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Kawasaki Disease

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REVIEW TOPIC OF THE WEEK

Kawasaki Disease

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ABSTRACT

Kawasaki disease is an acute, self-limited vasculitis of unknown etiology that occurs predominantly in infants and children. If not treated early with high-dose intravenous immunoglobulin, 1 in 5 children develop coronary artery aneurysms; this risk is reduced 5-fold if intravenous immunoglobulin is administered within 10 days of fever onset. Coronary artery aneurysms evolve dynamically over time, usually reaching a peak dimension by 6 weeks after illness onset. Almost all the morbidity and mortality occur in patients with giant aneurysms. Risk of myocardial infarction from coronary artery thrombosis is greatest in the first 2 years after illness onset. However, stenosis and occlusion progress over years. Indeed, Kawasaki disease is no longer a rare cause of acute coronary syndrome presenting in young adults. Both coronary artery bypass surgery and percutaneous intervention have been used to treat Kawasaki disease patients who develop myocardial ischemia as a consequence of coronary artery aneurysms and stenosis. (J Am Coll Cardiol 2016;67:1738–49) © 2016 by the American College of Cardiology Foundation.

Kawasaki disease (KD) is an acute, self-limited vasculitis of unknown etiology that occurs predominantly in infants and young children. Manifested initially by high fever, mucocutaneous inflammation, and cervical lymphadenopathy, KD targets the coronary arteries and other cardiovascular structures (1). Approximately 1 in 5 children who are not treated with intravenous immunoglobulin (IVIG) in the acute phase of illness develop coronary artery aneurysms (CAA). Indeed, KD has replaced rheumatic fever as the leading cause of acquired cardiac disease in children in the developed world. This review describes our current understanding, as well as knowledge gaps, of the pathophysiology of KD and general principles guiding the care and management of these patients in the absence of evidence-based guidelines (Central Illustration). Diagnostic criteria for complete and incomplete KD are detailed in the 2004 American Heart Association/American Academy of Pediatrics guidelines (2).

EPIDEMIOLOGY

The epidemiology of KD may yield important clues to the etiology of this mysterious disease. First, KD strikes predominantly infants and young children; 80% of patients are younger than 5 years of age, although the disease can occur even in adolescence. The young age of onset suggests that susceptibility may be linked to maturation of the immune system. Second, although KD has been recognized on every continent and in all racial groups (3), the incidence of disease varies widely among different populations. In Japan, the country of highest incidence, the numbers of cases are steadily increasing and the most recent survey reported an incidence of 265 cases per 100,000 children <5 years of age (4). In the United States, passive surveillance and analysis of administrative databases suggest a national incidence in children <5 years of age of 19 per 100,000, with a higher rate of 24.7 per 100,000 reported for California (5). An important genetic contribution to disease...
susceptibility is suggested by the higher incidence among U.S. children of Asian/Pacific Islander descent in Hawaii and California (210 and 50.4 per 100,000, respectively) (6,7). A distinct seasonality is coherent across the Northern Hemisphere (8).

The current KD paradigm is that an immunologic reaction is elicited in genetically susceptible hosts upon exposure to the KD trigger(s), thought to be widely dispersed in the environment and to enter through the upper respiratory tract (9). A subset of genetically susceptible children (~25%) will suffer irreversible damage to the coronary arterial wall. There is no evidence to support person-to-person spread, although temporal and spatial clustering of cases is well-documented (10). Two potential paradigms postulate that the trigger is either of the following: 1) an infectious agent that replicates in the superficial epithelial cells of the upper airway (11); or 2) an antigen widely dispersed in the environment. Recent intriguing data support the hypothesis that the trigger for KD is carried by large-scale tropospheric winds and that provinces in northeastern China serve as a source region for the seasonal clustering and annual epidemic of KD cases in Japan, Hawaii, and southern California (12).

**PATHOPHYSIOLOGY**

The complex picture that is emerging of the immune response in acute KD includes activation of both the innate and adaptive immune systems. Neutrophils are among the first responders to invade the arterial wall and are followed by CD8+ T cells, dendritic cells, and monocyte/macrophages (13,14). Strong support for activation of the interleukin (IL)-1 pathway includes increased transcript abundance for IL-1-related genes by microarray and quantitative real-time polymerase chain reaction, and by increased levels of IL-1 pathway proteins in plasma from acute KD patients (15). In KD, as in giant cell arteritis (16), 2 dominant cytokine clusters are recognized: the IL-6/T helper (Th)-17 axis and the IL-12/interferon gamma axis. IL-6, in combination with transforming growth factor beta (TGFβ), polarizes naïve T cells toward a Th-1 helper (Th) 17 phenotype, resulting in these cells invading the vessel wall and elaborating a proinflammatory cytokine profile (17,18). Evidence is accumulating that, in a subset of patients who develop CAA, the IL-12/interferon gamma axis may be activated and proinflammatory cytokines may play a role in inducing activation of Th-1 cells in the vessel wall (19-22).

Mouse models of coronary arteritis mimicking KD have been created by intraperitoneal injection of cell wall extracts of both *Lactobacillus casei* and *Candida albicans* into certain genetic strains (23). These models have been used to interrogate responses to different therapies and provide support for the use of IVIG, blockade of tumor necrosis factor alpha and IL-1, and, potentially, the use of atorvastatin to modulate the acute phase of vascular wall inflammation (24-26).

The complex genetics of KD is beginning to yield to efforts by multinational collaborative groups to determine the genetic influences on disease susceptibility and outcome (27). Roughly 65% of the genetic risk for KD susceptibility is accounted for by polymorphisms in calcium signaling pathways, the TGFβ pathway, and human leukocyte antigens (28-31).

**PATHOLOGY**

The pathological changes in KD affect medium-sized, extra-parenchymal muscular arteries, most commonly the coronary arteries. A recent comprehensive review of 32 KD autopsies and 8 explanted hearts described 3 linked vasculopathic processes in the arterial wall: necrotizing arteritis, subacute/chronic vasculitis, and luminal myofibroblastic proliferation (LMP) (32). The acute arteritis is characterized by a neutrophilic infiltrate originating from the lumen of the vessel and can be associated with extensive necrosis of all layers of the vessel wall in both the coronaries and other medium-size arteries (13). Neutrophil elastases may also play a role in destruction of the internal and external elastic laminae that provide recoil for the vessel wall and whose destruction contributes to aneurysm formation. Neutrophil elastase inhibitors have been used in Japan to block this pathway, but no randomized clinical trial data are available (33).

Subacute vasculitis begins weeks after the onset of fever, can still be detected months to years later, and is closely associated with the third process, LMP (32). The inflammatory infiltrate is predominantly lymphocytic and originates in the adventitia. CD8+ cytotoxic T lymphocytes have been documented in the media (14), suggesting that anti-T-cell therapies, such as the calcineurin inhibitors cyclosporine and tacrolimus, might be effective (34,35). LMP, with myofibroblasts possibly derived from medial smooth muscle cells, is a pathological process that is likely mediated by TGFβ (36,37). Polymorphisms in the TGFβ pathway are associated with increased susceptibility to aneurysm formation in KD patients (30). LMP can
result in luminal narrowing and consequent myocardial ischemia. A prominent feature of the late histology of aneurysms is the almost universal finding of layered thrombus in the aneurysms associated with calcification that can be detected by computed tomography (CT) calcium score (38).

It is important to note that only the most severe forms of vascular and myocardial pathology have been characterized, as the histological description of KD is largely on the basis of autopsies of individuals who died of complications of their vasculitis.

Coronary artery histology in individuals with a history of KD who died of unrelated causes has not been systematically studied. These data are needed to allow accurate counseling of patients about potential future cardiovascular complications.

**EVALUATION IN ACUTE PHASE OF ILLNESS**

In the absence of a pathognomonic laboratory test, the diagnosis of KD depends on recognition of clinical criteria (2). The most important elements in timely

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*Fever for at least 5 days plus rash, bilateral nonexudative conjunctivitis, oral changes (red, cracked lips, strawberry tongue, erythema of the oropharynx); extremity changes (swollen hands and feet, erythema of the palms and soles, and/or subungual desquamation at 2 weeks); cervical lymphadenopathy (≥1.5 cm, usually unilateral) or fever plus fewer criteria with coronary aneurysms. ASA = acetylsalicylic acid; CMR = cardiac magnetic resonance; CT = computed tomography; CV = cardiovascular; IVIG = intravenous immunoglobulin.
diagnosis and treatment are meticulous history-taking and thorough physical examination. The clinical signs may evolve over the first week of the illness or may be evanescent, particularly in infants <6 months of age. An unexplained high fever and marked irritability or lethargy may be the only initial findings in very young infants. Enumeration of diagnostic criteria must incorporate parents’ or other caregivers’ descriptions, as well as medical providers’ direct observation. Clinical laboratory investigation may be used to support the clinician’s suspicion of KD, to assist in the differential diagnosis, and to gauge the intensity of inflammation.

The evolution of clinical laboratory values over the acute and subacute phases of the illness has been summarized (39). Leukocytosis with a predominance of immature and mature granulocytes, normochromic, normocytic anemia, and elevated acute phase proteins are characteristic of the acute phase of KD. Thrombocytopenia may occur in the setting of consumption with intravascular clot formation and degradation, as evidenced by a markedly elevated D-dimer level. Thrombocytosis is a characteristic feature of the subacute phase of KD. Mild to moderate elevations in serum transaminase or gamma-glutamyl transpeptidase activity occur in ~35% of patients and mild hyperbilirubinemia in about 10%. Hypoalbuminemia is associated with more severe acute disease. Urinalysis may show sterile pyuria in up to 80% of children.

The echocardiogram is the mainstay of cardiac imaging during the acute phase. Japanese criteria (40,41) define the size of an aneurysm according to internal lumen dimensions: small, ≤4 mm; medium, >4 to ≤8 mm; and giant, >8 mm. For children age ≥5 years, aneurysm size can also be classified by the ratio of the internal diameter compared to an adjacent segment: small, 1.5×; medium, 1.5× to 4×; and giant, >4×. In North America, echocardiographic measurements of the internal dimension of the proximal coronary segments are normalized on the basis of body surface area and expressed in standard deviation units from the mean (42). CAA are considered small if z-scores are ≥2.5 to <5, medium if z-scores are ≥5 to <10, and large or giant if z-scores are either ≥10 or >8 mm in diameter (43).

When abnormal, echocardiography is a useful adjunct to diagnosis. However, a normal echocardiogram does not exclude the diagnosis of KD. Moreover, a normal baseline echocardiogram in the first week of illness does not exclude the possibility of later development of coronary aneurysms; thus, echocardiography should be repeated at 1 to 2 weeks and 4 to 6 weeks after treatment. Those with coronary z-scores >2 at baseline or with high-risk clinical features (e.g., persistent fever, IVIG resistance) should be studied more frequently.

Two-dimensional and M-mode echocardiography may also show transient left ventricular dilation, systolic dysfunction, pericardial effusion, or valvular, especially mitral, regurgitation (44). Systolic dysfunction on baseline echocardiography is a risk factor for coronary aneurysms (44). Rarely, patients may present with KD shock syndrome, generally warm shock with decreased peripheral vascular resistance (45), which can be confused with toxic shock syndrome or sepsis.

**TREATMENT IN THE ACUTE STAGE**

The goal of treatment is to abrogate systemic and tissue-level inflammation as rapidly as possible and to prevent thrombosis in developing aneurysms (Table 1). Clinical trials in the 1980s established that a high dose of IVIG plus aspirin administered within the first 10 days after fever onset could reduce the rate of CAA from 25% to 5% (46,47). In vitro studies with patient peripheral blood mononuclear cells have established 2 mechanisms of action of IVIG. The first is stimulation of a myeloid dendritic cell population by the constant region of the immunoglobulin molecule Fc to secrete IL-10 and influence T cell differentiation toward a regulatory phenotype (48). The second mechanism is the presentation of processed Fc peptides to a subset of regulatory T cells that expand and produce IL-10 (49). Peptide mapping studies have identified specific Fc regions that mediate this expansion (50). Because the effects of IVIG on cessation of fever and mucocutaneous signs are very rapid, other mechanisms, such as provision of anticytokine and anti-idiotype antibodies, may also be important, although specific data are lacking. The majority of patients experience rapid clinical improvement and cessation of fever following a single infusion of IVIG, but approximately 10% to 20% of patients will experience recrudescent fever and require additional anti-inflammatory treatment. These IVIG-resistant patients have a higher risk of developing CAA and require additional therapy to control inflammation (51). In Japan, clinical scores have been successfully used to identify these individuals. A recent randomized clinical trial showed a lower rate of CAA in high-risk patients selected with such a score who were treated with 3 to 5 weeks of oral steroids in addition to conventional IVIG (52). Unfortunately, these scoring systems do not perform well in mixed ethnic populations in the United States (53).
The progression of aneurysm formation in some patients, despite timely diagnosis and treatment, has fueled the search for more effective therapies. Rational selection of the optimal rescue therapy for IVIG-resistant patients would benefit from improved understanding of the mechanisms of resistance (54). One study has suggested differences in host protein sialylation as a potential mechanism (55). Genetic studies are being conducted to shed light on the mechanisms of IVIG-resistance (56). Treatment alternatives for this group of patients currently include a second infusion of IVIG, either alone or in combination with steroids and infliximab. In a 2-center, retrospective study of either second IVIG infusion or infliximab as the first retreatment, patients with IVIG resistance who were treated with infliximab had more rapid resolution of fever and inflammatory markers, fewer days in hospital, and lower costs of care (57). However, coronary artery outcomes were similar between groups. The efficacy of cyclosporine has been suggested by case series and observational studies (58). The cytotoxic agent cyclophosphamide, often in conjunction with corticosteroids, is used on rare occasions in the patient with severe progressive aneurysms refractory to other treatments (58). Enrollment of patients with evolving aneurysms is currently ongoing in a trial of the IL-1 receptor antagonist anakinra (Anakinra in Infants and Children With Kawasaki Disease and Coronary Artery Abnormalities; NCT01431105) can inhibit endothelial to mesenchymal transition and promote T-cell regulation. Finally, clinical trials are needed to refine the approach to KD treatment in resource-limited settings (59).

In the setting of severe inflammation, patients developing giant aneurysms have a high risk of coronary artery thrombosis; improved outcomes have been associated with aggressive systemic anticoagulation and antiplatelet therapy (60,61). One single-center observational series suggested that arterial remodeling was superior with low-molecular-weight heparin compared with warfarin (62). Levels of antithrombin III may be low, necessitating antithrombin supplementation to facilitate efficacy of heparin or use of direct thrombin inhibitors (63). Administration of dual antiplatelet therapy is reasonable in children with moderate-sized aneurysms (z-scores of 5 to <10 mm).

## Natural History

Risk factors for development of CAA include both demographic variables and those related to the severity of vasculitis on presentation (2,64,65). Even adjusting for their higher incidence of KD, boys are more likely than girls to develop aneurysms. Infants younger than 6 months of age have the highest incidence of CAA and are most likely to present with incomplete criteria; those older than 8 years of age also have high risk. Laboratory tests indicating worse systemic inflammation (e.g., higher C-reactive protein, worse anemia, lower platelet count, higher percentage of neutrophils, and lower serum sodium) are

### Table 1: Principles in Acute Management of KD

<table>
<thead>
<tr>
<th>Principle</th>
<th>Notes</th>
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<tbody>
<tr>
<td>1.</td>
<td>The goal of therapy is to reduce systemic and tissue-level inflammation as rapidly as possible. For this reason, patients should be treated as soon as diagnosis can be confidently established.</td>
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<tr>
<td>2.</td>
<td>All patients within the first 10 days of fever onset should be treated with IVIG. Patients diagnosed after 10 days should receive IVIG treatment if they are still febrile, have markedly elevated inflammatory parameters, or have coronary artery dilation.</td>
</tr>
<tr>
<td>3.</td>
<td>Recrudescence fever at least 36 h after the end of IVIG infusion without other explanation is a marker for persistent inflammation and should prompt immediate and aggressive anti-inflammatory therapy</td>
</tr>
<tr>
<td>a.</td>
<td>Antibody-mediated hemolysis has become common in KD patients who have received IVIG retreatment and have type A or B blood; rescue therapies other than IVIG (e.g., infliximab, corticosteroids) should be considered.</td>
</tr>
<tr>
<td>4.</td>
<td>Patients with coronary artery dilation (z-score &gt;2.0) should be followed with a repeat echocardiogram at least twice a week until dimensions stabilize; additional anti-inflammatory therapy should be considered.</td>
</tr>
<tr>
<td>5.</td>
<td>Patients with giant aneurysms should have frequent echocardiograms in the first 3 months of illness for thrombus surveillance, even after dimensions stabilize.</td>
</tr>
<tr>
<td>6.</td>
<td>Infants under 6 months of age are at extremely high risk of aneurysm formation, even with timely therapy. They require echocardiograms every few days until dimensions have stabilized.</td>
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<tr>
<td>7.</td>
<td>Patients with giant CAA (z-score &gt;10) are at highest risk for thrombosis during the first 3 months after fever onset</td>
</tr>
<tr>
<td>a.</td>
<td>Systemic anticoagulation together with an antiplatelet agent should be administered until coronary dimensions improve.</td>
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<tr>
<td>b.</td>
<td>Low-molecular-weight heparin is easier to regulate than warfarin in infants, as well as in patients of any age, during the acute phase of illness or until hsCRP normalizes.</td>
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</table>

**CAA** = coronary artery aneurysm; **hsCRP** = high-sensitivity C-reactive protein; IVIG = intravenous immunoglobulin; KD = Kawasaki disease.
also predictors of CAA. Patients whose coronary dimensions are small at the time of presentation are less likely to develop CAA (66). Finally, resistance to IVIG portends much higher risk of aneurysm development (65).

The architecture of CAA evolves dynamically over time (Figure 1) (67). Aneurysms may increase in size over the first 2 months of illness. Regression of aneurysms to normal lumen diameter generally occurs by 2 years after disease onset, whereas stenosis is progressive over many years (67,68). The natural history of aneurysms is highly related to the greatest degree of coronary enlargement in early months after illness onset, as well as to the number of coronary arteries involved (67,69,70).

The largest aneurysms, so-called giant aneurysms (Figure 2), historically have been defined as having an internal lumen dimension ≥8 mm; most natural history series performed in Japan have relied on this definition. North American investigators have redefined large or giant aneurysms as having a z-score ≥10 (43). The discrepancy between body surface area-adjusted and absolute criteria may explain why more than one-half of aneurysms >6 mm developed stenosis by 15 years of follow-up in 1 Japanese series (71). Virtually all of the morbidity and mortality associated with KD occurs in patients with giant aneurysms (72). In arterial segments affected by such aneurysms, LMP, as well as layering of mural thrombus, may reduce the internal lumen of aneurysms (Figure 3). These mechanisms pose a double-edged sword that also can cause progressive coronary stenosis, particularly at the entrance or exit of an aneurysm, or even complete occlusion (32). The low prevalence of

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**FIGURE 1** Natural History of Coronary Artery Architecture in Kawasaki Disease

![Diagram](http://content.onlinejacc.org)

Adapted with permission from Newburger et al. (99).
documented myocardial ischemia in infants and young children with aneurysms and thrombosis may, in part, be due to neoangiogenesis and the rapid recanalization of thrombosed aneurysms, as well as the growth of collateral arteries supplying the territory at risk.

Long-term studies of the natural history of giant aneurysms must be interpreted in light of historical differences in diagnosis and treatment. In a large single-center study, Suda et al. (72) followed 70 patients with giant aneurysms and reported a survival rate of 88% at 30 years. In a larger multicenter survey of 245 Japanese patients with giant aneurysms, Tsuda et al. (72) reported a survival rate of 90% at 30 years, with worse prognosis among those with bilateral (87%) versus unilateral (96%) coronary involvement. In contrast, the cardiac event-free rate at 30 years was only 36%, again with worse outcomes among those with bilateral (21%) versus unilateral (59%) involvement. By 30-year follow-up, coronary artery bypass graft (CABG) had been performed in one-half of giant aneurysm patients (69% with bilateral and 20% with unilateral giant aneurysms). Mortality and cardiac event-free survival in patients with giant aneurysms in North America (74) and Taiwan (67) have been consistent with the larger Japanese experience.

Myocardial infarction (MI) occurs most commonly in the first year after disease onset, with an especially
high risk in the period from 15 to 45 days after disease onset (75). Intravascular clot formation and degradation is a consequence of severe vascular inflammation during the early illness and altered hemodynamics in the aneurysm (76). Although the risk of MI appears to fall after 1 to 2 years, cases continue to occur, and adults can present with MI several decades after KD onset (77,78). Indeed, in a recent study in San Diego County, 5% of patients younger than age 40 years of age who presented with acute coronary syndromes had aneurysms secondary to KD in childhood (79). In a multicenter survey of Japanese patients with giant aneurysms, by 30 years, 26% had suffered at least 1 acute MI (unilateral aneurysms 15%, bilateral 3%) (72). Among 60 subjects with MI, survival was 79% at 20 years, and 50% of survivors had ventricular tachycardia (80).

Regression to normal internal lumen diameter is common in children with moderate or small aneurysms, but has been associated with late myointimal thickening of the coronary arterial wall on intravascular ultrasound (81) and optical coherence tomography (82). In such arterial segments, coronary vascular reactivity is impaired (83), and myocardial blood flow and coronary flow reserve may be decreased (84).

In the current era, the majority of children treated with IVIG in the acute phase of illness never develop coronary artery abnormalities. Some studies have raised concerns, even in this “always normal” group. Myocardial blood flow and coronary flow reserve with adenosine were diminished in 1 study (85), and some studies performed in Asia have suggested impaired brachial artery reactivity (86) and arterial stiffness (87). However, peripheral vascular studies in North America have not detected long-term changes in peripheral vascular function (88,89). Moreover, reassurance can be derived from the absence of late coronary artery calcification (38), clinical manifestations, or increased mortality in those with always-normal coronary arteries with more than 30 years of follow-up in Japan (90).

LONG-TERM MANAGEMENT

All patients with a history of CAA require lifelong surveillance. Goals of long-term management are to prevent coronary thrombosis and treat myocardial ischemia and associated complications (Table 2). There are few evidence-based studies to guide the optimal frequency and types of cardiovascular testing after KD. Thus, long-term management is based upon first principles and evidence in adults with atherosclerotic coronary artery disease. Because the arterial wall may be abnormal in remodeled coronaries, even when the internal lumen diameter measures in the normal range, both the current status of aneurysms and the worst-ever coronary artery dimension or z-score, must be considered in devising a plan for long-term management. Types and intervals for testing should be tailored to the severity of coronary involvement (2).

With respect to cardiovascular testing during long-term follow-up, echocardiographic measurements of the coronary artery lumen become progressively less reliable as children grow and the chest wall thickens. Echocardiography is also less reliable for detection of vascular stenosis or thrombosis than for dilation. For these reasons, advanced imaging techniques, including computerized tomographic angiography (CTA) and magnetic resonance angiography, are used with increasing frequency (91,92). As currently practiced at most centers, CTA provides greater detail of vascular structures (Figure 4), whereas cardiac magnetic resonance (CMR)/magnetic resonance angiography is superior for cardiovascular function and assessment of wall motion and myocardial fibrosis. The role of CT calcium scoring in the context of KD is still being defined, but preliminary data suggest that this low-radiation technique can be used to screen patients with a history of KD and an unclear history of echocardiographic abnormalities, as only young adults with aneurysms had a positive score (38).

Tests for inducible ischemia are chosen according to the patient’s age and institutional practice and are helpful in determining the need for coronary interventions. Wherever possible, the mode of stress testing should minimize risks of anesthesia and ionizing radiation. Children too young to exercise

<table>
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<tr>
<th>TABLE 2</th>
<th>Principles in the Long-Term Management of Patients With KD</th>
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<tbody>
<tr>
<td>1.</td>
<td>On the basis of available data, patients with no demonstrated coronary artery dilation by echocardiogram with excellent visualization of all arterial segments during the first weeks of illness appear to have normal cardiovascular status in early adulthood.</td>
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<tr>
<td>2.</td>
<td>Remodeling (so-called regression) of aneurysms, especially if moderate or large, to normal internal lumen diameter is often accompanied by luminal myofibroblastic proliferation and abnormal vascular reactivity.</td>
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<tr>
<td>3.</td>
<td>Patients with persistent CAA are at lifelong risk of progressive coronary artery stenosis or occlusion and worsening ischemia.</td>
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<tr>
<td>4.</td>
<td>Patients with CAA documented at any stage require lifelong cardiovascular surveillance tailored to disease severity and age.</td>
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<tr>
<td>5.</td>
<td>Testing should minimize exposure to ionizing radiation whenever possible.</td>
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<tr>
<td>6.</td>
<td>Sedentary life-style should be avoided.</td>
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<tr>
<td>7.</td>
<td>Women with coronary aneurysms can carry pregnancy successfully, but should have reproductive counseling.</td>
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<tr>
<td>8.</td>
<td>Monitoring and counseling regarding traditional CV risk factors is appropriate to reduce the likelihood of later atherosclerosis.</td>
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CV = cardiovascular; other abbreviations as in Table 1.
undergo pharmacological stress testing (e.g., dobutamine stress echocardiography or CMR, adenosine-stress CMR). For example, dobutamine stress echocardiography was shown to be an independent risk factor for major adverse cardiac events during follow-up of patients with KD and aneurysms (93). For older children, exercise stress testing with myocardial imaging using echocardiography, nuclear imaging, or positron emission tomography scan is preferable. Among children with MI, including those incidentally noted during CMR, annual Holter monitoring should be performed for surveillance of ventricular tachycardia.

With respect to medications, beta-blocker therapy is often used in the highest-risk patients with giant aneurysms (2), and some experts believe that statins may be beneficial for their pleotropic anti-inflammatory effects. For patients with giant aneurysms, a combination of antiplatelet therapy and anticoagulation is used to prevent coronary thrombosis (60,61). Indeed, patients with giant aneurysms and a recent history of coronary thrombosis are sometimes treated with anticoagulation and dual antiplatelet therapy (63).

Recommendations for participation in competitive sports are on the basis of coronary status, results of stress testing, and antithrombotic treatment (94). All KD patients should be encouraged to avoid a sedentary life-style. For patients with persistent giant CAA, multiple or complex aneurysms without obstruction, or coronary artery obstruction who do not have symptoms, or exercise-induced ischemia or arrhythmia on annual stress testing, and whose left ventricular ejection fraction is normal, it is reasonable to allow participation in noncontact low- to moderate-intensity static and dynamic competitive sports. Some experts do not restrict such patients from any noncontact sport. Patients who have had MI or coronary revascularization should follow exercise recommendations for adults with atherosclerotic coronary artery disease (94). Patients with small-to-medium-sized solitary coronary aneurysms in whom no exercise-induced ischemia or arrhythmia is present on stress testing every 1 to 2 years do not require exercise restrictions. Finally, those without a history of coronary aneurysms require neither stress testing nor exercise restriction.

Most coronary thrombosis is nonocclusive and detected in asymptomatic children during frequent echocardiography surveillance. If a new thrombus appears in the first few months after disease onset, when the risk of rapid progression to occlusion and MI is greatest, treatment with thrombolytic therapy, generally with tissue plasminogen activator, is indicated. Treatment with anticoagulation and dual antiplatelet therapy is generally administered for some months following thrombolytic therapy. After the first year of illness, the nonocclusive coronary thrombus noted incidentally by echocardiography may be followed with close surveillance during treatment with anticoagulation and aspirin.

Coronary revascularization (surgical or percutaneous) is performed for symptoms of angina or evidence of a significant territory of inducible ischemia on stress testing. No randomized trials of CABG versus percutaneous coronary intervention (PCI) have been performed in KD patients. CABG has been performed in young children, but graft longevity is better after 12 years of age; internal mammary artery grafts appear to grow with somatic growth (95). In the largest single-center series from Japan, cardiac event-free survival after bypass was 67% at 20 years (95). Graft failure is more common when CABG is performed in children without inducible ischemia.

Japanese guidelines for catheter intervention recommend PCI for patients with ischemic symptoms, inducible ischemia, or >75% stenosis in the left anterior descending coronary artery; the presence of complex aneurysms with multiple, ostial, or long-segment stenosis are considered a contraindication for PCI (96). In a survey of outcomes after PCI versus CABG, the primary composite endpoint of mortality or Q-wave MI were similar, but repeat target vessel revascularization was significantly more common among those treated with PCI (97). When considering stent placement, adult cardiologists should be aware that the walls of a stenotic artery may be composed of considerable thrombus; intravascular ultrasound may be helpful to assess the true lumen diameter. Finally,
cardiac transplantation is reserved for end-stage ischemic cardiomyopathy (98).

At the other end of the severity spectrum are KD patients whose coronary artery dimensions were always normal or only transiently dilated with z-scores <2.5. For these patients, (currently the majority of KD patients), aspirin therapy may be stopped at 4 to 8 weeks, once inflammatory markers have normalized and it is clear that no coronary abnormalities are present. A lipid profile should be checked 1 year after KD onset, and longer-term follow-up is primarily composed of preventive cardiology counseling (2).

CONCLUSIONS AND FUTURE DIRECTIONS

Despite 4 decades of research, the etiology of KD remains elusive, and a traditional pathogen seems unlikely as the trigger for the disease. The ambitious research agenda outlined in Table 3 will require multicenter collaboration that facilitates enrollment of patients with this uncommon disease at many centers. Moreover, surveillance of the earliest KD patients as they pass through middle age will further elucidate the natural history of the illness. Finally, a growing population of children with coronary aneurysms is reaching adulthood, a demographic shift that will have an impact on adult cardiology practices.

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<table>
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<th>TABLE 3 Research Priorities for the Next Decade</th>
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<tr>
<td>1. Pursue epidemiological clues to discover the etiology of KD.</td>
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<td>2. Biomarker studies to create a diagnostic test to improve timely treatment.</td>
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<td>3. Understand mechanisms of disease pathogenesis to allow replacement of IVIG with more targeted therapies.</td>
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<td>4. Create multicenter clinical networks to efficiently test new therapies to prevent aneurysm progression.</td>
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<td>5. Decipher genetic influences on disease susceptibility and outcome.</td>
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<tr>
<td>6. Create database registries for long-term follow-up of KD patients.</td>
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<tr>
<td>7. Standardize pathology protocols to maximize information from KD autopsies and explanted hearts.</td>
</tr>
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</table>

Abbreviations as in Table 1.

REFERENCES

Kawasaki Disease


KEY WORDS aneurysm, coronary aneurysm, coronary thrombosis, immunoglobulin, intravenous mucocutaneous lymph node syndrome, myocardial infarction