With Kawasaki Disease

<table>
<thead>
<tr>
<th>Location</th>
<th>Description</th>
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<tbody>
<tr>
<td>Left main coronary artery</td>
<td>Precordial short axis at level of aortic valve; parasternal midline (superior tangential); apical left ventricular long axis</td>
</tr>
<tr>
<td>Left anterior descending artery</td>
<td>Precordial short axis at level of aortic valve; parasternal superior tangential long axis of left ventricle; parasternal short axis of left ventricle</td>
</tr>
<tr>
<td>Left circumflex</td>
<td>Precordial short axis at level of aortic valve; apical four-chamber</td>
</tr>
<tr>
<td>Right coronary artery</td>
<td>Proximal segment: Precordial short axis at level of aortic valve; parasternal long axis (inferior tangential) of left ventricle; subcostal coronal projection of right ventricular outflow tract; subcostal short axis at level of atriocentric groove</td>
</tr>
<tr>
<td>Right coronary artery</td>
<td>Middle segment: Precordial long axis of left ventricle (inferior tangential); apical four-chamber; subcostal left ventricular long axis; subcostal short axis at level of atriocentric groove</td>
</tr>
<tr>
<td>Right coronary artery</td>
<td>Distal segment: Apical four-chamber (inferior); subcostal atrial long axis (inferior)</td>
</tr>
<tr>
<td>Posterior descending coronary</td>
<td>Apical four-chamber (inferior); subcostal atrial long axis (inferior)</td>
</tr>
<tr>
<td>Thoracocostal aorta</td>
<td>Subcostal parallel to sagittal plane of trunk</td>
</tr>
<tr>
<td>Celiac and mesenteric arteries</td>
<td>Subcostal parallel to sagittal plane of trunk</td>
</tr>
</tbody>
</table>
The usefulness of coronary angiography is limited in that the procedure does not specifically detect intramural changes in the coronary artery. Postmortem examinations of some patients with angiographically documented regression of coronary artery aneurysms have revealed intimal proliferation and fibrosis not apparent on angiogram. This suggests that larger aneurysms heal by a process of endothelial lamination that obscures the aneurysm. This process is manifested angiographically as a blunted response to coronary vasodilator provocation. The long-term clinical implications of these anatomic and functional changes are unknown at this time.

Serum Lipid Profiles

In several reports abnormal convalescent serum lipid profiles have been identified after the acute febrile phase of Kawasaki disease in a subset of patients. In most reports these profiles returned toward normal by 1 year after onset of the disease. Additional studies to confirm these observations are needed; for now, counseling of parents and patients should conform with standard recommendations on nutrition for children and adolescents. For patients whose lipid profiles are abnormal, the physician may remeasure lipid levels a year later.

Long-term Follow-up

Long-term management of patients with Kawasaki disease depends on the degree of coronary arterial involvement. Follow-up of a patient with coronary arterial aneurysms must be adapted to his or her clinical course and severity of the lesions. In all but a few patients, repeat cardiac ultrasound examination may be performed 6 to 8 weeks after the onset of illness if there has been no evidence of giant coronary artery aneurysms or thrombus formation and if clinical and laboratory signs of systemic inflammation have resolved. Follow-up echocardiographic examinations should identify progression or regression of aneurysms, and focal narrowing at the proximal and distal ends of an aneurysm should be noted. The physician may choose to perform an electrocardiogram when the echocardiographic study is done. A small subset of children with Kawasaki disease have valvar involvement; during follow-up examination of these children the possibility of mitral or aortic regurgitation should be considered.

Longitudinal follow-up of all patients begins 10 to 14 days after the onset of illness. In a great majority of patients who will develop coronary artery aneurysms, early signs of aneurysm formation are apparent at this time. In the absence of giant coronary arterial aneurysms or intraluminal coronary thrombi, repeat cardiac ultrasound examination may be performed 6 to 8 weeks after the onset of illness, when clinical and laboratory signs of systemic inflammation have subsided. Subsequent cardiac ultrasound studies for patients with no coronary arterial involvement or with ectasia or a solitary small aneurysm are performed 6 to 12 months after the onset of acute illness.

Stenosis or thrombus formation is most frequently seen in patients with giant aneurysms. Such patients
TABLE 2. Recommendations

<table>
<thead>
<tr>
<th>Risk level</th>
<th>Pharmacologic 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 initial 6 to 8 weeks</td>
<td>No restrictions beyond initial 6 to 8 weeks</td>
<td>None beyond first year unless cardiac disease suspected</td>
<td>None recommended</td>
</tr>
<tr>
<td>II (transient coronary artery ectasia that disappears during acute illness)</td>
<td>None beyond initial 6 to 8 weeks</td>
<td>No restrictions beyond initial 6 to 8 weeks</td>
<td>None beyond first year unless cardiac disease suspected. Physician may choose to see patient at 3- to 5-year intervals</td>
<td>None recommended</td>
</tr>
<tr>
<td>III (small to medium solitary coronary artery aneurysm)</td>
<td>3 to 5 mg/kg aspirin per day, at least until abnormalities resolve</td>
<td>For patients in first decade of life, no restriction beyond initial 6 to 8 weeks. For patients in second decade, physical activity guided by stress testing every other year. Competitive contact athletics with endurance training discouraged.</td>
<td>Annual follow-up with echocardiogram or electrocardiogram in first decade of life</td>
<td>Angiography, if stress testing or echocardiography suggests stenosis</td>
</tr>
<tr>
<td>IV (one or more giant coronary artery aneurysms, or multiple small to medium aneurysms, without obstruction)</td>
<td>Long-term aspirin (3 to 5 mg/kg per day) ± warfarin</td>
<td>For patients in first decade of life, no restriction beyond initial 6 to 8 weeks. For patients in second decade, annual stress testing guides recommendations. Strenuous athletics are strongly discouraged. If stress test rules out ischemia, noncontact recreational sports allowed.</td>
<td>Annual follow-up with echocardiogram ± electrocardiogram ± chest x-ray ± additional electrocardiogram at 6-month intervals. For patients in first decade of life, pharmacologic stress testing should be considered.</td>
<td>Angiography, if stress testing or echocardiography suggests stenosis. Elective catheterization may be done in certain circumstances.</td>
</tr>
<tr>
<td>V (coronary artery obstruction)</td>
<td>Long-term aspirin (3 to 5 mg/kg per day) ± warfarin. Use of calcium channel blockers should be considered to reduce myocardial oxygen consumption.</td>
<td>Contact sports, isometrics, and weight training should be avoided. Other physical activity recommendations guided by outcome of stress testing or myocardial perfusion scan.</td>
<td>Echocardiogram and electrocardiogram at 6-month intervals and annual Holter and stress testing</td>
<td>Angiography recommended for some patients to aid in selecting therapeutic options. Repeat angiography with new-onset or worsening ischemia.</td>
</tr>
</tbody>
</table>

± indicates with or without.

require more frequent follow-up during the acute febrile period and first year after onset of illness. The frequency of follow-up visits for patients with a giant or medium solitary aneurysm or multiple aneurysms is based on the patient's clinical condition. Routine follow-up of this higher-risk population typically includes echocardiographic and sometimes electrocardiographic studies. If these noninvasive studies or clinical symptoms (i.e., chest pain, congestive heart failure, or cardiovascular shock) suggest myocardial ischemia, then radioisotope myocardial perfusion scan, cardiac catheterization with selective coronary angiography, or both are indicated. Patients with no evidence of aneurysm or ectasia at the 1-year evaluation are not likely to benefit from further repeated echocardiographic examination, although patients with transient coronary artery ectasia early in the illness may be followed up at 3- to 5-year intervals.

Management Based on Risk Stratification

Clinical experience with Kawasaki disease permits stratification of patients according to relative risk of myocardial ischemia. Risk level categories are listed below and are summarized in Table 2. This stratification allows for patient management to be individualized with respect to (1) medical therapy to reduce the risk of thrombosis, (2) physical activity, (3) frequency of clinical follow-up and diagnostic testing, and (4) indications for cardiac catheterization and coronary angiography.

Patients with no coronary artery changes on echocardiography at any stage of the illness seem to have no greater risk of future coronary arterial disease than the general population, but longitudinal studies are necessary to test this observation. The risk level for a given patient with coronary arterial involvement may change over time because of changes in coronary artery morphology. For example, regression of aneurysms is assumed to reduce the risk of myocardial ischemia. On the other hand, development of thrombosis or stenosis related to an aneurysm increases the risk.

For patients at certain risk levels, long-term antiplatelet therapy with aspirin is recommended. Some physicians combine aspirin and dipyridamole for antiplatelet therapy, although there are currently no data to support the efficacy of this regimen.

Risk Levels

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

1. No antiplatelet therapy is needed beyond the initial 6 to 8 weeks after the onset of illness (therapy during
the initial weeks is discussed in a previous report from this committee).
2. No restriction on physical activity is necessary after 6 to 8 weeks.
3. Pediatric cardiology follow-up and diagnostic testing are not indicated beyond the first year unless cardiac disease is suspected by the primary care physician. Routine follow-up with the primary care physician should follow established practice of well-child care.
4. Coronary angiography is not recommended.

**Risk level II.** Patients with transient coronary artery ectasia (disappears during the acute illness) on echocardiography.
1. No antiplatelet therapy is needed beyond the initial 6 to 8 weeks after the onset of illness.
2. No restriction on physical activity is necessary after 6 to 8 weeks.
3. Pediatric cardiology follow-up and diagnostic testing are generally not indicated beyond the first year unless cardiac disease is suspected by the primary care physician. Some pediatric cardiologists, however, may want to see these patients at 3- to 5-year intervals. Routine follow-up with the primary care physician should follow established practices of well-child care.
4. Coronary angiography is not recommended.

**Risk level III**. Patients with a small to medium solitary coronary artery aneurysm on echocardiography or angiography.
1. Long-term antiplatelet therapy with aspirin (3 to 5 mg/kg once daily) should be administered, at least until abnormalities resolve. In the event of the patient’s exposure to varicella or influenza, aspirin may be discontinued temporarily to minimize the risk of Reye’s syndrome. Dipyridamole (2 to 3 mg/kg two or three times a day) may be substituted during this period (usually 2 weeks). To reduce the risk of Reye’s syndrome in patients on long-term aspirin therapy, administration of influenza vaccine is recommended.
2. Physical activity in infants and children in the first decade of life is permitted without restriction after the initial 6 to 8 weeks. Stress testing with myocardial perfusion scan may be useful in the second decade to guide recommendations for physical activity. Participation in competitive contact athletics with endurance training is discouraged.
3. Annual follow-up by a pediatric cardiologist is recommended. An annual echocardiogram and perhaps an annual electrocardiogram in patients 10 years of age or younger is recommended; in patients over 10 years of age such testing is at the cardiologist’s discretion. Stress testing every other year with or without myocardial perfusion imaging in patients over 10 years of age may be performed.
4. Coronary angiography may be indicated if a stress test or perfusion imaging study suggests myocardial ischemia or cardiac ultrasound suggests significant stenosis.

**Risk level IV.** Patients with one or more giant coronary artery aneurysms or multiple small to medium aneurysms, without obstruction by echocardiography, preferably confirmed by coronary angiography.
1. Long-term antiplatelet aspirin therapy (3 to 5 mg/kg once daily) is recommended, with or without adjunctive therapy with warfarin sodium (Coumadin) anticoagulation. When warfarin is used, an International Normalized Ratio (INR) of 2.0 to 3.0 (or thrombin time 1.2 to 1.5 times control) should be maintained to provide protection with minimal bleeding complications. (For comments on Reye’s syndrome, see “Risk level III.”)
2. Physical activity in infants and children in the first decade of life is permitted without restriction. Beginning in the second decade, annual stress testing with myocardial perfusion scan is recommended to monitor for ischemia and to form the basis for future recommendations about physical activity. Competitive contact athletics with endurance training and isometric or weight training should be strongly discouraged. Participation in noncontact recreational sports is allowed if the stress test has ruled out stress-induced myocardial ischemia.
3. Pediatric cardiology reevaluation with echocardiogram and perhaps electrocardiogram and chest x-ray should be done at 1-year intervals. Additional electrocardiograms at 6-month intervals may be advisable for certain patients. Stress testing with evaluation of myocardial perfusion should be performed annually in patients over 10 years of age (see “Risk level III”); for younger patients or those unable to perform dynamic exercise, a pharmacologic stress test with myocardial perfusion scan should be considered.
4. Cardiac catheterization with selective coronary angiography should be performed if noninvasive studies suggest myocardial ischemia. Elective cardiac catheterization in the absence of noninvasive evidence of myocardial ischemia may be useful to conclusively rule out subclinical major coronary artery obstructions in some situations, such as when a patient has atypical chest pain, his or her ability to perform dynamic exercise is limited by age, or unique activity restrictions or insurability recommendations are needed.

**Risk level V.** Patients with coronary artery obstruction confirmed by angiography.
1. Long-term antiplatelet therapy with or without adjunctive therapy with warfarin anticoagulation is recommended (see “Risk level IV”). Calcium channel-blocking drugs should be considered to reduce myocardial oxygen consumption. (For comments on Reye’s syndrome, see “Risk level III.”)
2. Recommendations about noncompetitive dynamic physical activities at low to moderate intensity should be made on the basis of the patient’s response to stress testing or myocardial perfusion scan. Recommendations about participation in noncontact recreational sports should be based on the outcome of stress testing. Isometric or weight training should be avoided.
3. Pediatric cardiology evaluation should be obtained at 6-month intervals with an echocardiogram and electrocardiogram. An annual Holter monitor test should be performed to determine the presence of arrhythmias or myocardial ischemia. Stress testing with evaluation of myocardial perfusion should be performed annually in patients in the second decade of life; for younger patients or those unable to perform dynamic exercise, a pharmacologic stress test with myocardial perfusion scan should be considered.
4. Cardiac catheterization with selective coronary angiography is recommended to address the therapeutic options of bypass grafting or balloon angioplasty and to identify the extent of collateral perfusion. Repeated cardiac catheterization and selective coronary angiog-
raphy are indicated when new-onset or worsening myocardial ischemia is suggested by noninvasive diagnostic testing or clinical presentation.

**Thrombolytic Therapy**

Some patients may develop acute myocardial infarction, usually related to thrombosis. In this situation, prompt thrombolytic therapy is indicated. Myocardial infarction should be suspected in patients with chest pain, abdominal discomfort, nausea or vomiting, or weakness with pallor, diaphoresis, and inconstant crying. Diagnosis is confirmed by electrocardiographic changes and elevation of the MB isoenzyme of creatine kinase. Newly developed thrombi may be observed in the aneurysmal coronary artery lumen. The patient should be transferred to the nearest pediatric tertiary care facility only if transport would take less than 1 hour. If rapid transfer is not possible, thrombolysis should be initiated at a local hospital in consultation with an adult or pediatric cardiologist. The patient should be monitored for evolution of cardiac arrhythmias, extension of infarct, and bleeding. Chronic warfarin therapy (see “Risk level IV”) is usually initiated after recovery from the acute infarction.

**Surgical Revascularization**

In some patients coronary artery obstruction may be severe enough to warrant surgical revascularization. Technical limitations and low graft patency rate confound surgical management of coronary artery obstruction in patients under 5 years of age. The patency rate of saphenous vein grafts is generally unsatisfactory, and bypasses using the internal thoracic (mammary) artery are technically problematic in the younger population. In older children, internal thoracic and gastroepiploic artery grafts appear to offer better long-term patency and growth in caliber than saphenous vein grafts. Although the available data are few and anecdotal, percutaneous transluminal coronary angioplasty has not produced consistent or lasting improvement in myocardial perfusion in patients with Kawasaki disease.

**Summary**

Long-term management of patients with Kawasaki disease should be tailored to the degree of coronary arterial involvement. This committee has made recommendations for each risk level about antiplatelet and anticoagulant therapy, physical activity, follow-up assessment by a pediatric cardiologist or primary care physician, 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 changes in coronary artery morphology. The recommendations for management presented here are intended as practical interim guidelines until additional prospective or retrospective data are compiled to define more clearly the natural history of Kawasaki disease.

**References**


**Additional Reading**


Guidelines for long-term management of patients with Kawasaki disease. Report from the Committee on Rheumatic Fever, Endocarditis, and Kawasaki Disease, Council on Cardiovascular Disease in the Young, American Heart Association.
A S Dajani, K A Taubert, M Takahashi, F Z Bierman, M D Freed, P Ferrieri, M Gerber, S T Shulman, A W Karchmer and W Wilson

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