Diagnosis, Treatment, and Long-Term Management of Kawasaki Disease

A Scientific Statement for Health Professionals From the American Heart Association

BACKGROUND: Kawasaki disease is an acute vasculitis of childhood that leads to coronary artery aneurysms in ≈25% of untreated cases. It has been reported worldwide and is the leading cause of acquired heart disease in children in developed countries.

METHODS AND RESULTS: To revise the previous American Heart Association guidelines, a multidisciplinary writing group of experts was convened to review and appraise available evidence and practice-based opinion, as well as to provide updated recommendations for diagnosis, treatment of the acute illness, and long-term management. Although the cause remains unknown, discussion sections highlight new insights into the epidemiology, genetics, pathogenesis, pathology, natural history, and long-term outcomes. Prompt diagnosis is essential, and an updated algorithm defines supplemental information to be used to assist the diagnosis when classic clinical criteria are incomplete. Although intravenous immune globulin is the mainstay of initial treatment, the role for additional primary therapy in selected patients is discussed. Approximately 10% to 20% of patients do not respond to initial intravenous immune globulin, and recommendations for additional therapies are provided. Careful initial management of evolving coronary artery abnormalities is essential, necessitating an increased frequency of assessments and escalation of thromboprophylaxis. Risk stratification for long-term management is based primarily on maximal coronary artery luminal dimensions, normalized as *Z* scores, and is calibrated to both past and current involvement. Patients with aneurysms require life-long and uninterrupted cardiology follow-up.

CONCLUSIONS: These recommendations provide updated and best evidence-based guidance to healthcare providers who diagnose and manage Kawasaki disease, but clinical decision making should be individualized to specific patient circumstances.

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Kawasaki disease (KD) is an acute, self-limited febrile illness of unknown cause that predominantly affects children <5 years of age. When initially described, the potential for coronary artery complications was not appreciated. KD is now the most common cause of acquired heart disease in children in developed countries. In the absence of pathognomonic tests, the diagnosis continues to rest on the identification of principal clinical findings and the exclusion of other clinically similar entities with known causes. Timely initiation of treatment with intravenous immunoglobulin (IVIG) has reduced the incidence of coronary artery aneurysms defined from absolute luminal dimensions from 25% to ≈4%. Ongoing studies with additional therapies have not substantially reduced this residual risk. The long-term prognosis is determined by the initial and current level of coronary artery involvement. Certain subsets of patients are at risk for myocardial ischemia from coronary artery thrombosis and stenoses. Medical management of such patients hinges on judicious use of thromboprophylaxis and vigilance to identify evolving stenoses. Invasive revascularization procedures might be required for selected patients.

In 2004, the American Heart Association (AHA) published guidelines for the diagnosis, treatment, and long-term management of KD.[1] The current scientific statement incorporates new evidence regarding underlying pathological processes, an algorithm to ensure capture of incomplete KD during the effective window of therapy, improved management of the acute illness that includes the use of additional therapies for IVIG-refractory patients, greater use of *Z* scores for classifying coronary artery involvement, greater specification of long-term management based on both initial and current coronary artery involvement, and acknowledgment of the care needs of a growing population of adults with a previous history of KD and coronary artery aneurysms. The current scientific statement incorporates recommendation statements that reflect the associated grade and level of evidence.

The writing group included content experts from all disciplines related to KD (pediatric and adult cardiology, infectious disease, pathology, rheumatology, immunology, and nursing). The group also included experts from Taiwan and Japan, where the incidence of KD is 3- to 15-fold higher than in North America. All potential conflicts of interest were reported, vetted, tracked, and recorded and updated throughout the guideline development, review, and publication process. After drafting a detailed outline and performing a careful review of the 2004 AHA scientific statement, as well as existing guidelines, assigned writing group members carefully reviewed published literature, focusing on reports published since the last guidelines. Background sections were drafted to provide context for recommendations. The methodology outlined in Methodologies and Policies from the American College of Cardiology/AHA Task Force on Practice Guidelines was followed.[2,3] Recommendations were generated as stand-alone statements and graded by the class of the recommendation and the level of evidence as outlined in Table 1. This classification determined the wording of recommendation statements. All recommendation statements were reviewed by the entire writing group and approved before submission for peer review and again before final publication.

EPIDEMIOLOGY

In the past, the illness may have masqueraded in various guises, and old reports on infantile polyarteritis nodosa in Western countries describe pathological findings identical to those of fatal KD.[4–8] First described in Japan, KD has now been described worldwide.[9–17] However, the disease is markedly more prevalent in children in Japan, where the annual incidence was 243.1 per 100 000 children <5 years of age in 2011 and 264.8 per 100 000 in 2012. The greater susceptibility of children of Japanese ancestry to KD is also evidenced by epidemiological data from Hawaii, where children of Japanese descent had the highest incidence (210.5 per 100 000 children <5 years of age); white children had the lowest incidence (13.7 per 100 000 children <5 years of age).[18] In the continental United States, the incidence of KD has been best estimated from hospital discharge data at ≈25 per 100 000 children <5 years of age.[19–21] An estimated 5523 hospitalizations associated with KD occurred in the United States in 2006, at a mean age of 3 years, for an annual incidence of 20.8 per 100 000 children <5 years of age.[21] The incidence was highest among Asians and Pacific Islanders (30.3 per 100 000 children <5 years of age) and in boys versus girls (24.2 versus 16.8, respectively).[21] Epidemiological comparisons between countries and regions should be viewed in light of often differing methods and completeness of case ascertainment and reporting.

Rates of recurrence and familial occurrence of KD are best documented in literature from Japan; recurrence rates could be lower in other races and ethnicities. In Japan, the recurrence rate of KD has been reported to be ≈3% in one study,[22] and in a review of 4560 patients, it was noted to be 5.21 episodes per 1000 patient-years of follow-up, highest in the first 2 years after the index episode.[23] From the nationwide surveys in Japan, the recurrence rate was reported to be 6.89 episodes per 1000 patient-years of follow-up.[24] A comparison of surveillance data from the United States (1984–2008) and Japan (2001–2002) showed a rate of 1.7% in the United States, which increased to 3.5% in Asians and Pacific Islanders, which was similar to the rate of 3.5% in Japan.[25] In Canada, a review of 1010 patients showed a recurrence rate of 2.9 episodes per 1000 patient-years of

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Table 1. Applying Classification of Recommendations and Level of Evidence

ESTIMATE OF CERTAINTY (PRECISION) OF TREATMENT EFFECT	SIZE OF TREATMENT EFFECT: CLASS I *Benefit >>> Risk* Procedure/Treatment **SHOULD** be performed/ administered	CLASS IIa *Benefit >> Risk* *Additional studies with focused objectives needed* **IT IS REASONABLE** to perform procedure/administer treatment	CLASS IIb *Benefit ≥ Risk* *Additional studies with broad objectives needed; additional registry data would be helpful* Procedure/Treatment **MAY BE CONSIDERED**	CLASS III *No Benefit* or CLASS III *Harm* Procedure/ Test / Treatment COR III: No benefit — Not Helpful — No Proven Benefit COR III: Harm — Excess Cost w/o Benefit or Harmful — Harmful to Patients
LEVEL A Multiple populations evaluated* Data derived from multiple randomized clinical trials or meta-analyses	■ Recommendation that procedure or treatment is useful/effective ■ Sufficient evidence from multiple randomized trials or meta-analyses	■ Recommendation in favor of treatment or procedure being useful/effective ■ Some conflicting evidence from multiple randomized trials or meta-analyses	■ Recommendation's usefulness/efficacy less well established ■ Greater conflicting evidence from multiple randomized trials or meta-analyses	■ Recommendation that procedure or treatment is not useful/effective and may be harmful ■ Sufficient evidence from multiple randomized trials or meta-analyses
LEVEL B Limited populations evaluated* Data derived from a single randomized trial or nonrandomized studies	■ Recommendation that procedure or treatment is useful/effective ■ Evidence from single randomized trial or nonrandomized studies	■ Recommendation in favor of treatment or procedure being useful/effective ■ Some conflicting evidence from single randomized trial or nonrandomized studies	■ Recommendation's usefulness/efficacy less well established ■ Greater conflicting evidence from single randomized trial or nonrandomized studies	■ Recommendation that procedure or treatment is not useful/effective and may be harmful ■ Evidence from single randomized trial or nonrandomized studies
LEVEL C Very limited populations evaluated* Only consensus opinion of experts, case studies, or standard of care	■ Recommendation that procedure or treatment is useful/effective ■ Only expert opinion, case studies, or standard of care	■ Recommendation in favor of treatment or procedure being useful/effective ■ Only diverging expert opinion, case studies, or standard of care	■ Recommendation's usefulness/efficacy less well established ■ Only diverging expert opinion, case studies, or standard of care	■ Recommendation that procedure or treatment is not useful/effective and may be harmful ■ Only expert opinion, case studies, or standard of care
Suggested phrases for writing recommendations	should is recommended is indicated is useful/effective/beneficial	is reasonable can be useful/effective/beneficial is probably recommended or indicated	may/might be considered may/might be reasonable usefulness/effectiveness is unknown/unclear/uncertain or not well established	COR III: No Benefit: is not recommended; is not indicated; should not be performed/ administered/ other; is not useful/ beneficial/ effective COR III: Harm: potentially harmful; causes harm; associated with excess morbidity/mortality; should not be performed/ administered/ other
Comparative effectiveness phrases†	treatment/strategy A is recommended/indicated in preference to treatment B treatment A should be chosen over treatment B	treatment/strategy A is probably recommended/indicated in preference to treatment B it is reasonable to choose treatment A over treatment B		

A recommendation with Level of Evidence B or C does not imply that the recommendation is weak. Many important clinical questions addressed in the guidelines do not lend themselves to clinical trials. Although randomized trials are unavailable, there may be a very clear clinical consensus that a particular test or therapy is useful or effective.

*Data available from clinical trials or registries about the usefulness/efficacy in different subpopulations such as sex, age, history of diabetes mellitus, history of prior myocardial infarction, history of heart failure, and prior aspirin use.

†For comparative effectiveness recommendations (Class I and IIa; Level of Evidence A and B only), studies that support the use of comparator verbs should involve direct comparisons of the treatments or strategies being evaluated.

follow-up, with recurrences occurring at a median of 1.5 years after the index episode and with similar features and outcomes.[26] However, Nakamura et al[27] reported a higher risk of developing coronary artery sequelae with the recurrent episode, regardless of the sequelae developed with the index episode. The proportion of cases with a positive family history is ≈1%.[22,24] Within 1 year after the onset of the first case in a family, the rate in a sibling is 2.1%, a relative risk of ≈10-fold compared with the Japanese population in general; approximately half of the second cases develop within 10 days of the first case.[28] The risk of concordance in identical twins is ≈13%.[28–30] Higher rates of KD in siblings of index cases and twins are consistent with a genetic predisposition that interacts with exposure to the pathogenic agent or agents in the environment.[28,29,31,32] The reported occurrence of KD in children of parents who themselves had the illness in childhood also supports the contribution of genetic factors.[33–36]

In the continental United States, KD is more common during the winter and early spring, boys with the disease outnumber girls by ≈1.5–1.7:1, and 76% of affected chil-

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dren are <5 years of age.[19,20,25] From a global perspective, regions in the extratropical northern hemisphere have seasonal peaks in the winter, with low numbers of cases in the late summer and fall.[37] A lack of a seasonal cycle has been noted in the tropics and the extratropical southern hemisphere.

Epidemiological studies demonstrating that KD is associated with antecedent respiratory illness and exposure to carpet cleaning have not been consistently confirmed.[38–44] Other factors reportedly associated with KD include eczema,[45] humidifier use,[44] and residence near a standing body of water.[46] Recent epidemiological studies have pointed to some potential environmental risk factors for KD. Although the findings have not been replicated, a study in the state of Washington suggested that the risk for KD might be linked to perinatal exposures, including older maternal age, maternal group B streptococcal colonization, and hospitalization in early infancy for a bacterial illness, which was associated with a 2.8-fold higher risk.[47] Epidemiological analyses have correlated the incidence of KD cases in Japan, Hawaii, and San Diego with tropospheric wind currents originating in northeastern China, which suggests that a wind-borne agent could trigger the illness.[48,49]

The case fatality rate in KD in Japan is 0.015% (4 deaths in 26 691 patients from 2011 to 2012).[22,50] The standardized mortality ratio (SMR; 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 higher than normal only for males with coronary artery aneurysms (SMR, 2.55; 95% confidence interval, 1.23–4.70).[51] A more recent study from Japan showed that the SMR beyond the acute illness was elevated for all patients with cardiac sequelae (SMR, 1.86; 95% confidence interval, 1.02–3.13), thus, stressing the importance of long-term surveillance for this subgroup of patients.[52] Patients without cardiac sequelae after the acute phase had a lower mortality relative to the general population (SMR, 0.65; 95% confidence interval, 0.41–0.96). In the continental United States, using administrative data that could include readmissions for coronary disease, the in-hospital mortality rate is ≈0.17%.[53] Virtually all deaths in patients with KD result from its cardiac sequelae.[54] The peak mortality occurs 15 to 45 days after onset of fever, during which time well-established coronary artery vasculitis occurs concomitantly with marked elevation of the platelet count and a hypercoagulable state.[55] However, sudden death of myocardial infarction (MI) can occur many years later in children and adults with coronary artery aneurysms and stenoses. Many cases of fatal and nonfatal MI in young adults have now been attributed to "missed" KD in childhood.[56] Indeed, among adults <40 years of age with suspected myocardial ischemia who underwent coronary angiography in San Diego, CA, ≈5% had lesions consistent with late sequelae of KD.[57]

Key Points: Epidemiology

- The cause is unknown.
- The estimated incidence in North America is ≈25 cases per 100 000 children <5 years of age per year.
- The highest relative risk is in Asian children, especially of Japanese ancestry.
- The ratio of males to females is ≈1.5:1.
- KD affects predominantly, but not exclusively, young children.
- It is most common in winter and early spring in North America.
- Predisposing factors have been reported inconsistently.
- Nonspecific symptoms are common in the 10 days before diagnosis.
- In Japan, the recurrence rate is ≈3%, and the relative risk in siblings is 10-fold higher.
- The case fatality rate is <0.1% in Japan.
- Coronary artery aneurysms from KD account for 5% of acute coronary syndromes (ACS) in adults <40 years of age.

GENETICS

Evidence for a genetic component to KD susceptibility includes the observation of an increased incidence among Japanese children and among children of Japanese descent residing outside of Japan, the increased incidence of a history of KD among the parents of a KD patient, and the increased incidence among siblings and extended family members of an index case.[18,35,58–60] Family linkage studies and genome-wide association studies with subsequent validation studies have implicated single-nucleotide polymorphisms in 6 genes or gene regions: FcγR2a, caspase 3 (*CASP3*), human leukocyte antigen class II, B-cell lymphoid kinase (*BLK*), inositol 1,4,5-trisphosphate kinase-C (*ITPKC*), and CD40 (Table 2). Variants in genes in the transforming growth factor (TGF)-β signaling pathway (*TGFβ2*, *TGFβR2*, and *SMAD3*) were associated with increased risk of aneurysm formation in patients of European descent by use of a case-control study design and the transmission disequilibrium test, which assesses transmission of candidate risk alleles from heterozygous parents to their affected offspring.[64,65] A genome-wide association study in Japan identified a human leukocyte antigen determinant that influenced susceptibility among Japanese and Taiwanese children but not children of European descent.[59] Taken together, these results suggest that KD susceptibility and disease outcome, including aneurysm formation and response to IVIG, are influenced by variants in several different genes and signaling pathways. These polymorphisms likely vary across populations, and when the sum total of genetic influences for KD are eventually described, it is predicted that there

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Table 2. Genes Implicated in Susceptibility to KD With Replication in Independent Cohorts

Gene	Chromosome Location	Genetic Methods	Validation Populations	Potential Significance	Reference and Year
FCGR2A	1q23	GWAS	European descent, Taiwanese, Koreans, Han Chinese	Low-affinity receptor for Fc fragment of IgG; risk allele has lower binding affinity	Khor et al[61] 2011
CASP3	4q34-35	Linkage analysis Candidate gene study	Japanese, Taiwanese, Koreans, Chinese, Euro-Americans	Mediates apoptosis in immune cells and cardiomyocytes Risk allele decreases gene transcription	Onouchi et al[62] 2010
HLA class II	6p21.3	GWAS	Japanese, Taiwanese, Koreans	Activation marker for immune cells; antigen presentation	Onouchi et al[63] 2012
BLK	8p23-22	GWAS	Japanese, Taiwanese, Koreans	B-cell receptor signal transduction	Onouchi et al[63] 2012
IPTKC	19q13.2	Linkage analysis TDT	Japanese, Taiwanese, Koreans, Chinese, Euro-Americans	Negative regulator of calcineurin-NFAT signaling pathway; risk allele increases signaling	Onouchi et al[64] 2008
CD40	20q12-13.2	GWAS	Japanese, Taiwanese, Koreans	Risk alleles associated with increased translation	Onouchi et al[63] 2012

BLK indicates B-cell lymphoid kinase; CASP3, caspase 3; FCGR, Fcγ receptor; GWAS, genome-wide association study; HLA, human leukocyte antigen; IgG, immunoglobulin G; ITPKC, inositol 1,4,5-trisphosphate kinase-C; KD, Kawasaki disease; NFAT, nuclear factor of activated T cells; and TDT, transmission disequilibrium test.

will be important differences in allele frequency that will explain the increased incidence of disease among Asian populations. The preliminary understanding of genetic influences on disease susceptibility have already led to clinical trials of cyclosporine to interrupt the calcineurin-NFAT (nuclear factor of activated T cells) pathway and to trials of statins to block downstream effects of the TGF-β signaling pathway on myofibroblast formation and matrix metalloproteinase secretion.

CAUSES AND PATHOGENESIS

Despite 4 decades of investigation, the cause of KD remains unknown. Current understanding of the immune response suggests response to a classic antigen that is protective against future exposure in most patients.[66] An impressive list of candidate pathogens has been tested and discarded. One line of investigation suggests infection with a novel RNA virus that enters through the upper respiratory tract.[67,68] Intracytoplasmic inclusion bodies in bronchial epithelial cells and multiple other cell types throughout the body appear to contain RNA and could be linked to the KD agent. Efforts to characterize the molecular details of these inclusion bodies have been hampered by the paucity of autopsy tissues available for study. The study of relevant tissues (eg, coronary arteries) in surviving patients treated for KD is not feasible except in the case of cardiac explantation at transplantation, and polyclonal B-cell activation makes serological studies challenging. Another line of evidence links the seasonality of KD to tropospheric wind patterns, which suggests the transport of an agent that, when inhaled by genetically susceptible children, triggers the immunologic cascade of KD.

Although early studies provided evidence for an immune response triggered by a superantigen, subsequent studies favored a canonical response to a conventional antigen. Activation of the innate immune system is an early event, with high numbers of activated, circulating neutrophils and evidence for activation of the interleukin (IL) 1, IL-6, and tumor necrosis factor (TNF) signaling pathways.[69] Study of the adaptive immune response demonstrated that both proinflammatory and regulatory T cells can be found in the circulation in the first week after fever onset.[66] Expansion of the regulatory T-cell population after IVIG administration is associated with cessation of fever and clinical improvement.[70] The self-limited nature of the disease coupled with a low rate of recurrence suggests emergence of T- and B-cell memory that is protective against future encounters with the KD agent.

PATHOLOGY

Although inflammation of the coronary arteries results in the most important clinical outcomes, KD is characterized by systemic inflammation in all the medium-sized arteries and in multiple organs and tissues during the acute febrile phase,[71] leading to associated clinical findings: liver (hepatitis), lung (interstitial pneumonitis), gastrointestinal tract (abdominal pain, vomiting, diarrhea, gallbladder hydrops), meninges (aseptic meningitis, ir-

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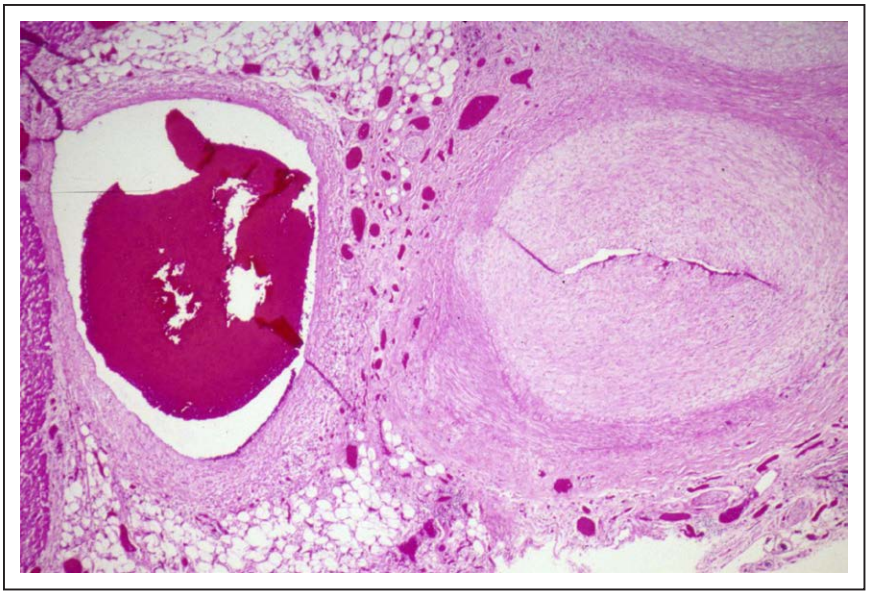

Figure 1. Epicardial coronary artery (right) and epicardial vein (left) from a 19-month-old child who died 10 months after Kawasaki disease onset.
The epicardial vein contains blood and shows mild thickening of the wall, while the coronary artery shows almost complete occlusion by luminal myofibroblastic proliferation with a fine slit-like lumen.

ritability), heart (myocarditis, pericarditis, valvulitis), urinary tract (pyuria), pancreas (pancreatitis), and lymph nodes (lymphadenopathy). Unfortunately, lymph node pathology is nonspecific and nondiagnostic. Intracytoplasmic inclusion bodies are commonly observed in ciliated bronchial epithelial cells in autopsied cases.[67,68,72]

A recently proposed model of KD arteriopathy identified 3 pathological processes. The first is a necrotizing arteritis that consists of a synchronized neutrophilic process complete within 2 weeks after fever onset. It is the only self-limited process and progressively destroys the arterial wall into the adventitia, causing aneurysms. The second process is a subacute/chronic vasculitis characterized by an asynchronous infiltration of lymphocytes, plasma cells, and eosinophils with fewer macrophages that begins in the first 2 weeks after fever onset but can continue for months to years in a small subset of patients and is closely linked to the third process. The third process is luminal myofibroblastic proliferation (LMP), which is characterized by a unique medial smooth muscle cell–derived myofibroblastic process that begins in the first 2 weeks and persists for months to years, with the potential to cause progressive arterial stenosis. LMP is composed of myofibroblasts and their matrix products accompanied by subacute or chronic inflammatory cells (Figure 1).[73] This model, based on careful study of arterial tissues from 41 KD patients, includes pathological features described in prior reports.[54,74–77] The model goes further to demonstrate the distinct natures of neutrophilic necrotizing arteritis and subacute/chronic arteritis, the persistence of subacute/chronic arteritis for months to years after onset in a small subset of patients, and the electron microscopic evidence that LMP is an active proliferative process (rather than scar) that begins in the first few weeks after onset and is itself a key component of KD arteritis, with the potential to cause progressive arterial stenosis in KD patients with coronary artery abnormalities.

Pathological outcomes of coronary artery damage depend on the severity of the lesions. Very mildly dilated and inflamed arteries may be able to return to normal. Large saccular aneurysms have lost their intima, media, and elastica, which cannot be regenerated. The rim of remaining adventitia can rupture or undergo sequential thrombosis that can organize, recanalize, and calcify. Fusiform aneurysms with partially preserved media can thrombose or develop progressive stenosis from LMP. Large aneurysms can appear to "resolve" when the lumen size decreases because of layered mural thrombi or LMP. The largest aneurysms ("giant aneurysms") have generally lost virtually all of the media, with only a rim of adventitia remaining. These aneurysms develop successive layers of thrombi, with organization and calcification of the oldest thrombi closest to the remaining adventitia. Giant aneurysms can rupture in the first 2 to 3 weeks after fever onset but rarely do so thereafter. MI can occur from acute or progressive thrombosis or from stenosis caused by LMP.[73] A recent study of pediatric vasculitis fatalities over the past 50 years from Japan indicated that the vast majority of such deaths were the result of KD and that fatality rates markedly decreased around the time IVIG therapy was introduced, in the mid to late 1980s.[78]

Key Points: Pathology

- KD vasculopathy primarily involves muscular arteries and is characterized by 3 linked processes: (1) necrotizing arteritis; (2) subacute/chronic vasculitis; and (3) LMP.
- Large or giant coronary artery aneurysms ≥8 mm in diameter or with a *Z* score ≥10 do not "resolve," "regress," or "remodel." They rarely rupture and

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virtually always contain thrombi (the oldest of which may calcify) that can become occlusive.
- Aneurysms with markedly damaged but partially preserved media may develop decreases in lumen diameter over time as the result of LMP or thrombi and can become progressively stenotic.
- Atherosclerotic features are not characteristic of KD vasculopathy even in late deaths or transplants.
- Pericarditis and myocarditis result from subacute/chronic inflammation, which is usually concentrated around coronary arteries.

DIAGNOSIS

Clinical criteria are used to diagnose KD.[1,79] Table 3 describes the clinical features that constitute the epidemiological case definition, as well as other clinical and laboratory findings. Patients who meet the case definition based on principal clinical findings are said to have complete KD (also sometimes referred to as typical or classic KD). Patients who do not have sufficient principal clinical findings may be diagnosed with incomplete KD (also sometimes referred to as atypical KD). In the absence of a specific diagnostic test, other clinical, laboratory, and echocardiographic findings can support the diagnosis of incomplete KD in a patient whose clinical presentation suggests KD but whose clinical features do not meet the epidemiological case definition.

Principal Clinical Findings

The diagnosis of classic KD is based on the presence of ≥5 days of fever (first calendar day of fever is illness day 1) and the presence of ≥4 of the 5 principal clinical features (Table 3, Figure 2).[1] In the presence of ≥4 principal clinical criteria, particularly when redness and swelling of the hands and feet are present, the diagnosis may be made with only 4 days of fever. Similarly, experienced clinicians who have treated many KD patients may make the diagnosis in rare instances with only 3 days of fever in the presence of a classic clinical presentation. Typically the clinical features are not all present at a single point in time, and it is generally not possible to establish the diagnosis very early in the course. Similarly, some clinical features may have abated in patients who present after 1 to 2 weeks of fever, and a careful review of prior signs and symptoms can help establish the diagnosis.

Fever

Fever is typically high spiking (>39°C to 40°C) and remittent. In the absence of appropriate therapy, fever continues for 1 to 3 weeks. The spontaneous resolution of fever after 7 days should not be regarded as evidence that the diagnosis of KD has been excluded. Fever usually resolves within 36 hours after IVIG infusion has been completed; if not, the patient is considered to have resistance to IVIG, and further therapy is required.

Extremity Changes

Changes in the extremities are distinctive. Erythema of the palms and soles and firm and sometimes painful induration of the hands or feet often occur in the acute phase. 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 involve the palms and soles. At 1 to 2 months after fever onset, deep transverse grooves across the nails (Beau's lines) may be noted.

Rash

An erythematous rash usually appears within 5 days of fever onset. Most commonly, this is a diffuse maculopapular eruption. Scarlatiniform erythroderma and erythema multiforme-like rashes are also common. Less commonly, urticarial or fine micropustular eruptions are observed. The rash is usually extensive, primarily involving the trunk and extremities, and accentuation in the groin with early desquamation is a characteristic feature. An unusually severe form of psoriasis with plaques and pustular features can rarely occur during or after the acute KD illness.[80] Patients may also experience a flare of new-onset atopic dermatitis during the subacute phase. Bullous, vesicular, and petechial rashes are not consistent with KD and should prompt a search for an alternative diagnosis.

Conjunctivitis

Bilateral bulbar nonexudative conjunctival injection usually begins shortly after fever onset and often spares the limbus, an avascular zone around the iris. Anterior uveitis is often observed by slit-lamp examination during the first week of fever.[81,82] Subconjunctival hemorrhage and punctate keratitis are occasionally observed.[82,83]

Oral Changes

Changes of the lips and oral cavity include (1) erythema, dryness, fissuring, peeling, cracking, and bleeding of the lips; (2) a "strawberry tongue," with erythema and prominent fungiform papillae; and (3) diffuse erythema of the oropharyngeal mucosa. Oral ulcers and pharyngeal exudates are not consistent with KD.

Cervical Lymphadenopathy

Cervical lymphadenopathy is the least common of the principal clinical features. Lymph node swelling is usually unilateral, ≥1.5 cm in diameter, and confined to the anterior cervical triangle. In a small subset of patients, lymph node findings may be the most notable and sometimes only initial clinical finding, prompting a clinical diagnosis of bacterial lymphadenitis and significantly delaying KD diagnosis.[84] In such cases, fever persists, and other typical KD features, such as rash and conjunctival injection, will follow. Imaging studies including ultrasound and computed tomography (CT) can be helpful in differentiating KD lymphadenopathy from bacterial lymphadenitis.

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Table 3. Diagnosis of Classic KD

Classic KD is diagnosed in the presence of fever for at least 5 d (the day of fever onset is taken to be the first day of fever) together with at least 4 of the 5 following principal clinical features. In the presence of ≥4 principal clinical features, particularly when redness and swelling of the hands and feet are present, the diagnosis of KD can be made with 4 d of fever, although experienced clinicians who have treated many patients with KD may establish the diagnosis with 3 d of fever in rare cases (Figure 2):
1. Erythema and cracking of lips, strawberry tongue, and/or erythema of oral and pharyngeal mucosa
2. Bilateral bulbar conjunctival injection without exudate
3. Rash: maculopapular, diffuse erythroderma, or erythema multiforme-like
4. Erythema and edema of the hands and feet in acute phase and/or periungual desquamation in subacute phase
5. Cervical lymphadenopathy (≥1.5 cm diameter), usually unilateral
A careful history may reveal that ≥1 principal clinical features were present during the illness but resolved by the time of presentation.
Patients who lack full clinical features of classic KD are often evaluated for incomplete KD (Figure 3). If coronary artery abnormalities are detected, the diagnosis of KD is considered confirmed in most cases.
Laboratory tests typically reveal normal or elevated white blood cell count with neutrophil predominance and elevated acute phase reactants such as C-reactive protein and erythrocyte sedimentation rate during the acute phase. Low serum sodium and albumin levels, elevated serum liver enzymes, and sterile pyuria can be present. In the second week after fever onset, thrombocytosis is common.
Other clinical findings may include the following:
Cardiovascular
Myocarditis, pericarditis, valvular regurgitation, shock
Coronary artery abnormalities
Aneurysms of medium-sized noncoronary arteries
Peripheral gangrene
Aortic root enlargement
Respiratory
Peribronchial and interstitial infiltrates on CXR
Pulmonary nodules
Musculoskeletal
Arthritis, arthralgia (pleocytosis of synovial fluid)
Gastrointestinal
Diarrhea, vomiting, abdominal pain
Hepatitis, jaundice
Gallbladder hydrops
Pancreatitis
Nervous system
Extreme irritability
Aseptic meningitis (pleocytosis of cerebrospinal fluid)
Facial nerve palsy
Sensorineural hearing loss
Genitourinary
Urethritis/meatitis, hydrocele
Other
Desquamating rash in groin
Retropharyngeal phlegmon
Anterior uveitis by slit lamp examination
Erythema and induration at BCG inoculation site
The differential diagnosis includes other infectious and noninfectious conditions, including the following:
Measles
Other viral infections (eg, adenovirus, enterovirus)
Staphylococcal and streptococcal toxin-mediated diseases (eg, scarlet fever and toxic shock syndrome)
Drug hypersensitivity reactions, including Stevens Johnson syndrome
Systemic onset juvenile idiopathic arthritis
With epidemiologic risk factors:
Rocky Mountain spotted fever or other rickettsial infections
Leptospirosis

BCG indicates bacillus Calmette-Guérin; CXR, chest radiography; and KD, Kawasaki disease.

In KD, multiple lymph nodes are enlarged, and retropharyngeal edema or phlegmon is common. In contrast, bacterial lymphadenitis is most frequently associated with a single node with a hypoechoic core.[84] It has been increasingly recognized that cervical lymphadenopathy can be associated with deep neck inflammation leading to parapharyngeal and retropharyngeal edema and nonsuppurative phlegmon.[84,85]

Other Illnesses With Similar Features

Other illnesses with similar clinical features (Table 3) should be considered before the diagnosis of KD is made, because the principal clinical findings that fulfill the diagnostic criteria are not specific. The presence of exudative conjunctivitis, exudative pharyngitis, oral ulcerations, splenomegaly, and vesiculobullous or petechial rashes should prompt consideration of another diagnosis.[46] Measles shares many clinical features with KD and should be considered in the differential diagnosis in any unimmunized infant or child. KD occurs more commonly in the winter and spring in nontemperate climates, when many respiratory viruses circulate,

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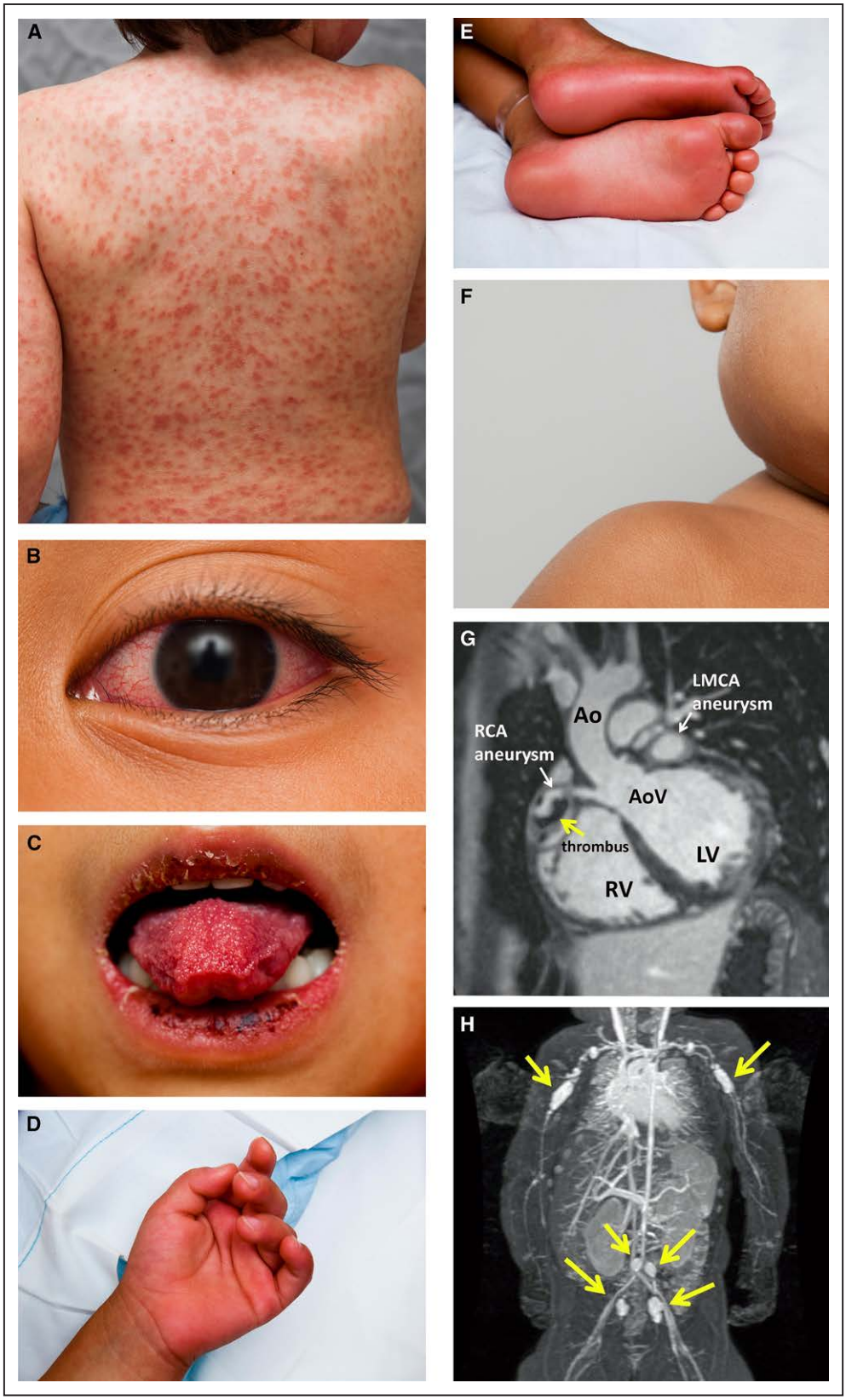

Figure 2. Clinical features of classic Kawasaki disease.
A, Rash: Maculopapular, diffuse erythroderma, or erythema multiforme-like. **B,** Conjunctivitis: Bulbar conjunctival injection without exudate; bilateral. **C,** Oral changes: Erythema and cracking of lips (cheilitis); strawberry tongue; erythema of oral and pharyngeal mucosa. **D** and **E,** Palmar and plantar erythema: Usually accompanied by swelling; resolves with subsequent periungual desquamation in the subacute phase. **F,** Cervical adenopathy: Usually unilateral, node ≥1.5 cm in diameter. (*Continued*)

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Figure 2 Continued. G, Coronary artery aneurysms: Magnetic resonance image of the left ventricular outflow tract showing a giant right coronary artery (RCA) aneurysm with nonocclusive thrombus (yellow arrow) and a giant left main coronary artery (LMCA) aneurysm. Ao indicates aorta; AoV, aortic valve; LV, left ventricle; and RV, right ventricle. **H,** Peripheral artery aneurysms: Magnetic resonance image showing aneurysms in the axillary and subclavian arteries and the iliac and femoral arteries (yellow arrows). Patient photographs used with permission from the Kawasaki Disease Foundation, Inc.

and a child with KD may have concurrent infection with a respiratory viral pathogen. In a child with clinical findings compatible with classic KD, the detection of respiratory viruses such as respiratory syncytial virus, metapneumovirus, coronaviruses, parainfluenza viruses, or influenza viruses does not exclude the diagnosis of KD.[86–88] The detection of adenovirus in a nasopharyngeal sample from a patient with suspected KD poses a particular challenge, because the illnesses have some similar clinical features.[89] Adenoviruses (particularly species C) can persist in tonsil or adenoid tissue, potentially confusing diagnosis of a subsequent febrile illness.[90] In a patient with fever, exudative pharyngitis, exudative conjunctivitis, and a nasopharyngeal sample positive for adenovirus by respiratory polymerase chain reaction assay, KD is extremely unlikely; however, the diagnosis of KD should still be considered if adenovirus is detected in a patient with nonexudative pharyngitis. Other diagnostic features of KD not commonly observed in adenovirus infection include erythema and swelling of the hands and feet, strawberry tongue, and a desquamating groin rash.[91] In children with some clinical features of KD and a positive rapid test or culture for group A streptococcus who do not improve after 24 to 48 hours of effective antibiotic therapy (streptococcal carriers), the diagnosis of KD should be again considered.

Incomplete (Atypical) KD

Although the presence of fever for ≥4 days with 4 of the 5 other principal clinical findings establishes the diagnosis of complete KD, these criteria unfortunately do not identify all children with the illness. KD should be considered in the differential diagnosis of prolonged unexplained fever in childhood associated with any of the principal clinical features of the disease, and the diagnosis can be considered confirmed when coronary artery aneurysms are identified in such patients by echocardiography. However, coronary artery dilatation is generally not detected by echocardiography until after the first week of illness, and a normal echocardiogram in the first week of illness does not rule out the diagnosis of KD. Patients with incomplete KD, particularly those <6 months of age and those lacking eye or oral mucosal changes, may experience significant delays in diagnosis.[92] Studies evaluating the incomplete KD diagnostic algorithm first proposed in the 2004 guidelines[1] suggest its usefulness in identifying patients who require treatment and in preventing coronary artery aneurysms.[93,94] Incomplete KD occurs most commonly in infants, who are at substantial risk of developing coronary artery abnormalities and who may have prolonged fever as the sole clinical finding or have subtle or fleeting clinical signs in addition to fever. Laboratory findings and cardiovascular sequelae in incomplete and complete cases appear the same. Although there are no pathognomonic laboratory findings, the presence of certain laboratory features may raise the clinical suspicion of KD. The finding of coronary artery *Z* scores (based on body surface area [BSA]) of ≥2.5 for the left anterior descending (LAD) or right coronary artery (RCA) branches lacks sensitivity but has a very high specificity for the diagnosis.[95,96]

Diagnosis of Incomplete KD

The diagnosis of incomplete (sometimes referred to as *atypical*) KD should be considered in any infant or child with prolonged unexplained fever, fewer than 4 of the principal clinical findings, and compatible laboratory or echocardiographic findings (Figure 3).

Common Pitfalls in Diagnosis

A high index of suspicion for the diagnosis is particularly important in certain clinical situations. In the infant <6 months of age, prolonged fever and irritability may be the only clinical manifestations of KD, and these children are at high risk of developing coronary artery abnormalities. Delayed diagnosis is common in older children and adolescents with KD, and they appear to have a high prevalence of coronary artery abnormalities.[97] The presence of fever and pyuria in an infant or young child can be mistakenly attributed to a urinary tract infection, and subsequent development of rash, red eyes, and red lips to an antibiotic reaction. Likewise, irritability and a culture-negative pleocytosis of the cerebrospinal fluid in an infant with prolonged fever suggestive of aseptic meningitis (or if antibiotics have been given, partially treated meningitis) may cause a diagnosis of KD to be overlooked. Patients with cervical lymphadenitis as the primary clinical manifestation can be misdiagnosed as having bacterial adenitis, and many such patients will have concurrent retropharyngeal phlegmon that is attributed to bacterial infection.[84] Patients with prominent gastrointestinal symptoms are sometimes admitted to a surgical service, and other physical findings of KD can be overlooked. Patients who present with shock may be misdiagnosed as hav-

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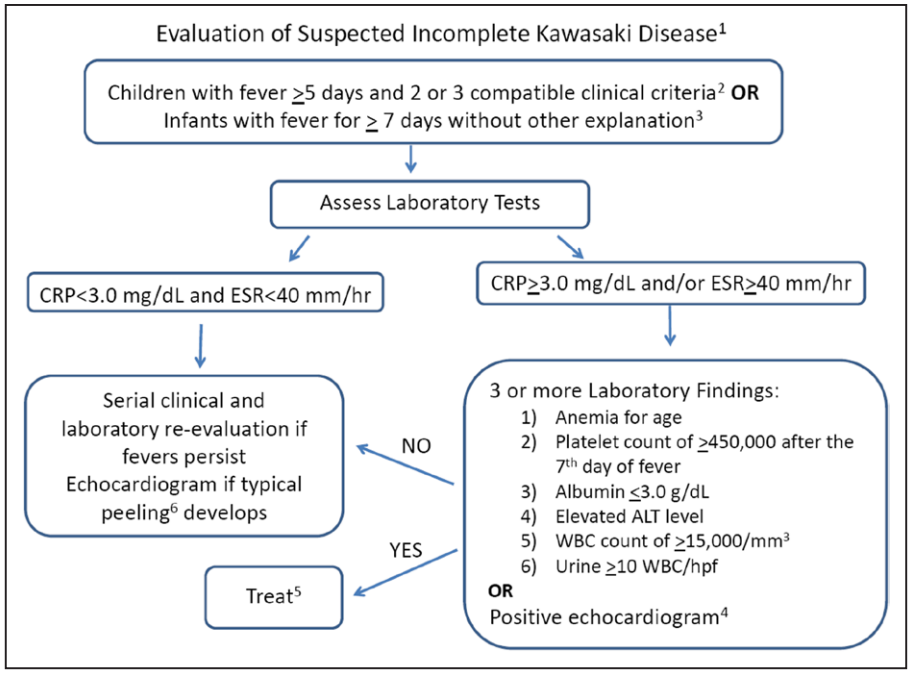

Figure 3. Evaluation of suspected incomplete Kawasaki disease.
(1) In the absence of a "gold standard" for diagnosis, this algorithm cannot be evidence based but rather represents the informed opinion of the expert committee. Consultation with an expert should be sought any time assistance is needed. (2) Clinical findings of Kawasaki disease are listed in Table 3. Characteristics suggesting that another diagnosis should be considered include exudative conjunctivitis, exudative pharyngitis, ulcerative intraoral lesions, bullous or vesicular rash, generalized adenopathy, or splenomegaly. (3) Infants ≤6 months of age are the most likely to develop prolonged fever without other clinical criteria for Kawasaki disease; these infants are at particularly high risk of developing coronary artery abnormalities. (4) Echocardiography is considered positive for purposes of this algorithm if any of 3 conditions are met: *Z* score of left anterior descending coronary artery or right coronary artery ≥2.5; coronary artery aneurysm is observed; or ≥3 other suggestive features exist, including decreased left ventricular function, mitral regurgitation, pericardial effusion, or *Z* scores in left anterior descending coronary artery or right coronary artery of 2 to 2.5. (5) If the echocardiogram is positive, treatment should be given within 10 days of fever onset or after the tenth day of fever in the presence of clinical and laboratory signs (C-reactive protein [CRP], erythrocyte sedimentation rate [ESR]) of ongoing inflammation. (6) Typical peeling begins under the nail beds of fingers and toes. ALT indicates alanine transaminase; and WBC, white blood cells.

ing bacterial sepsis or staphylococcal or streptococcal toxic shock syndrome. In these clinical scenarios, consultation with an expert in the diagnosis of KD can be useful.

Key Points: Consider KD in the Differential Diagnosis of Certain Infants or Children

- Infants <6 months old with prolonged fever and irritability
- Infants with prolonged fever and unexplained aseptic meningitis
- Infants or children with prolonged fever and unexplained or culture-negative shock
- Infants or children with prolonged fever and cervical lymphadenitis unresponsive to antibiotic therapy
- Infants or children with prolonged fever and retropharyngeal or parapharyngeal phlegmon unresponsive to antibiotic therapy

Other Clinical and Laboratory Findings

Other Clinical Findings

Although important long-term sequelae are confined to the arterial tree (in particular, the coronary arteries), multiple other organs and tissues are inflamed during the acute illness and cause clinical symptoms. Common neurological findings include extreme irritability exceeding that observed in other febrile illnesses and aseptic meningitis in those children who undergo lumbar puncture.[98] Transient unilateral, and rarely bilateral, peripheral facial nerve palsy has been noted in rare case reports.[99] Profound sensorineural hearing loss is a rare but serious complication.[100,101] Common gastrointestinal findings include hepatitis, diarrhea, vomiting, abdominal pain, and gallbladder hydrops; pancreatitis and jaundice are less common. Genitourinary findings include urethritis, which is common, and hydrocele and phimosis, which are less common. Musculoskeletal findings include arthralgia and arthritis, involving multiple small interphalangeal joints and large weight-bearing joints during the first

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week of illness and predominantly large weight-bearing joints, especially the knees and ankles, in the second to third week of illness.[102,103] Respiratory findings include peribronchial and interstitial infiltrates on chest radiography; nodular infiltrates occur rarely. Erythema and induration at the site of a previous vaccination with bacille Calmette-Guérin is common in children with KD born in countries where it is used widely.[104] Macrophage activation syndrome occurs rarely and is often associated with IVIG resistance.[105]

Laboratory Findings

Laboratory tests, although nonspecific, provide support for a diagnosis of KD in patients with nonclassic but suggestive clinical features. Clinical experience suggests that KD is unlikely if the erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), and platelet count are normal after day 7 of illness. In addition, low white blood cell count and lymphocyte predominance suggest an alternative diagnosis.

The evolution of the laboratory findings during and after the acute KD illness was summarized recently.[106] Leukocytosis is typical during the acute stage of illness, with a predominance of immature and mature granulocytes. Leukopenia and lymphocyte predominance suggest an alternative diagnosis. Anemia occurs commonly, is normochromic and normocytic, and resolves with resolution of inflammation. Elevation of acute-phase reactants such as ESR and CRP is nearly universal; the degree of elevation of ESR and CRP may be discrepant. The CRP normalizes more quickly than the ESR during resolution of inflammation. Moreover, the ESR is elevated by IVIG therapy, and therefore, a decreased ESR during follow-up should not be used to assess response to treatment with IVIG. The CRP is more useful as a marker of inflammation after treatment of the acute illness. Finding of a minimally elevated ESR in the setting of severe clinical disease should prompt investigation for disseminated intravascular coagulation.[55]

Thrombocytosis is a characteristic feature of KD but generally does not occur until the second week, peaking in the third week (mean ≈700 000 per mm^3) and normalizing by 4 to 6 weeks after onset in most cases. Thrombocytopenia is rare but may occur in the first 1 to 2 weeks of illness. Thrombocytopenia can be a sign of disseminated intravascular coagulation and is a risk factor for the development of coronary artery abnormalities. In patients with arthritis, arthrocentesis typically yields purulent-appearing fluid with a white blood cell count of 125 000 to 300 000 per mm^3, a normal glucose level, and negative Gram stain and cultures.

Mild to moderate elevations in serum transaminases or gammaglutamyl transpeptidase occur in 40% to 60% of patients, and mild hyperbilirubinemia occurs in ≈10%.[106,107] Hypoalbuminemia is common and associated with more severe and more prolonged acute disease. Urinalysis may show pyuria in up to 80% of children, although this finding lacks specificity for KD.[108] In children who undergo lumbar puncture, ≈30% demonstrate pleocytosis with a mononuclear cell predominance, normal glucose levels, and generally normal protein levels.[98]

In the absence of a diagnostic test, identification of serum or urine biomarkers of KD is an active area of research, but no biomarkers presently available have been demonstrated to be superior to elevated CRP or ESR. N-terminal moiety of B-type natriuretic peptide (NT-proBNP), likely indicative of myocardial involvement, may be elevated in some patients with KD, but this biomarker may not have sufficient discriminative ability to differentiate KD, and cut-point values for a positive result have not been clearly defined.[109,110]

Cardiovascular Findings

Cardiovascular manifestations and complications represent the major contributors to morbidity and mortality related to KD, both during the acute illness and in the long-term. Prompt and accurate recognition and management are essential.

Clinical Findings

Cardiovascular manifestations can be prominent during the acute KD episode and are the leading cause of long-term morbidity and mortality. The pericardium, myocardium, endocardium including valves, and the coronary arteries all may be inflamed. Clinical findings during the acute illness may include a hyperdynamic precordium and tachycardia. Innocent systolic flow murmurs may be accentuated, and a gallop rhythm suggesting decreased compliance (diastolic dysfunction) of the ventricle secondary to myocardial inflammation and edema may be present. The presence of a pericardial rub, or clinical signs of pericardial tamponade, is very rare, although echocardiographic findings of small pericardial effusions are common. Valvar dysfunction occurs in ≈25% of patients regardless of coronary artery involvement and most often involves the mitral valve.[111] Children with clinically important mitral regurgitation (MR) may have a pansystolic murmur heard best between the low left sternal border and the apex. A diastolic murmur associated with important aortic regurgitation (AR) is rare.

Electrocardiographic Changes

During the acute illness, electrocardiography may show arrhythmia, including sinus node and atrioventricular node functional abnormalities, with prolonged PR interval and nonspecific ST and T-wave changes or low voltage if there is myocardial or pericardial involvement.[112] Increased QT dispersion, abnormalities of ventricular repolarization, and electrocardiographic signs suggestive of left ventricular (LV) dilation have been reported.[113,114] Rarely, malignant ventricular arrhythmias may be seen in the setting of myocarditis or myocardial ischemia.[115,116]

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Cardiovascular Collapse

Approximately 5% of children with KD in the continental United States present with cardiovascular collapse and hypotension requiring the initiation of volume expanders, the infusion of vasoactive agents, or transfer to the intensive care unit. The presence of thrombocytopenia and coagulopathy in such cases is notable, and a diagnosis of bacterial sepsis is frequently suspected at the outset. In such cases, when bacterial cultures are negative and fever persists, the diagnosis of KD should be considered. Children with shock presentation appear to be at higher risk of IVIG resistance, coronary artery abnormalities, MR, and prolonged myocardial dysfunction.[117–119]

Myocardial Dysfunction

Myocarditis occurs frequently in acute KD. Reports of myocardial biopsies performed early in the disease course suggested a nearly universal incidence.[120] More recent data indicate that myocardial inflammation can be documented in 50% to 70% of patients using gallium citrate Ga 67 scans and technetium Tc 99m–labeled white blood cell scans.[121] Recently, it has been demonstrated that myocardial inflammatory changes in KD occur before coronary artery abnormalities and that without concurrent ischemic damage, there is myocardial edema but little associated permanent cellular disruption or cell loss.[122] Thus, most often, myocarditis in KD develops early, and acute LV dysfunction is generally transient and responds readily to anti-inflammatory treatment.[111] The rapid improvement in LV function differs from that observed in other causes of myocarditis. Myocarditis in KD likely improves rapidly as the inflammatory process subsides because it results from interstitial edema and inflammation and only rarely from myocardial cell necrosis.[73,122] Infrequently, acute myocardial inflammation is associated with overt ventricular ectopy, although recent information indicates more common repolarization impact than may be clinically apparent (see Long-Term Management, Arrhythmias). The exception to the more typical short-term impact of mild myocarditis in KD is the KD shock syndrome.

Valvular and Aortic Abnormalities

Early studies in KD found wide variability in the incidence of MR depending on techniques of diagnosis and variability of inclusion and exclusion criteria.[123,124] However, other clinical studies, including a contemporary multicenter US study,[111] have demonstrated a more consistent incidence of MR of 23% to 27% acutely. When detected early, the preponderance of MR as assessed with echocardiography is in the mild to moderate range of severity and does not appear to persist on follow-up. MR has been correlated with other laboratory markers of inflammation early in the course of KD, and it has been postulated to result from a pancarditis, or a "shared inflammatory mechanism" with other KD changes during the acute illness.

AR is much less common at presentation (1% of patients).[111] AR in KD is usually associated with aortic root dilation and becomes apparent early in the course of the disease. It is associated with coronary artery dilation as well.[111,125] Aortic root dilation (as indicated by an increased ascending aortic *Z*-score measurement) has been reported in ≈10% of patients during the acute illness.[111]

Coronary Artery Abnormalities

The pathophysiology and pathology of coronary artery abnormalities are described in previous sections. Clinically, coronary artery abnormalities have been detected and defined based on luminal dimensions, as assessed with echocardiography or angiography. The presence of coronary artery abnormalities is considered a specific criterion supportive of the diagnosis of KD, particularly for those patients who do not meet the full clinical criteria for a diagnosis of complete KD. The coronary artery abnormalities associated with KD can be differentiated from lesser degrees of dilation that may be rarely present with other febrile illnesses.[95] The prevalence of coronary artery abnormalities in a clinical trial of initial treatment was 23% at 4 weeks after enrollment, reduced to 8% with 4 infusions of low-dose IVIG.[126] In a subsequent trial of single high-dose IVIG, this was further reduced to ≈4%.[127] These trials used absolute luminal dimensions and Japanese Ministry of Health cut points to define abnormalities and did not exclude patients with abnormalities at baseline.

Coronary artery abnormalities during the acute illness range from dilation only to aneurysms of various numbers, sizes, and characteristics, with the involvement occurring first in proximal segments and then extending distally. It is very rare to have distal involvement without some abnormalities being evident in proximal segments. In up to 80% of those patients who have significant dilation or aneurysms as noted on later echocardiograms, some abnormality is evident on the initial baseline echocardiogram obtained in the first 10 days of illness.[128] The largest proportion of patients with coronary artery abnormalities will have dilation only, characterized by luminal measurements outside the normal range but with a maximal *Z* score of <2.5. Dilation resolves within 4 to 8 weeks in the majority. Some patients will have coronary artery dimensions always within the normal range but with serial measurements will demonstrate reductions in luminal dimensions suggestive of dilation, using the patient as his or her own control.[129,130] The prevalence of these patients may range from 32% to 50%, which may indicate that coronary artery dilation may be more common than previously thought. However, it is unclear whether such reductions in dimensions represent resolution of inflammatory changes in the arterial walls or hemodynamic or functional factors related to fever and circulating inflammatory mediators.[95,96]

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Patients with severe coronary artery involvement (extensive or large/giant aneurysms) do not have cardiac symptoms unless myocardial ischemia develops secondary to severe coronary artery flow disturbances or thromboses. Symptoms and signs of myocardial ischemia/infarction may be atypical and nonspecific, particularly in infants. There have been rare case reports of rupture of a coronary artery aneurysm with subsequent myocardial ischemia and pericardial tamponade. This usually occurs during the acute illness, when aneurysms may be rapidly enlarging.

Other Arterial Abnormalities

Patients with severe coronary artery involvement may also develop aneurysms of other medium-sized arteries, with rare occurrences of thromboses or rupture at these sites.[73,131] Common sites include the axillary, subclavian, brachial, femoral, iliac, splanchnic, and mesenteric arteries, usually near or at branching points. These may present clinically as pulsatile masses and bruits. The pathology is probably similar to that of coronary artery involvement, with a similar natural history that can lead to thromboses and stenoses, although often not associated with clinical symptoms, signs, or sequelae during childhood, because collateralization is common. Another rare but important complication is peripheral gangrene, often with resulting loss of digits.[132,133]

Evaluation for Cardiovascular Abnormalities

Echocardiography

Echocardiography is the primary imaging modality for cardiac assessment because it is noninvasive and has a high sensitivity and specificity for the detection of abnormalities of the proximal coronary artery segments.[134] 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. Because detailed echocardiographic imaging is compromised if a child is uncooperative, sedation is frequently needed for those <3 years of age and may also be required in older, irritable children.[135] If a poor-quality initial echocardiogram is obtained because sedation was not administered, a sedated study should be repeated as soon as possible within the 48 hours after diagnosis and initial treatment. This initial study establishes a baseline for longitudinal follow-up monitoring of coronary artery morphology, LV wall motion, valvular regurgitation, and pericardial effusion. An initial echocardiogram in the first week of illness is typically normal and does not rule out the diagnosis.

Imaging Standards

Echocardiography should be performed with equipment with appropriate transducers and should be supervised by an experienced pediatric echocardiographer. The 2-dimensional (2D) imaging should be performed with the highest-frequency transducer possible, even for older children, because these probes allow for high-resolution detailed evaluation of the coronary arteries. Studies should be recorded in a dynamic video or digital cine format that enables future review and comparison with subsequent studies. In addition to standard anatomic and physiological imaging from parasternal, apical, subcostal, and suprasternal notch windows, 2D echocardiographic evaluation of patients with suspected KD should focus on imaging the left main coronary artery (LMCA), LAD, left circumflex, 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 4).[136] Maximal efforts should be made to visualize all major coronary artery segments. In order of highest to lowest frequency of occurrence, typical sites of coronary artery aneurysms include the proximal LAD and proximal RCA, followed by the LMCA, left circumflex, distal RCA and, least often, the junction between the RCA and posterior descending coronary artery.

Table 4. Echocardiographic Views of Coronary Arteries in Patients With KD

LMCA
Precordial short axis at level of aortic valve; precordial long axis of left ventricle (superior tangential); subcostal ventricular long axis
LAD coronary artery
Precordial short axis at level of aortic valve; precordial superior tangential long axis of left ventricle; precordial short axis of left ventricle
Left circumflex branch
Precordial short axis at level of aortic valve; apical 4-chamber
RCA, proximal segment
Precordial short axis at level of aortic valve; precordial long axis (inferior tangential) of left ventricle; subcostal coronal projection of right ventricular outflow tract; subcostal short axis at level of atrioventricular groove
RCA, middle segment
Precordial long axis of left ventricle (inferior tangential); apical 4-chamber; subcostal left ventricular long axis; subcostal short axis at level of atrioventricular groove; RCA proximal (#1) and mid (#2) are observed in the atrioventricular groove from the third intercostal space at the left and right sternal border
RCA, distal segment
Apical 4-chamber (inferior); subcostal atrial long axis (inferior)
Posterior descending coronary artery
Apical 4-chamber (inferior); subcostal atrial long axis (inferior); precordial long axis (inferior tangential) imaging; posterior interventricular groove

KD indicates Kawasaki disease; LAD, left anterior descending; LMCA, left main coronary artery; and RCA, right coronary artery.

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Table 5. *Z*-Score Methods for Normalizing Coronary Artery Luminal Dimensions From Echocardiography

	De Zorzi et al[138]	Kurotobi et al[142]	Tan et al[143]*	McCrindle et al[139]	Olivieri et al[144]	Kobayashi et al[145]	Dallaire et al[146]
Year of publication	1998	2002	2003	2007	2009	2009	2011
Number of subjects	89	71	390	221	432	5344	1036
Country	USA	Japan	Singapore	USA	USA	Japan	Canada
Regression method for model fitting of BSA	Linear	Linear	Linear	Exponential	Logarithmic	LMS	Square root
BSA calculation method	NS	NS	NS	Haycock	Dubois	Haycock	Haycock
Values for left circumflex	No	No	No	No	No	Yes	Yes

BSA indicates body surface area; LMS, lambda-mu-sigma; NS, not stated; and USA, United States of America.
*Age range limited to 2 months to 8 years; also provided for age, sex, and to the aortic annulus.

Qualitative and Quantitative Assessment

Echocardiographic 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. Exception should be made for some patients who develop a small aneurysm at the bifurcation or trifurcation of the LMCA, which may cause blunting of the sharp angulations that are usually found between the LAD, left circumflex, and sometimes a diagonal branch (so-called webbing). The number and location of aneurysms and the presence or absence of intraluminal thrombi and stenotic lesions should also be assessed, although thrombi and stenotic lesions may not be fully elucidated by standard transthoracic echocardiography.

If the patient has risk factors for intracoronary thrombosis (ie, giant aneurysms), part of the examination should be performed with a wider gray scale to capture freshly formed thrombus. Aneurysms are classified as saccular if axial and lateral diameters are nearly equal or as fusiform if symmetrical dilation with gradual proximal and distal tapering is seen. Sometimes aneurysms occur in series with interposing narrow segments. When a coronary artery is 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. Enlargement of the LMCA caused by KD does not involve the orifice and rarely occurs without associated dilation either of the LAD, the left circumflex, or both arteries.

Quantitative assessment of luminal dimensions allows for more accurate classification of coronary artery abnormalities. The Japanese guidelines classify coronary arteries by absolute or relative internal lumen diameter.[137] Dilation or small aneurysms are defined as a localized dilation of the internal lumen diameter but <4 mm, or if the child is ≥5 years of age, dilation but with an internal diameter of a segment measuring ≤1.5 times that of an adjacent segment. Medium aneurysms are defined as an internal lumen diameter >4 mm but ≤8 mm, or if the child is ≥5 years of age, an internal diameter of a segment measuring 1.5 to 4 times that of an adjacent segment. Large or giant aneurysms are defined as those with an internal lumen diameter >8 mm, or if the child is >5 years of age, an internal diameter of a segment measuring >4 times that of an adjacent segment. These criteria do not account for patient size, which can substantially affect normal coronary artery dimensions, potentially leading to underdiagnosis and underestimation of the true prevalence of coronary artery dilation.[138]

Normalization of dimensions for BSA as *Z* scores (standard deviation units from the mean) based on regression equations allows for standardization as a continuous measure,[139] as well as within a classification scheme,[140] and allows for comparisons across time and populations.[141] Several different formulas for calculating *Z* scores have been derived (Table 5).[138,139,142–146] These systems differ regarding the number, age range, and race of the normal subjects, the formula used to calculate BSA, and the regression method used for analysis. The previous AHA guidelines provided nomograms for generating *Z* scores but did not specify the source of the normative data, the method of calculating BSA, and the regression method used for analysis.[1] The most rigorous systems, based on larger populations and with careful statistical modeling, are those reported for Japanese subjects by Kobayashi et al[145] using a lambda-mu-sigma method for regression analysis of BSA and those reported for Canadian subjects by Dallaire et al[146] using a square root function of BSA. Both systems used the Du Bois[147] and Haycock[148] formulas for estimating BSA, although the report by Dallaire et al[146] further employed the Mosteller[149] formula. These systems also have the advantage of providing normative data for the left circumflex branch. These 2 systems were shown to perform equally well when the Canadian system was applied to a Japanese population and when the Japanese system was applied to the US population, with the Canadian system defining a higher proportion of abnormalities.[141] In addition to the use of these available regression equations and tables, online calculators are

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available. The use of different *Z*-score systems can yield variation in *Z* scores for a given luminal dimension and BSA, with the differences being greater with larger aneurysm dimensions.[150]

Definition of Abnormality

As a mathematical construct, a *Z* score ≥2.5 in 1 coronary artery branch would be expected to occur in ≈0.6% of the normal afebrile population, and a *Z* score ≥3.0 in ≈0.1%. Having a coronary artery *Z* score ≥2.5 in both the proximal RCA and LAD branches would be very uncommon in the general population. Anatomic variations are frequent in the LMCA, where the *Z* score must be interpreted with caution. Other anatomic variations occur, such as a dominant left or right coronary artery system, which is not associated with luminal irregularities and usually becomes evident when serial measurements do not show a decrease in luminal diameter over several months. Another limitation of normal values is that they are not uniformly provided for the left circumflex branch in different *Z*-score systems. *Z*-score measurements also only reflect normal values for proximal segments. Additional use of a criterion of a dimension >1.5 times the surrounding segments could be useful for defining abnormalities for distal segments. It might also be useful for defining involvement in other noncoronary arterial beds.

Impact of Fever

Normative measurements from which coronary artery *Z* scores are derived are based on assessment of populations of healthy afebrile children. Of note, coronary artery enlargement has been reported in patients with other inflammatory, genetic, and infectious diseases.[151] Recently, 2 studies have more systematically assessed coronary dimensions in children with febrile illnesses other than KD. Muniz et al[95] reported that coronary artery dimensions in patients with febrile illnesses other than KD were significantly larger than in the afebrile normative population but smaller than in KD patients. Two of 43 patients had coronary artery *Z* scores >2.0. One of these patients had osteomyelitis with an LAD *Z* score of 2.8, which resolved over time. Of note, febrile non-KD patients had lower white blood cell counts and ESR than KD patients. No febrile patients reported by Bratincsak et al[96] had a coronary artery *Z* score >2.5, but their duration of fever and degree of systemic inflammation were not described. Taken together, these studies suggest that cut points between 2.0 and 2.5 might reliably differentiate coronary artery involvement secondary to KD, with a *Z* score ≥2.5 differentiating KD with a 98% specificity.

Classification of Coronary Artery Abnormalities

The previous 2004 AHA scientific statement[1] used a *Z*-score cut point of ≥2.5 to define abnormality but classified aneurysms on the basis of absolute dimensions, similar to the 2008 guidelines from Japan.[137] In long-term follow-up studies, this classification did have a relationship with thromboses, stenoses, and cardiovascular events and presumably reflects the more severe vascular pathology underlying an increasing size of the lumen. However, this classification fails to account for body size. For example, a 5-mm aneurysm in a 3-month-old patient represents much greater severity and a higher risk of thrombosis than a 5-mm aneurysm in a 14-year-old patient. The use of *Z* scores better allows for evaluation of the severity of coronary artery dilation by correcting for BSA. Manlhiot et al proposed a classification scheme based solely on *Z* scores using the formulas provided in the study from the National Heart, Lung, and Blood Institute Pediatric Heart Network.[139,140] One potential limitation of this study is that regression formulas for the LAD were used to derive *Z* scores for the left circumflex branch (normal values for the circumflex are not available with the *Z*-score system that was used). A classification scheme based solely on *Z* scores was proposed, which has been adapted and recommended in these guidelines:

Z-Score Classification

1. No involvement: Always <2
2. Dilation only: 2 to <2.5; or if initially <2, a decrease in *Z* score during follow-up ≥1
3. Small aneurysm: ≥2.5 to <5
4. Medium aneurysm: ≥5 to <10, and absolute dimension <8 mm
5. Large or giant aneurysm: ≥10, or absolute dimension ≥8 mm

One caveat to be considered when using *Z* scores is that a small error in measurement of the coronary artery diameter can translate into a larger difference in *Z* scores, such that the patient's risk category might change. In addition, accurate measurement of weight and particularly height is important to enable calculation of an accurate BSA. For irritable young infants and toddlers, measurement of height might need to be rechecked if it was initially obtained under less than ideal circumstances.

Limitations of Echocardiography for Coronary Artery Assessment

It is important to recognize the limitations of echocardiography in the evaluation and follow-up of patients with KD. 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. This also impacts visualization of more distal segments. For assessment of aneurysms in the long term, dystrophic calcification in the coronary arterial walls can also hinder clear visualization of the lumen. It is reasonable to obtain advanced imaging studies such as computed tomographic angiography (CTA), cardiac magnetic resonance imaging (CMRI), or invasive angiography on patients with

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severe proximal coronary artery abnormalities in the acute phase when management decisions depend on visualization of distal segments that are not well seen by echocardiography. Of note, cardiac catheterization in the acute phase of KD has been associated with a greater incidence of adverse vascular events at the site of an arterial access vessel potentially affected by KD vasculitis.[152]

Assessment of Ventricular Form and Function

Although the echocardiographic examination of patients with KD is focused on the coronary arteries, other information must also be obtained. Myocardial involvement with LV dysfunction is present in 20% of patients at diagnosis and is associated with coronary artery dilation.[111] Therefore, assessment of ventricular systolic and diastolic function should be a part of the echocardiographic evaluation of all patients with suspected KD. LV end-diastolic and end-systolic dimensions and a shortening fraction should be measured, usually from standard M-mode tracings. Additional apical imaging allows estimation of LV end-diastolic and end-systolic volumes and ejection fraction. Evaluation of regional wall motion can also be useful, especially in children with coronary artery abnormalities.

Assessment of the Aortic Root

The aortic root also should be imaged, measured, and compared with references for BSA. Aortic root *Z* scores >2 have been reported for 10% of KD patients.[111]

Assessment of Pericardial Effusion

Pericarditis can be associated with the vasculitis and myocarditis seen in patients with KD, and the presence and severity of a pericardial effusion should be noted. Hemodynamically important pericardial effusions are very rare.

Valvular Regurgitation

Standard pulsed and color flow Doppler interrogation should be performed to assess the presence and degree of valvular regurgitation (in particular for mitral and aortic valves). Color flow Doppler with a low Nyquist limit setting should be used to demonstrate coronary artery flow in the proximal right and left coronary artery lumens.

Other Cardiovascular Imaging Modalities

Transesophageal echocardiography, invasive angiography, CMRI, and CTA can be of value in the assessment of selected patients but are not routinely indicated for diagnosis and management of the acute illness. Invasive angiography is rarely performed during the acute illness. Transesophageal echocardiography, CTA, and CMRI can be useful for the evaluation of older children and adolescents in whom visualization of the coronary arteries with transthoracic echocardiography is inadequate.[153,154] Evaluation of potential aneurysmal involvement in other arterial beds can be assessed with CMRI, CTA, and, rarely, invasive angiography, but such assessment is best performed after recovery from the acute illness, and usually for patients with severe coronary artery involvement or symptoms or signs, such as the presence of a pulsatile axillary mass.[155,156]

Recommendations for Cardiovascular Assessment for Diagnosis and Monitoring During the Acute Illness

1. **Echocardiography should be performed when the diagnosis of KD is considered, but unavailability or technical limitations should not delay treatment *(Class I; Level of Evidence B)*.**
2. **Coronary arteries should be imaged, and quantitative assessment of luminal dimensions, normalized as *Z* scores adjusted for body surface, should be performed *(Class I; Level of Evidence B)*.**
3. **For uncomplicated patients, echocardiography should be repeated both within 1 to 2 weeks and 4 to 6 weeks after treatment *(Class I; Level of Evidence B)*.**
4. **For patients with important and evolving coronary artery abnormalities (*Z* score >2.5) detected during the acute illness, more frequent echocardiography (at least twice per week) should be performed until luminal dimensions have stopped progressing to determine the risk for and presence of thrombosis *(Class I; Level of Evidence B)*.**
5. **To detect coronary artery thrombosis, it may be reasonable to perform echocardiography for patients with expanding large or giant aneurysms twice per week while dimensions are expanding rapidly and at least once weekly in the first 45 days of illness, and then monthly until the third month after illness onset, because the failure to escalate thromboprophylaxis in time with the rapid expansion of aneurysms is a primary cause of morbidity and mortality *(Class IIa; Level of Evidence C)*.**

TREATMENT OF THE ACUTE ILLNESS

Initial Treatment of KD

The goal of therapy in the acute phase is to reduce inflammation and arterial damage and to prevent thrombosis in those with coronary artery abnormalities. The original guidelines for diagnosis of KD were created by a committee appointed by the Japanese Ministry of Health in 1970, at which time the coronary artery complications of KD were not yet appreciated and there was neither effective treatment nor a noninvasive method of assessing coronary artery abnormalities. The case definition was created, therefore, for epidemiological surveillance and has evolved over time. The mainstay

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of initial treatment for both complete and incomplete KD is a single high dose of IVIG together with acetylsalicylic acid (ASA), which is supported by clinical trial evidence.[127,157]

This section covers treatment from onset of the acute illness until resolution of acute systemic inflammation and when coronary artery luminal dimensions have stabilized and are no longer expanding.

Patient Selection for Treatment

All patients meeting the AHA diagnostic criteria for KD (Table 3) should be treated as soon in the course of illness as the diagnosis can be established.

Although the current case definition provides a specific tool for epidemiological surveillance, it might not be optimal for aiding clinicians in the recognition of children with a systemic vasculitis that requires prompt treatment. An algorithm to aid the clinician in deciding which patients with fever and fewer than 4 classic criteria, that is, *suspected incomplete KD*, should be treated is summarized in Figure 3. Use of the algorithm appears to be largely successful in ensuring that children at highest risk are treated with IVIG.[93,94] In view of the low risks associated with IVIG administration and the high risks of coronary artery aneurysms among children who do not receive timely treatment, the current algorithm should be applied to the child with suspected incomplete KD until an evidence-based algorithm or a specific diagnostic test for KD becomes available.

IVIG should be instituted as early as possible within the first 10 days of illness onset of fever, that is, as soon as the diagnosis can be established. Patients with a delayed diagnosis of KD (ie, later than day 10 of fever) may still be candidates for treatment. IVIG should also be administered to children presenting after the tenth day of illness (ie, in whom the diagnosis was missed earlier) if they have ongoing systemic inflammation as manifested by elevation of ESR or CRP (CRP >3.0 mg/dL) together with either persistent fever without other explanation or coronary artery aneurysms (luminal dimension *Z* score >2.5). Those in whom fever has resolved and laboratory values have normalized and whose echocardiograms are normal do not require IVIG treatment. Patients with recurrent KD, defined as a repeat episode of complete or incomplete KD after complete resolution of the previous episode, should receive standard therapy with IVIG and ASA.

Primary Treatment

Intravenous Immunoglobulin

The efficacy of IVIG administered in the acute phase of KD is well established to reduce the prevalence of coronary artery abnormalities.[126,158,159] Meta-analyses of IVIG compared with placebo have shown a conclusive decrease in new coronary artery abnormalities among IVIG-treated patients.[157,160] The mechanism of action of IVIG in treatment of KD is unknown. IVIG appears to have a generalized anti-inflammatory effect. Possible mechanisms of action include modulation of cytokine production, neutralization of toxins or other pathogenic agents, augmentation of regulatory T-cell activity, suppression of antibody synthesis, and provision of anti-idiotypic antibodies.[161]

Patients should be treated with IVIG 2 g/kg as a single infusion, usually given over 10 to 12 hours, together with ASA.[160] A variety of dose regimens have been used in Japan and the United States in the past. Two meta-analyses have demonstrated a dose-response effect, with higher doses given in a single infusion having the greatest efficacy.[126,158,159,162] Furthermore, peak adjusted serum immunoglobulin G levels are lower among patients who subsequently develop coronary artery abnormalities and are inversely related to fever duration and laboratory indices of acute inflammation.[126,163] The association of lower peak immunoglobulin G levels with worse outcomes lends further support to the concept of a relationship between serum immunoglobulin G concentration and therapeutic effectiveness.

IVIG 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.[164–166] Recently, Coombs-positive hemolytic anemia complicating IVIG administration has been reported, especially in individuals with AB blood type.[167–169] Aseptic meningitis can occur as a result of IVIG infusion, but it resolves quickly without neurological sequelae.[170] Clinical studies comparing the efficacy of different immune globulin products have been conflicting.[171–173]

Measles, mumps, and varicella immunizations should be deferred for 11 months after receiving high-dose IVIG.[174] However, children in whom risk of exposure to measles is high may receive vaccination earlier and then be re-immunized at least 11 months after IVIG administration if they have an inadequate serological response.

Even when treated with high-dose IVIG regimens within the first 10 days of illness, 20% of children will develop transient coronary artery dilation in the proximal LAD or proximal RCA by *Z*-score criteria, 5% will develop coronary artery aneurysms (*Z* >2.5), and 1% will develop giant aneurysms according to the Japanese Ministry of Health Criteria.[158,159,175] An even greater percentage of patients (30%) will be classified as having coronary artery dilation when a *Z*-score cut point of 2.0 is used to define dilation.[111,140,176]

Additional therapies of potential benefit are discussed below, but optimal treatment awaits delineation of the specific agent(s)/trigger(s) and pathogenesis of KD.

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Acetylsalicylic Acid

ASA has been used in treatment of KD for many years. Although ASA has important anti-inflammatory activity (at high doses) and antiplatelet activity (at low doses), it does not appear to lower the frequency of development of coronary abnormalities.[177] During the acute phase of illness, ASA is administered every 6 hours, with a total daily dose of 80 to 100 mg·kg^{-1}·d^{-1} in the United States and 30 to 50 mg·kg^{-1}·d^{-1} in Japan and Western Europe (see Reye Syndrome). There are no data to suggest that either dose of ASA is superior. Practices regarding duration of high-dose ASA administration vary across institutions, with many centers reducing the ASA dose after the child has been afebrile for 48 to 72 hours. Other clinicians continue high-dose ASA until the 14th day of illness and at least 48 to 72 hours after cessation of fever. When high-dose ASA is discontinued, low-dose ASA (3 to 5 mg·kg^{-1}·d^{-1}) is begun and continued until the patient has no evidence of coronary changes by 6 to 8 weeks after onset of illness. For children who develop coronary abnormalities, ASA may be continued indefinitely. Of note, concomitant use of ibuprofen antagonizes the irreversible platelet inhibition induced by ASA[178]; thus, ibuprofen generally should be avoided in children with coronary artery aneurysms taking ASA for its antiplatelet effects.

Reye Syndrome

Reye syndrome is a risk in children who receive salicylates while they are experiencing active infection with varicella or influenza and has also been reported in patients taking high-dose ASA for a prolonged period of time after KD.[179–181] The low-dose therapy used for antiplatelet effect has not been associated with the development of Reye syndrome. In the patient who presents with influenza and KD, administration of high-dose IVIG without aspirin and use of alternative antipyretic drugs (ie, acetaminophen) as needed for fever should be considered. An alternative antiplatelet agent should be considered for a minimum of 2 weeks.

All children ≥6 months should receive a seasonal influenza vaccine, as should their family members. Only inactivated vaccine should be administered to children on aspirin therapy. Children with acute KD during influenza season who have not yet been immunized should receive the inactivated influenza vaccine before leaving the hospital, as should any family members who have not yet been vaccinated for the season. Those who are taking chronic ASA therapy should receive an annual inactivated influenza vaccine.[174] Although the vaccine manufacturer recommends that salicylates be avoided for 6 weeks after 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. Some physicians substitute another antiplatelet medication for ASA during the 6-week period. Parents of children receiving chronic ASA therapy should be instructed to contact their child's physician promptly if the child develops symptoms of or is exposed to either influenza or varicella.

Recommendations for Initial Treatment With IVIG and ASA

1. **Patients with complete KD criteria and those who meet the algorithm criteria for incomplete KD should be treated with high-dose IVIG (2 g/kg given as a single intravenous infusion) within 10 days of illness onset but as soon as possible after diagnosis *(Class I; Level of Evidence A)*.**
2. **It is reasonable to administer IVIG to children presenting after the 10th day of illness (ie, in whom the diagnosis was missed earlier) if they have either persistent fever without other explanation or coronary artery abnormalities together with ongoing systemic inflammation, as manifested by elevation of ESR or CRP (CRP >3.0 mg/dL) *(Class IIa; Level of Evidence B)*.**
3. **Administration of moderate- (30–50 mg·kg^{-1}·d^{-1}) to high-dose (80–100 mg·kg^{-1}·d^{-1}) ASA is reasonable until the patient is afebrile, although there is no evidence that it reduces coronary artery aneurysms *(Class IIa; Level of Evidence C)*.**
4. **IVIG generally should not be administered to patients beyond the tenth day of illness in the absence of fever, significant elevation of inflammatory markers, or coronary artery abnormalities *(Class III; Level of Evidence C)*.**
5. **The ESR is accelerated by IVIG therapy and therefore should not be used to assess response to IVIG therapy. A persistently high ESR alone should not be interpreted as a sign of IVIG resistance *(Class III; Level of Evidence C)*.**

Adjunctive Therapies for Primary Treatment

Patients believed to be at high risk for development of coronary artery aneurysms may benefit from primary adjunctive therapy.

Corticosteroids

Although corticosteroids are the treatment of choice in other forms of vasculitis, their use has been controversial for children with KD.[182] Corticosteroids were used as the initial therapy for KD long before the first report of IVIG efficacy by Furusho et al in 1984,[159] and studies have shown either no ill effects or possible benefit. In a randomized trial of high-dose intravenous methylprednisolone plus heparin compared with heparin alone, Ki-

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jima et al[183] found that steroid therapy was associated with a greater rate of improvement in coronary artery abnormalities. In a retrospective review, Shinohara et al[184] found that treatment regimens that included prednisolone were associated with significantly shorter fever duration and a lower prevalence of coronary artery aneurysms. In a prospective randomized trial in 178 children treated with IVIG (1 g/kg for 2 consecutive days) and ASA (30 mg·kg^{-1}·d^{-1}) plus intravenous prednisolone (2 mg·kg^{-1}·d^{-1}) followed by an oral taper, Inoue et al[185] reported a lower incidence of coronary artery abnormalities and retreatment, shorter duration of fever, and more rapid decrease in CRP levels in the steroid group.

The National Heart, Lung, and Blood Institute's Pediatric Heart Network conducted a randomized, double-blinded, placebo-controlled trial to assess the efficacy of a single dose of pulsed intravenous methylprednisolone (30 mg/kg per dose) added to IVIG (2 g/kg for 1 day) and ASA (80–100 mg·kg^{-1}·d^{-1}).[176] The trial showed similar coronary dimensions expressed as *Z* scores adjusted for BSA, absolute dimensions, and changes in dimensions, although a post hoc subgroup analysis suggested that primary corticosteroid therapy might be beneficial in preventing coronary artery abnormalities in children at highest risk for resistance to initial IVIG.

In Japan, 3 clinical studies were conducted to assess the efficacy of steroid therapy for patients at high risk for nonresponse to IVIG defined by scoring systems. Okada et al[186] reported a multicenter study to assess the effectiveness of pulse methylprednisolone (30 mg·kg^{-1}·d^{-1} for a single infusion) with IVIG (2 g/kg for a day) and aspirin (30 mg·kg^{-1}·d^{-1}) as a primary treatment for high-risk patients defined by the Sano score. The steroid group had a lower incidence of coronary artery abnormalities and treatment failure compared with a historical control group. Egami et al[187] and Ogata et al[188] reported a single-center randomized trial to assess the efficacy of single-dose methylprednisolone (30 mg/kg per dose) with IVIG (2 g/kg for 1 day) and ASA (30 mg·kg^{-1}·d^{-1}) as a primary treatment for those predicted to be at high risk for resistance to IVIG treatment based on the Egami score. They noted that the steroid group had a lower incidence of coronary artery abnormalities defined by *Z* scores and treatment resistance. From a total of 248 patients predicted to be resistant to IVIG defined by the Kobayashi score,[189] the RAISE (Randomized Controlled Trial to Assess Immunoglobulin Plus Steroid Efficacy for Kawasaki Disease) Study Group conducted a multicenter, prospective, randomized, open-label, blinded end-points trial to assess the efficacy of IVIG (2 g/kg for 1 day) and ASA (30 mg·kg^{-1}·d^{-1}) plus intravenous prednisolone (2 mg·kg^{-1}·d^{-1}) for 5 days followed by an oral taper over weeks.[190] The steroid group had a lower incidence of coronary artery abnormalities and treatment resistance, lower coronary artery *Z* scores, and more rapid resolution of fever and decline in CRP levels. A recent meta-analysis that included these trials, using different regimens of steroids and different prediction scores, found that a combination of corticosteroid with standard-dose IVIG as an initial treatment in high-risk patients reduced the rate of coronary artery abnormalities.[191] Thus, the addition of corticosteroid therapy to IVIG and ASA in the primary therapy of KD lowers the prevalence of coronary artery abnormalities, duration of fever, and inflammation among Japanese children at highest risk for IVIG resistance. However, the Japanese scoring systems for IVIG resistance and aneurysms have low sensitivity in North American populations.[192] Further research is thus needed to develop predictive instruments or scores for reliable identification of high-risk children outside Japan and to test the efficacy of the RAISE steroid regimen in this population.

Infliximab

Early studies from Japan documented high levels of the proinflammatory cytokine TNF-α in the plasma of patients with acute KD.[193] Levels were highest in patients who went on to develop coronary artery abnormalities.

Infliximab, a chimeric monoclonal antibody that binds with high affinity to TNF-α, was the first anti-TNF-α monoclonal antibody therapy to be approved for pediatric patients. Numerous case reports and small series described successful use of infliximab to halt inflammation in highly resistant KD.[194,195] In a study of 11 KD patients with IVIG resistance who were treated with infliximab as rescue therapy, there was an apparent clinical response. Proinflammatory cytokine levels fell after infliximab treatment, but markers of vasculitis, including vascular endothelial growth factor and the S100 proteins, remained elevated.[196] This suggested the possibility that infliximab was effective in reducing systemic levels of inflammation but not in suppressing the vasculitis.

A 2-center, randomized, double-blind, placebo-controlled trial of infliximab plus IVIG for intensification of initial treatment enrolled 196 subjects.[197] The study was powered for the primary outcome measure of reducing IVIG resistance from 20% to 5%. Secondary outcome measures included reduction of inflammatory parameters and the change in coronary artery *Z* scores. Although the number of fever days was shortened and inflammatory parameters normalized more rapidly in the infliximab-treated subjects, the rates of IVIG resistance were identical between the 2 arms. A striking finding was the complete prevention of IVIG infusion reactions in children randomized to the infliximab arm compared with a 13% reaction rate in subjects who received placebo before their IVIG infusion. There was a significant decrease in *Z* score for the LAD in favor of infliximab. However, there was no difference in the rate of coronary artery aneurysms between the groups, although the study was inadequately powered for this end point. On

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Table 6. Treatment Options for IVIG-Resistant KD Patients

Agent	Description	Dose	References
Most frequently administered			
IVIG: Second infusion	Pooled polyclonal IG	2 g/kg IV	211
IVIG + prednisolone	IVIG + steroid	IVIG: 2 g/kg IV + prednisolone 2 mg·kg^{-1}·d^{-1} IV divided every 8 h until afebrile, then prednisone orally until CRP normalized, then taper over 2–3 wk	212
Infliximab	Monoclonal antibody against TNF-α	Single infusion: 5 mg/kg IV given over 2 h	194, 213, 214
Alternative treatments			
Cyclosporine	Inhibitor of calcineurin-NFAT pathway	IV: 3 mg·kg^{-1}·d^{-1} divided every 12 h PO: 4–8 mg·kg^{-1}·d^{-1} divided every 12 h Adjust dose to achieve trough 50–150 ng/mL; 2-h peak level 300–600 ng/mL	215, 216
Anakinra	Recombinant IL-1β receptor antagonist	2–6 mg·kg^{-1}·d^{-1} given by subcutaneous injection	217, 218
Cyclophosphamide	Alkylating agent blocks DNA replication	2 mg·kg^{-1}·d^{-1} IV	219
Plasma exchange	Replaces plasma with albumin	Not applicable	220

IVIG resistance is defined as persistent or recrudescent fever at least 36 hours and <7 days after completion of first IVIG infusion. The top 3 treatments have been most commonly used, although no comparative effectiveness trial has been performed. Pulsed high-dose steroid treatment is not recommended. The alternative treatments have been used in a limited number of patients with KD.

CRP indicates C-reactive protein; IG, immunoglobulin; IL, interleukin; IV, intravenous; IVIG, intravenous immunoglobulin; KD, Kawasaki disease; NFAT, nuclear factor of activated T cells; PO, by mouth; and TNF, tumor necrosis factor.

the basis of current information, addition of infliximab to initial therapy with IVIG is safe but does not prevent recrudescent fever.

Etanercept

A more limited experience with etanercept (soluble TNF receptor) plus IVIG for intensification of initial therapy was reported recently.[198] In this prospective, open-label study of 15 patients, etanercept was administered subcutaneously after IVIG infusion and again at 1 and 2 weeks later. Most patients received 0.8 mg/kg per dose. The pharmacokinetics were similar to those reported in older children, and there were no adverse reactions attributable to etanercept. On the basis of these results, a phase III randomized, placebo-controlled trial was initiated and is still enrolling subjects.[199] Recommendations for primary adjunctive treatment with etanercept await publication of the results of this clinical trial. The potential advantage of etanercept might be the shorter half-life if secondary infections are of concern. However, the soluble receptor only binds to circulating and not cell-bound TNF-α, which could reduce the anti-inflammatory effect.

Recommendations for Adjunctive Therapies for Primary Treatment

1. **Single-dose pulse methylprednisolone should not be administered with IVIG as routine primary therapy for patients with KD *(Class III; Level of Evidence B)*.**
2. **Administration of a longer course of corticosteroids (eg, tapering over 2–3 weeks), together with IVIG 2 g/kg and ASA, may be considered for treatment of high-risk patients with acute KD, when such high risk can be identified in patients before initiation of treatment *(Class IIb; Level of Evidence B)*.**

IVIG Resistance

Approximately 10% to 20% of patients with KD develop recrudescent or persistent fever at least 36 hours after the end of their IVIG infusion and are termed IVIG resistant.[176,200,201] The immunologic basis of IVIG resistance is unknown, in part because the mechanism of action of IVIG is poorly understood. It is likely that host genetic factors, such as polymorphisms in the Fc gamma receptors, play a role in both the response and resistance to IVIG.[61,202,203]

Risk Scores for Predicting Nonresponse to IVIG

Approximately 10% to 20% of patients with KD have persistent or recurrent fever after primary therapy with IVIG plus ASA.[204,205] Many studies have shown that patients who are resistant to initial IVIG are at increased risk of developing coronary artery abnormalities.[171,206,207] Thus, scoring systems have been constructed to identify patients likely to be resistant to IVIG and who may benefit from more aggressive initial therapy. In 2006, 3 Japanese groups devised scoring systems to predict resistance to IVIG.[187,189,208,209] However, currently available

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risk prediction models for Asian populations are insufficiently accurate to be clinically useful in North American patients in predicting response to initial treatment with IVIG.[192,210] Better predictive models, perhaps incorporating biomarkers or genetic variants, will need to be developed for use outside Japan.

Treatment of IVIG Resistance

There are no robust data from clinical trials to guide the clinician in the choice of therapeutic agents for the child with IVIG resistance. We summarize below the experience with different therapeutic approaches (Table 6). Cost-effectiveness comparisons between different approaches have not been reported.

IVIG Retreatment

Many experts recommend retreatment with IVIG 2 g/kg. The putative dose-response effect of IVIG forms the theoretical basis for this approach. Retrospective series have suggested efficacy, but IVIG retreatment has never been tested in an adequately powered randomized trial.[171,211]

Corticosteroids

Corticosteroids have also been used to treat patients who have failed to respond to initial therapy for KD.[182] Several small case series and observational studies have described children with KD with recrudescent or persistent fever despite IVIG treatment in whom the administration of steroid therapy was associated with an improvement in symptoms and the absence of an important progression in coronary artery abnormalities or adverse effects.[219,221–225] In a study of first-line rescue therapy, Furukawa et al[226] reported 63 IVIG-resistant patients, of whom 44 were then given intravenous methylprednisolone (30 mg·kg^{-1}·d^{-1} for 3 consecutive days) followed by oral methylprednisolone tapered over 7 days; 19 patients were given a second infusion of IVIG. The incidence of coronary artery abnormalities and treatment failure was similar between the 2 treatment groups, although power was limited by the small sample size. Fever tended to recur more frequently in the group treated with pulse steroids. Ogata et al[227] compared the effectiveness of treatment strategies for 27 IVIG-resistant patients: 14 patients were treated with additional IVIG (2 g/kg for 1 day), and 13 were treated with pulse intravenous methylprednisolone (30 mg/kg for 3 consecutive days). Patients in the steroid group had shorter duration of fever and lower medical costs. Three patients (21%) treated with IVIG and no patients treated with steroids had coronary artery abnormalities. Again, the study was underpowered to show a significant difference between the groups. Teraguchi et al[228] studied 41 IVIG-resistant patients and reported that intravenous methylprednisolone (30 mg·kg^{-1}·d^{-1} for 3 consecutive days) followed by prednisolone (1 mg·kg^{-1}·d^{-1}) for 7 days did not improve clinical or coronary artery outcomes compared with IVIG retreatment. Kobayashi et al[212] reported a retrospective study to assess the efficacy of intravenous prednisolone followed by an oral taper (2 mg·kg^{-1}·d^{-1} tapered over 2 weeks after CRP normalized) using a database of 359 consecutive IVIG-resistant patients. Patients treated with IVIG plus prednisolone had significantly lower rates of persistent or recrudescent fever and coronary artery abnormalities than the group that received IVIG monotherapy. It is hypothesized that the improved outcomes associated with the longer steroid course in the Japanese studies might be attributed to suppression of persistent vascular inflammation, although there have been no clinical trials comparing different steroid regimens for patients who do not respond to an initial or a second dose of IVIG. The optimal steroid regimen is therefore not known, and both pulsed and longer-term steroid therapy remain options.

Infliximab

A phase I multicenter, randomized, open clinical trial of infliximab (5 mg/kg intravenously over 2 hours) versus a second infusion of IVIG (2 g/kg) was performed to determine the safety, tolerability, and pharmacokinetics of infliximab for rescue therapy for patients who had fever at least 36 hours after the end of the initial IVIG infusion.[195] The study enrolled 24 subjects with IVIG-resistant KD and determined that infliximab was well tolerated in infants and children with KD and that the pharmacokinetics were similar to adults, with circulating levels of the monoclonal antibody detected out to 10 weeks. In the Japanese trial, 20 KD patients resistant to 2 consecutive IVIG infusions (2 g/kg each) were treated with infliximab (5 mg/kg), and an apparent clinical response was achieved in 18 (90%).[229] The 2 unresponsive patients were treated with plasma exchange with resolution of their inflammation. The coronary artery abnormalities detected by echocardiogram all subsequently resolved. There were no adverse reactions attributed to infliximab among the study subjects.

A retrospective review of 2 centers that consistently administered either a second dose of IVIG or infliximab to IVIG-resistant patients suggested that patients receiving infliximab had shorter hospitalization and fewer days of fever, but coronary artery outcomes and adverse events were similar.[213] On the basis of these retrospective data, infliximab can be considered as an alternative to a second infusion of IVIG for resistant patients.

Other Treatments

Highly inflamed patients who fail to respond to either a second infusion of IVIG, steroids, or infliximab require additional therapy to control inflammation.

Cyclosporine

Interest in the calcineurin inhibitor cyclosporine for KD patients grew out of 2 observations. First, immunohis-

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tochemical studies of coronary arteries from autopsies suggested that CD8+ T cells contribute to the inflammatory process in the arterial wall.[230] Second, genetic studies in children of Japanese or European descent have implicated activation of the NFAT-calcineurin calcium signaling pathway as a contributor to both disease susceptibility and coronary artery aneurysm formation.[231,232] Cyclosporine is a specific inhibitor of calcineurin, and a protocol for its administration and monitoring has been used successfully in a small number of highly resistant patients.[216] Dosing is provided in Table 6; levels are monitored to arrive at the appropriate dose but not monitored thereafter. Once the patient is afebrile and clinically improving and the CRP is ≤1.0 mg/dL, or after 2 weeks of therapy, the dose can be tapered by 10% of the initial dose every 3 days and discontinued when the dose has reached 1 $mg \cdot kg^{-1} \cdot d^{-1}$. A small, open, single-arm pilot trial in Japan studied cyclosporine treatment in 28 children who remained febrile after administration of 2 doses of IVIG.[215] After receiving an oral dose of 4 to 6 $mg \cdot kg^{-1} \cdot d^{-1}$, 18 patients (64%) were afebrile after 3 days of therapy. Overall, 78% of patients responded. Nine patients developed hyperkalemia, but none had serious adverse effects; however, cyclosporine levels were not monitored. Four patients had coronary artery aneurysms, 2 before cyclosporine had been administered. In a separate report, the levels of soluble IL-6 and IL-2 receptors dropped to control levels by 7 days after initiation of cyclosporine.[169] Randomized trials are needed to determine whether calcineurin inhibitors such as cyclosporine or tacrolimus reduce the rate of coronary artery aneurysms; however, these small studies suggest that cyclosporine has few serious adverse events and is a well-tolerated option for treatment of highly refractory patients, although further study is needed.

Other Monoclonal Antibody Therapy

Two case reports describe the successful use of anakinra, a recombinant, nonglycosylated form of the human IL-1 receptor antagonist, for treatment of highly refractory KD.[217,218] Clinical trials are in progress to evaluate the efficacy of IL-1 blockade in children with acute KD.

Plasma Exchange

Plasma exchange has been reported in uncontrolled clinical trials to be an effective therapy in patients who are refractory to IVIG and to lower the incidence of coronary artery aneurysms.[220,233] Because of its risks, plasma exchange should be reserved for patients in whom all reasonable medical therapies have failed.

Cytotoxic Agents

Cytotoxic agents such as cyclophosphamide, in conjunction with oral steroids, have been used for exceptional patients with particularly refractory acute KD.[219] This therapy is used widely to treat other severe vasculitides. There are insufficient studies of cyclophosphamide in KD to formulate recommendations for its use, but the risks of cytotoxic agents are such that its use should only be considered in the most severe cases, which are resistant to other agents.

Recommendations for Additional Therapy in the IVIG-Resistant Patient

1. **It is reasonable to administer a second dose of IVIG (2 g/kg) to patients with persistent or recrudescent fever at least 36 hours after the end of the first IVIG infusion *(Class IIa; Level of Evidence B)*.**
2. **Administration of high-dose pulse steroids (usually methylprednisolone 20–30 mg/kg intravenously for 3 days, with or without a subsequent course and taper of oral prednisone) may be considered as an alternative to a second infusion of IVIG or for retreatment of patients with KD who have had recurrent or recrudescent fever after additional IVIG *(Class IIb; Level of Evidence B)*.**
3. **Administration of a longer (eg, 2–3 weeks) tapering course of prednisolone or prednisone, together with IVIG 2 g/kg and ASA, may be considered in the retreatment of patients with KD who have had recurrent or recrudescent fever after initial IVIG treatment *(Class IIb; Level of Evidence B)*.**
4. **Administration of infliximab (5 mg/kg) may be considered as an alternative to a second infusion of IVIG or corticosteroids for IVIG-resistant patients *(Class IIb, Evidence Level C)*.**
5. **Administration of cyclosporine may be considered in patients with refractory KD in whom a second IVIG infusion, infliximab, or a course of steroids has failed *(Class IIb; Level of Evidence C)*.**
6. **Administration of immunomodulatory monoclonal antibody therapy (except TNF-α blockers), cytotoxic agents, or (rarely) plasma exchange may be considered in highly refractory patients who have failed to respond to a second infusion of IVIG, an extended course of steroids, or infliximab *(Class IIb; Level of Evidence C)*.**

Treatment of Acute Myocardial Dysfunction/ Cardiovascular Collapse

As noted previously, myocarditis that consists of myocardial interstitial edema, cellular infiltration (mainly monocytes, as well as neutrophils/macrophages), and (rarely) degeneration and necrosis of myocytes can occur during the acute stage of KD, even earlier than the

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occurrence of coronary arteritis.[73,120,122,234] Because the myocardial cells are preserved in most of the patients, LV function usually normalizes promptly with IVIG therapy.[111,235,236] However, severe myocarditis can still occur, can manifest as hemodynamic instability, and rarely can be a cause of death in the acute phase of KD.[117–119,237] In most cases, the development of a shock syndrome more often reflects decreased peripheral vascular resistance, with a smaller contribution from decreased LV contractility. The incidence of KD shock syndrome (KDSS) is estimated to be ≈7%.[118,119] KDSS can be defined as the presence of hypotension and shock requiring the initiation of volume expanders, the infusion of vasoactive agents, or transfer to intensive care units. Shock in KDSS is often moderate, with low lactate values and the need for treatment with inotropic and vasopressor agents.[117] Although hemodynamic instability generally improves quickly once therapy with diuretic agents and vasopressor agents is initiated, a mild degree of ventricular diastolic dysfunction can persist after acute management.[118] The causes of KDSS may involve the release of endogenous molecules that mediate a decrease in peripheral vascular resistance, myocardial dysfunction from myocarditis with or without myocardial ischemia, and capillary leakage, but the exact underlying mechanisms remain unclear. KDSS is often associated with more severe laboratory markers of inflammation and higher risk of coronary arterial dilation.[111,118] Such cases are also more likely to be resistant to IVIG therapy and to require additional anti-inflammatory treatment.[111,118]

Because KDSS can manifest before the diagnosis of KD becomes clear, it is critical to recognize the early signs of KD so that IVIG therapy can be initiated promptly. Treatment of the underlying inflammation is important in the resolution of KDSS. The shock in patients with KDSS can be cardiogenic, distributive, or mixed. The distributive component of shock might result from high levels of circulating inflammatory cytokines. Of note, there are no clinical trials focusing on KDSS patients. In most of the published case series, management followed the guidelines for pediatric septic shock.[238,239] The underlying pathophysiology of KDSS appears to be similar to septic shock with pathological vasodilation, relative and absolute hypovolemia, myocardial dysfunction, and altered distribution of blood volume. Because these patients have high circulating levels of vascular endothelial growth factor, they are susceptible to capillary leak, and vigorous volume replacement without concomitant anti-inflammatory therapy can result in complications from interstitial fluid accumulation. Therefore, an important aspect of hemodynamic stabilization in these patients remains administration of IVIG along with fluid and inotropic and vasoactive agents as necessary to support blood pressure. The inotropic support reported in case series has included dobutamine, epinephrine, norepinephrine, and dopamine.[117–119,237,240]

The administration of IVIG after the diagnosis of KD has been shown to improve LV function, because it improves inflammation and systemic manifestations.[111,235,236]

Prevention and Treatment of Thrombosis in Patients With Coronary Artery Aneurysms

Other than rupture of a coronary artery aneurysm, which is rare, the most serious complication during the acute illness is thrombotic occlusion of a coronary artery aneurysm precipitating MI or sudden death. Contributing factors to thrombosis include the presence of thrombocytosis and increased platelet adhesion, inflammation, and endothelial dysfunction, together with abnormal flow conditions through areas of severe dilation. For patients with evolving coronary artery aneurysms, follow-up assessments with echocardiography should be performed frequently to monitor for increases in luminal dimensions and hence increasing thrombotic risk, as well as for the presence of thrombosis or signs of ventricular dysfunction. Failure to increase the intensity of antithrombotic therapy in the presence of rapidly expanding aneurysms is the most important contributor to sudden cardiovascular events during the acute illness. MIs in young children and infants are either silent or associated with nonspecific symptoms, such as unusual fussiness, vomiting, or shock. Sudden worsening in ventricular function or change in electrocardiographic findings should heighten suspicion for coronary artery thrombosis.

Prevention of Coronary Artery Thrombosis

To date, no randomized clinical trials have evaluated the safety and efficacy of antithrombotic regimens for prophylaxis of coronary thrombosis in KD, in part because the power for such trials is limited by small patient numbers and few thrombotic events. For this reason, recommendations for use of antithrombotic agents have relied on reasoning from first principles, retrospective studies, practices in atherosclerotic coronary artery disease (CAD), and expert consensus.

Antiplatelet agents are considered to be standard of care in the therapeutic armamentarium for patients with coronary artery aneurysms. For patients with small coronary artery aneurysms, monotherapy with low-dose ASA therapy is sufficient for prophylaxis of thrombosis. In patients with moderate but not large or giant aneurysms, ASA therapy may be combined with a thienopyridine (eg, clopidogrel) to antagonize ADP-mediated platelet activation, a practice supported by the superior efficacy of such a regimen, compared with ASA alone, among adults with coronary artery or cerebrovascular disease.[241–244] Finally, ibuprofen and other nonsteroidal anti-inflammatory drugs with known or potential involvement of the cyclooxygenase pathway interfere with the antiplatelet effect of ASA to prevent thrombosis. If nonsteroidal anti-inflammatory drugs are needed for treatment of arthritis

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in patients with coronary artery aneurysms who are taking ASA, alternative antiplatelet therapies (eg, thienopyridines) should be considered.

Patients with large or giant aneurysms, that is, with an internal luminal diameter *Z* score ≥10 or absolute dimension ≥8 mm, are at particularly high risk for coronary artery thrombosis. In affected arterial segments, coronary artery thrombosis is promoted by markedly abnormal flow conditions, with low wall sheer stress and stasis, together with activation of platelets, clotting factors, and the endothelium. Over time, stenoses often develop, causing activation of platelets and endothelial dysfunction from turbulence of flow when located proximally and occluding flow and worsening stasis when located distal to an aneurysm. Indeed, most giant aneurysms seen at postmortem examination are lined by chronic thrombus.[73] Because both platelets and humoral clotting factors promote thrombus formation within giant aneurysms, patients are treated with a combination of antiplatelet and anticoagulant therapy, most commonly low-dose ASA together with either warfarin, maintaining an international normalized ratio of 2.0. to 3.0, or low-molecular-weight heparin (LMWH).[245]

Anticoagulation with therapeutic doses of LMWH is generally substituted for warfarin in infants and is also occasionally used in the older child in whom the international normalized ratio cannot be adequately controlled. Transition from LMWH to warfarin may be considered once aneurysms have stopped expanding and the patient is stable. During the acute phase, the anti-inflammatory actions of the LMWH could be an added advantage. Transient low levels of antithrombin occur in more than half of KD patients during the acute illness, are related to increased antithrombin consumption, and can affect the antithrombotic action of LMWH.[55] If patients fail to achieve the desired activated factor Xa level (0.5–1.0) on an appropriate dose (Table 7), then antithrombin levels should be measured. If deficient, fresh-frozen plasma or antithrombin supplementation may be given.

More aggressive regimens may be used in patients with exceptionally high risk for coronary artery thrombosis. Infants and children who recently required thrombolysis for coronary artery thrombosis may be maintained for a limited time on 3 agents, that is, ASA, a thienopyridine, and an anticoagulant. Because the risk of bleeding is greater with such a regimen, clinicians must consider its risk/benefit ratio on an individual basis. Newer oral direct factor Xa inhibitors or direct thrombin inhibitors are not yet approved for use in pediatrics but could supplant warfarin and LMWH in the future.

Recommendations for Prevention of Thrombosis During the Acute Illness

1. **Low-dose ASA (3–5 mg·kg^{-1}·d^{-1}) should be administered to patients without evidence of coronary artery changes until 4 to 6 weeks after onset of illness *(Class I; Level of Evidence C)*.**
2. **For patients with rapidly expanding coronary artery aneurysms or a maximum *Z* score of ≥10, systemic anticoagulation with LMWH or warfarin (international normalized ratio target 2.0–3.0) in addition to low-dose ASA is reasonable *(Class IIa; Level of Evidence B)*.**
3. **For patients at increased risk of thrombosis, for example, with large or giant aneurysms (≥8 mm or *Z* score ≥10) and a recent history of coronary artery thrombosis, "triple therapy" with ASA, a second antiplatelet agent, and anticoagulation with warfarin or LMWH may be considered *(Class IIb; Level of Evidence C)*.**
4. **Ibuprofen and other nonsteroidal anti-inflammatory drugs with known or potential involvement of cyclooxygenase pathway may be harmful in patients taking ASA for its antiplatelet effects *(Class III; Level of Evidence B)*.**

Treatment of Coronary Artery Thrombosis

Because of its rarity, treatment of acute coronary thrombosis in KD patients has not been tested in randomized controlled trials. Rather, recommendations for therapy are based on guidelines in adults with ACS and small pediatric case series, with goals of reestablishing coronary artery patency and flow, salvaging myocardium, and improving survival.[247–249] Compared with coronary artery thrombosis in the adult with atherosclerotic CAD, thrombus mass in the KD patients is typically much greater. Furthermore, coronary artery thrombosis in the adult with CAD is most often caused by plaque rupture or inflammation, with exposure of lipids and extracellular matrix to the coagulation system, whereas highly abnormal flow characteristics form the basis for coronary artery thrombosis in KD patients. Methods used to reestablish coronary artery perfusion can vary with the size of the patient and expertise of caregivers; the optimal treatment is that which re-establishes blood flow most rapidly. Coronary artery thrombosis with actual or impending occlusion of the arterial lumen should be treated with thrombolytic therapy or, in patients of sufficient size, by mechanical restoration of coronary artery blood flow at cardiac catheterization.

Thrombolytic therapy with tissue-type plasminogen activator (tPA) is the most commonly administered therapeutic regimen for occlusive or near-occlusive coronary artery thrombosis in infants and children (Table 7). A common regimen of tPA is 0.5 mg·kg^{-1}·h^{-1} over 6 hours.[250] Of note, an alternative regimen of tPA, used in adult coronary artery thrombosis, is 0.2 mg/kg

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Table 7. Antithrombotic and Fibrinolytic Therapy in KD[246]

Drug	Mechanism of Action	Indications	Dose	Target Range	Monitoring	Adverse Effects
Anticoagulants						
UFH	Potentiates the inhibition of factors XIIa, Xia, Xa, IXa, IIa by antithrombin Hepatic and renal clearance; reversible with protamine sulfate	Treatment of acute coronary artery thrombosis, usually in conjunction with tPA; bridging for patients undergoing invasive procedures requiring reversal of anticoagulation	Age-dependent dosing: <12 mo of age: 28 U·kg^{-1}·h^{-1} ≥12 mo of age: 20 U·kg^{-1}·h^{-1} Low dose: commonly 10–15 U·kg^{-1}·h^{-1} Titrate to PTT target range Given as continuous parenteral infusion	Anti–factor Xa 0.35–0.70 U/mL PTT 1.5–3 times baseline PTT, depending on local laboratory values	Every 24 h at minimum	Bleeding, heparin-induced thrombocytopenia, association with bone mineral loss
LMWH	Same as UFH but greater inhibition of factor Xa Renal clearance; not fully reversible; hold for 24 h before invasive procedures	Chronic thromboprophylaxis option for patients with large or giant coronary artery aneurysms or previous thrombosis, particularly for young infants or those with expanding aneurysms early in the course of their illness; bridging for patients between UFH and warfarin	Age- and agent-dependent dosing	Anti–factor Xa level 0.5–1.0 U/mL	Every month at minimum	Bleeding, bruising at injection sites
Enoxaparin			Given every 12 h subcutaneously: <2 mo of age: 1.5 mg/kg per dose >2 mo of age: 1.0 mg/kg per dose Higher doses may be needed in neonates; titrate to anti–factor Xa target range		Obtain levels 4–6 h after dose	
Tinzaparin			Given every 24 h subcutaneously: 0–2 mo: 275 U/kg per dose 2–12 mo: 250 U/kg per dose 1–5 y: 240 U/kg per dose 5–10 y: 200 U/kg per dose >10 y: 175 U/kg per dose Titrate to anti–factor Xa target range		Age-dependent monitoring: <5 y: 2 h after dose ≥5 y: 4 h after dose	
Warfarin	Inhibits the gamma-carboxylation of the vitamin K–dependent factors II, VII, IX, and X and protein C, S, and Z Hepatic metabolism; oral administration; many food, drug, and illness interactions; reversible with vitamin K administration	Long-term thromboprophylaxis for patients with large or giant coronary artery aneurysms or previous thrombosis	Load with 0.2 mg·kg^{-1}·d^{-1}, then 0.1 mg·kg^{-1}·d^{-1}; titrate dose to INR target level	INR level 2–3	INR daily until in target range, thereafter minimum monthly testing; test INR with illness, medication, or diet change	Bleeding, tracheal calcification, hair loss, decreased bone mineral density
Antiplatelet therapy						
ASA	Inhibition of COX-1 and COX-2 activity Irreversible platelet inhibition; some patients are ASA resistant; discontinue 7 d before invasive procedures; precaution for concomitant use of ibuprofen or other nonsteroidal anti-inflammatory agents (usually given to treat arthritis/arthralgias); risk of Reye syndrome with varicella and influenza infections (see Reye Syndrome section in Treatment of the Acute Illness), given orally	Thromboprophylaxis for all patients from the acute illness until 4–6 wk; continue long term for patients with ongoing coronary artery involvement (see Thromboprophylaxis section in Long-Term Management)	3–5 mg·kg^{-1}·d^{-1}, maximum 81–325 mg/d			Bruising, confusion, vertigo, nausea, vomiting, tinnitus, abdominal pain, cramping, burning, fatigue, bleeding

(*Continued*)

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Table 7. Continued

Drug	Mechanism of Action	Indications	Dose	Target Range	Monitoring	Adverse Effects
Clopidogrel	Inhibition of ADP-induced platelet aggregation, no effects on arachidonic acid metabolism Renal clearance, hepatic metabolism; some patients fail to respond; given orally	Thromboprophylaxis together with ASA and anticoagulation (triple therapy) for selected patients with very severe/complex coronary artery aneurysms at high risk of thrombosis or with evidence of previous thrombosis Thromboprophylaxis together with ASA (dual antiplatelet therapy) for patients with moderate coronary artery aneurysms or large or giant aneurysms that have reduced to moderate size Can be used in place of ASA for patients who are ASA resistant or allergic to ASA	0.2–1.0 $mg \cdot kg^{-1} \cdot d^{-1}$			Fatigue, vertigo, stomach upset or pain, bruising, bleeding, diarrhea
Dipyridamole	Inhibits adenosine reuptake, increasing cAMP, and inhibits platelets	Usually used in place of ASA for patients who are taking ibuprofen, resistant or allergic to ASA, or at risk of Reye syndrome; not generally used for long-term thromboprophylaxis	1–5 $mg \cdot kg^{-1} \cdot d^{-1}$ given orally			Chest pain, angina pectoris, headache, abnormalities of ECG
Abciximab	Inhibits glycoprotein IIb–IIIa, prevents binding of fibrinogen to von Willebrand factor, inhibiting platelet aggregation Monoclonal antibody, renal excretion	Limited use, usually reserved for patients with coronary artery aneurysms who develop thrombosis (both occlusive and nonocclusive) and given as a single course	0.25 mg/kg bolus, then 0.125 $\mu g \cdot kg^{-1} \cdot min^{-1}$ every 12 h			Bleeding, hypertension, nausea, vomiting, vertigo, irritation at injection site
Thrombolytic therapy						
Alteplase	tPA converts plasminogen into plasmin; plasmin degrades fibrin (crosslinked) and fibrinogen Reversible with aminocaproic acid; contraindicated if active bleeding or recent surgery or trauma	Reserved for patients with coronary artery aneurysm thrombosis, particularly if occlusive	For coronary artery thrombosis, data are lacking Dosing regimens that have been used include: 0.1–0.6 (commonly 0.5) $mg \cdot kg^{-1} \cdot h^{-1}$ IV for 6 h As per adult guidelines, 0.2 mg/kg IV bolus (maximum 15 mg), then 0.75 mg/kg over 30 min (maximum 50 mg), then 0.5 mg/kg over 60 min (maximum 35 mg), for a maximum total dose of 100 mg Low-dose alteplase combined with abciximab Administration: give fresh-frozen plasma 10–20 mL/kg infusion before using alteplase as a plasminogen source; keep fibrinogen >100 mg/dL and platelets >50 000/mm^3; continue UFH at an age-appropriate dose during administration of alteplase; alteplase may be given as an intermittent (recommended) or continuous usual or low-dose systemic infusion or directed locally toward the thrombus by catheters at a lower dose		Reassess thrombus with imaging at completion of the infusion; retreatment may be indicated once hematologic parameters are acceptable; careful patient observation is required, with prompt investigation if there is any suspicion of internal bleeding	Major and minor bleeding

ASA indicates acetylsalicylic acid; COX, cyclooxygenase; INR, international normalized ratio; IV, intravenous; KD, Kawasaki disease; LMWH, low-molecular-weight heparin; PTT, partial thromboplastin time; tPA, tissue plasminogen activator; and UFH, unfractionated heparin.

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intravenously (maximum 15 mg), then 0.75 mg/kg over 30 minutes (maximum 50 mg) followed by 0.5 mg/kg over 60 minutes (maximum 35 mg).[137] It should be administered together with low-dose ASA and low-dose intravenous heparin (10 $U \cdot kg^{-1} \cdot h^{-1}$) with careful monitoring of coagulation parameters to prevent bleeding, maintaining the fibrinogen level >100 mg/dL and platelet count >50 000/mm^3.[251] After completion of tPA, heparin dosage is increased as appropriate for age. The coronary artery thrombus should be reassessed with echocardiographic imaging after completion of the tPA infusion.

The large thrombus burden in the KD patient with coronary artery thrombosis, as well as the tendency for rebound thrombosis in such patients, has led some clinicians to use reduced-dose thrombolytic therapy together with a glycoprotein IIb/IIIa inhibitor, such as the monoclonal antibody abciximab (0.25 mg/kg bolus over 30 minutes, followed by an infusion of 0.125 $\mu g \cdot kg^{-1} \cdot min^{-1}$ for 12 hours).[252,253] In adults with ACS, inhibition of this receptor has been shown to improve outcomes, both with and without the use of thrombolytic drugs.[254–256] It may be reasonable to treat coronary artery thrombosis with substantial thrombus burden and high risk of occlusion with a reduced-dose thrombolytic therapy and abciximab. When echocardiographic surveillance in the first weeks of the illness reveals a small mural coronary artery thrombus that does not pose an urgent threat of occlusion, it may be reasonable to use abciximab rather than tPA to prevent clot extension.

Recommendations for Treatment of Coronary Artery Thrombosis*

1. **Coronary artery thrombosis with actual or impending occlusion of the arterial lumen should be treated with thrombolytic therapy or, in patients of sufficient size, by mechanical restoration of coronary artery blood flow at cardiac catheterization *(Class I; Level of Evidence C)*.**
2. **Thrombolytic agents should be administered together with low-dose ASA and low-dose heparin, with careful monitoring for bleeding *(Class I; Level of Evidence C)*.**
3. **Treatment of coronary artery thrombosis with substantial thrombus burden and high risk of occlusion with a combination of reduced-dose thrombolytic therapy and abciximab may be considered *(Class IIb; Level of Evidence C)*.**

LONG-TERM MANAGEMENT

Long-term management begins at the end of the acute illness, usually at 4 to 6 weeks after fever onset, when symptoms and signs have resolved and the coronary artery involvement has reached its maximal extent and luminal dimensions. The goals of long-term management are to prevent thrombosis and myocardial ischemia while maintaining optimal cardiovascular health. There are no specific treatments that target the pathological processes of ongoing subacute/chronic vasculitis and LMP in those patients with coronary artery aneurysms, although there may be a potential role for statins in this setting.[257] Thromboprophylaxis and careful surveillance for coronary artery stenoses/obstructions and myocardial ischemia are the cornerstones of management. Selected patients with myocardial ischemia may be candidates for revascularization with catheter interventions or coronary artery bypass surgery or, rarely, cardiac transplantation. Survival with optimal functional, psychosocial, and reproductive outcomes into adulthood will require the development of effective and collaborative programs between pediatric and adult cardiology providers to facilitate the transition process into adult-oriented care systems.

Long-Term Outcomes

Long-term outcomes are primarily driven by the consequences of resolving and ongoing cardiovascular pathology that contribute to morbidity, cardiovascular events, and mortality. Arterial pathology in noncoronary peripheral artery beds can cause ongoing morbidity in a small subset of patients and is somewhat correlated with the extent of coronary artery pathology.[131] However, the main culprit is the coronary arteries. The pathological process of necrotizing arteritis during the acute illness, which results in destruction and weakening of the arterial wall leading to aneurysms, may be accompanied by subacute or chronic inflammation and luminal myofibroblastic proliferation. Superimposed on these processes are the effects of acute and organized thrombus. The degree to which conventional atherosclerosis may contribute to chronic pathological changes is not known. These processes may lead to both acute (usually precipitated by thrombus or arrhythmia) and chronic (usually precipitated by occlusions or stenoses) cardiovascular morbidity and events. Although the chronic processes may result in normalization of the internal luminal dimension, the arterial wall architecture and function remain abnormal and may progress to stenosis or occlusion over time.[73] Nonetheless, normalization of the luminal dimension does reduce abnormal flow characteristics (low sheer stress, stasis) and hence thrombosis risk. The terms *regression* and *resolution* have been used to describe normalization of luminal dimensions; however, important abnormalities may remain, particularly with large or giant aneurysms, and these terms may give the false impression that the coronary arteries have healed and are normal. The natural history of coronary artery abnormalities is shown in Figure 4. These processes are the primary determinants of prognosis.

*See Diagnosis section for recommendations regarding echocardiographic monitoring for thrombosis.

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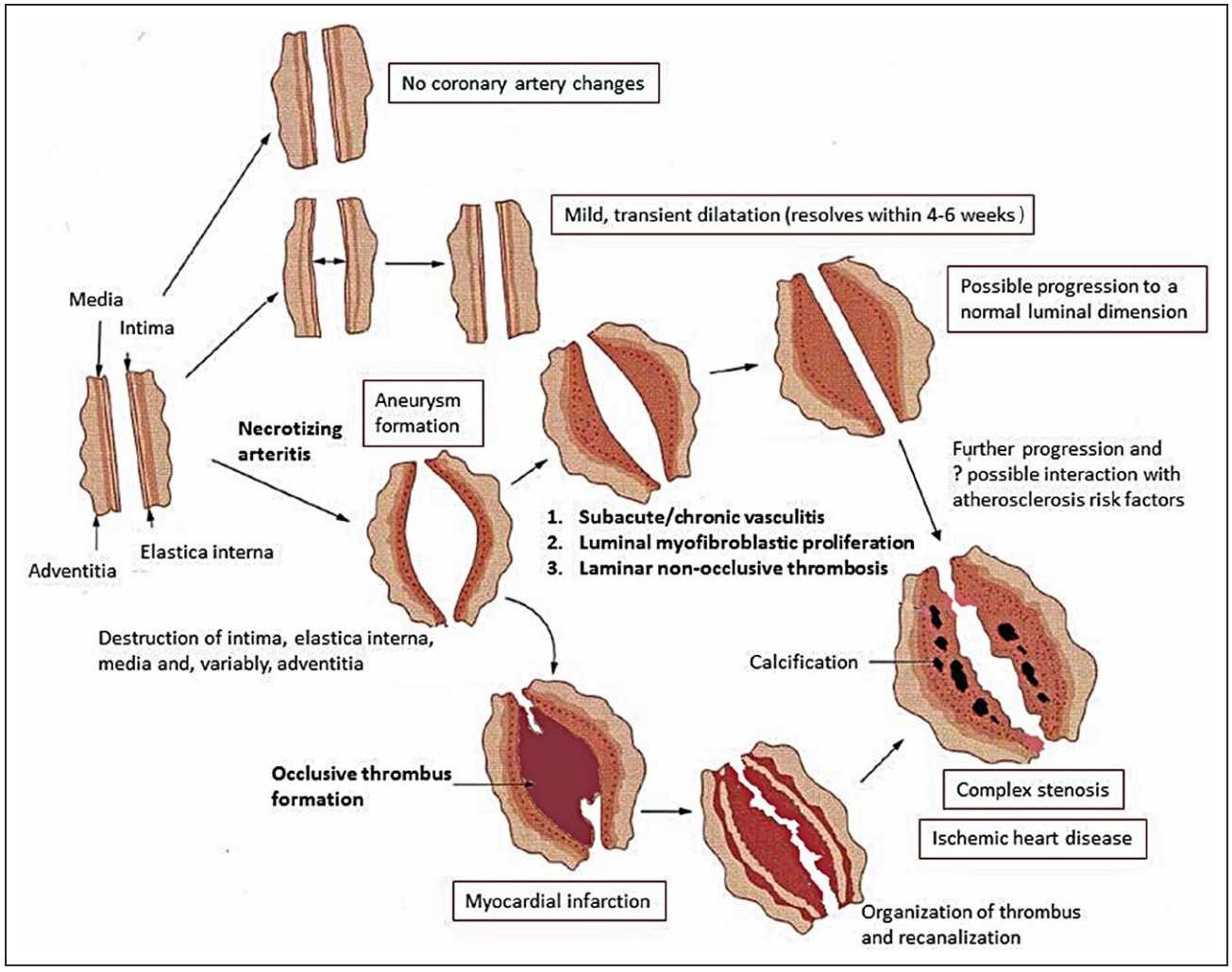

Figure 4. Natural history of coronary artery abnormalities.
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Coronary Artery Abnormalities

Prevalence

The original descriptions of KD did not recognize the presence of coronary artery abnormalities until it was observed that 1% to 2% of patients died suddenly of cardiac complications.[259] An angiographic study of 1100 patients showed coronary artery lesions in 24%, with aneurysms in 8% and a number of patients with stenoses and occlusions.[260] The early reports of the prevalence of abnormalities vary widely given the lack of uniformity in the timing of angiography and the definition of abnormalities, and they predate echocardiography and treatment with IVIG. The clinical trial of 4-day IVIG treatment with strict entry criteria (classic KD presenting within 10 days of fever onset) and using the 1984 Japanese Ministry of Health criteria (based on absolute luminal dimensions) noted a prevalence of coronary artery abnormalities of 23% in the ASA-only group versus 8% in the IVIG-plus-ASA group at 2 weeks, with a lower prevalence at 7 weeks.[176] A similar subsequent trial of a single high dose of IVIG showed coronary artery abnormalities, again using Japanese Ministry of Health criteria, at 2 weeks in 9.1% of those treated with 4-day IVIG treatment versus 4.6% in those treated with high-dose IVIG (further reduced to 2.4% when those with coronary artery abnormalities at presentation were excluded).[127] Using a cut point of a *Z* score of 2.5 together with the Japanese Ministry of Health criteria, a further trial of single-dose methylprednisolone in addition to high-dose IVIG showed a prevalence of coronary artery abnormalities of 30% in both groups at 1 week.[176] The incorporation of dilation into the definition results in a higher prevalence of coronary artery abnormalities. The prevalence of dilation is further increased if one includes those patients whose coronary artery *Z* scores were below the cut point for abnormality (<2) but decreased significantly during follow-up.[129,130]

These studies define the prevalence of coronary artery abnormalities in homogenous populations; however, some patients in clinical populations may have incom-

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plete criteria, present late, have a missed diagnosis, or have not received appropriate treatment, all of which are risk factors for more severe coronary artery involvement. In addition, some patients presenting within 10 days of fever onset may have coronary artery abnormalities at the time of initial echocardiogram and before or at the time that IVIG is given.[261] Michihata et al[262] showed that patient treatment that followed existing guidelines was associated with a 4.9% prevalence of aneurysms versus 9.9% if it did not. A classification system based on *Z* scores alone in a clinical population of 1356 patients with serial echocardiograms has been proposed and showed overlap in *Z* scores for classifications based on absolute dimensions only.[140] An analysis of 1082 patients from centers in the United States and Japan used 2 different sources of normal values for calculation of *Z* scores.[141] Using the *Z*-score equations of Kobayashi et al,[145] 26% of US subjects and 39% of Japanese subjects had a maximal *Z* score ≥2.5, with 4.1% and 3.1%, respectively, having a *Z* score ≥5. Using the *Z*-score equations of Dallaire et al,[146] 30% of US subjects and 44% of Japanese subjects had a maximal *Z* score ≥2.5, with 5.8% and 6.2%, respectively, having a *Z* score ≥5. The higher *Z* scores in Japanese patients remained significant after adjustment for younger age, male sex, late treatment, and failure to respond to initial IVIG. Thus, many factors need to be considered when determining and comparing the prevalence of coronary artery abnormalities, particularly the population and definitions.

Natural History and Cardiovascular Disease Events

Initial definition of the natural history of coronary artery abnormalities was determined from tracking luminal dimensions from serial angiography together with clinical follow-up for events. Kato et al[263] reported outcomes in 598 patients diagnosed from 1973 to 1983 and followed up for up to 10 to 21 years. Aneurysms were diagnosed in 25%, with 49% of these having reduced to a normal luminal dimension 6 to 18 months later, increasing to 55% with ongoing follow-up. All aneurysms that reduced in size to a normal luminal dimension were originally small or moderate in size. Stenoses developed in 28 patients and showed a more constant risk over time. Coronary artery bypass surgery was performed in 7 patients, 2 had interventional catheter procedures, and 16 required thrombolytic treatment. MI occurred in 11 patients (8 with giant aneurysms), all with severe stenotic lesions in 2 or 3 branches. Patients without coronary artery abnormalities had no symptoms or events during follow-up. Akagi et al[264] reported similar outcomes in a cohort of 583 patients and showed that normalization of luminal dimensions occurred more frequently and more rapidly in those with smaller aneurysms and did not occur for giant aneurysms, with MI occurring only in those with giant aneurysms. This remained true in a subsequent study of 1356 patients diagnosed from 1990 to 2007 and followed up with serial echocardiograms for up to 15.7 years.[140] Coronary artery events (thrombosis, stenosis, intervention, MI, death) occurred in 1% of those with an aneurysm *Z* score <10 and an absolute dimension <8 mm, in 29% of those with a *Z* score ≥10 but an absolute dimension <8 mm, and in 48% of those with both a *Z* score ≥10 and an absolute dimension ≥8 mm. Longitudinal studies of outcomes based on *Z*-score classifications alone have yet to be performed.

Late development or increases in size of aneurysms have been reported in case reports.[265–267] Tsuda et al[268] in an angiography study of 562 patients noted new dilated or expanding lesions in 15 patients. The new aneurysms occurred at sites where previous aneurysms had diminished in size but were all associated with a localized stenosis, although none were associated with cardiac events.

MI as a result of thrombotic occlusion of an aneurysm or the development of critical stenosis attributable to LMP occurs mainly in those patients with more severe coronary artery abnormalities and can cause sudden death. In young patients, it can be clinically silent or present with atypical symptoms.[263] The gradual progression of LMP and laminar thrombosis to obstructive lesions may be accompanied by the development of collateral vessels, particularly in the presence of segmental stenosis and in younger patients, regardless of the occurrence of MI.[269] Prompt and effective management of acute MI can improve outcomes, although the reported experience is limited.[270] Myocardial dysfunction present shortly after MI can improve, although some patients will develop adverse ventricular remodeling and ventricular aneurysms if the damage is extensive.[271] Patients who have had an MI are at further risk of subsequent MI, although the risk is reduced with effective revascularization. Tsuda et al[272] reported long-term outcomes up to 33 years after surviving MI in 60 patients. The 30-year survival rate was 63%, and the 25-year ventricular tachycardia–free survival rate was 29%. Low post-MI LV ejection fraction was predictive of poor outcomes.

Subclinical Vascular Outcomes

Long-term changes in coronary artery structure and function precede clinical events and reflect chronic pathological vascular processes in areas that were acutely involved by KD. Arterial wall structure can be imaged noninvasively and has provided insights into the natural history. Intravascular ultrasound (IVUS) has been used to demonstrate symmetrical and asymmetrical wall thickening in aneurysms, particularly in those aneurysmal segments that have progressed toward normal luminal dimensions.[273,274] IVUS has also been used to characterize wall elements, noting areas of fibrofatty changes, necrotic core, and dense calcification.[275] More recently, these changes have been assessed with optical coherence tomography (OCT).[276] Studies have been more

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equivocal as to whether or not wall thickening may be evident in coronary artery segments without previous dilation or aneurysm.

These structural findings are associated with functional abnormalities, with impaired dilation in response to nitroglycerin[277] or adenosine,[278] resulting in impaired coronary artery flow reserve. Iemura et al[274] studied KD patients with various degrees of coronary artery involvement who had all progressed to a normal luminal dimension on angiography. They noted that those segments that previously had large aneurysms showed paradoxical vasoconstriction in response to acetylcholine and diminished vasodilation in response to nitroglycerin. On positron emission tomography (PET) imaging, sites of previous aneurysms showed both impaired vasodilation coupled with reduced myocardial blood flow and flow reserve, particularly in segments with stenosis.[279] In contrast, a small case-control study of KD patients with no history of coronary artery abnormalities showed reduced myocardial flow reserve on PET.[280] PET has also been used to demonstrate persistent inflammation in patients with aneurysms, which may be reduced with statin therapy.[281] It would appear that long-term structural and functional coronary artery abnormalities are evident and associated with both maximal and current coronary artery status, with the greatest abnormalities in those with a history of large or giant aneurysms that have diminished to normal luminal dimensions. Whether or not long-term abnormalities occur in those patients who had no luminal abnormalities or only transient dilation remains a subject of debate, although the majority of evidence, including the absence of cardiovascular disease (CVD) events and lack of calcification on CT, suggests a normal long-term prognosis.

KD is a systemic vasculitis, and hence, the potential presence of generalized long-term abnormalities of systemic arterial structure and function has been a subject of controversy. Abnormal brachial artery reactivity or abnormal flow-mediated dilation, reflective of endothelial dysfunction, after KD was initially reported by Dhillon et al[282] in a case-control study. Since then, there have been many reports comparing noninvasive surrogate vascular markers, some additionally including measures of arterial stiffness and intima-media thickness. A systematic review and meta-analysis of 30 studies showed important heterogeneity between studies.[283] Similar to studies of coronary artery structure and function, evidence for systemic arterial endothelial dysfunction was most commonly reported for KD patients in general but more consistently for those with aneurysms, whereas results for those without a history of coronary artery abnormalities were not consistent. Similar findings were noted for arterial stiffness, whereas increased mean carotid intima-media thickness was not noted for KD patients, although studies of maximal carotid intima-media thickness were conflicting. The authors concluded that surrogate vascular markers were abnormal only in KD patients with aneurysms. Serological evidence of ongoing systemic inflammation has been noted in those patients with persistent aneurysms, with higher serum amyloid A and IL-6[284] and CRP,[285] and imaging evidence has been suggested on PET scanning.[286] Nonetheless, the clinical impact of these abnormalities has not been defined.

Valvular Regurgitation

When detected early, the preponderance of MR as assessed with echocardiography is in the mild to moderate range of severity and does not appear to persist on follow-up. MR can occur after the acute stage from myocardial ischemia. Late-onset valvulitis of the mitral and aortic valves can occur very rarely and may require valve replacement.[263,287] MR that becomes severe or that persists into late phases of KD appears to occur with lower frequency and can result from persistent ischemia or, rarely, from more resistant inflammatory processes that result in fixed structural abnormalities of the valve apparatus.[287,288] This circumstance indicates more serious valvular pathology and may require surgical intervention.

AR in KD is usually associated with aortic root dilation (as indicated by an increased aortic sinus *Z* score) and becomes apparent early in the course of the disease. AR is of lesser severity and appears to persist more consistently, and it is less reliably associated with other inflammatory markers. Nevertheless, progressive aortic valve dysfunction associated with severe AR has been reported in a patient with recurrent KD,[289] and aortic valve replacement was required.

Aortic Abnormalities

Patients after KD have been shown to have functional and anatomic abnormalities of the aorta. Assessment of aortic distensibility has been used in adults in the early screening of atherosclerosis. In a study that compared 40 KD patients without coronary artery aneurysms to 168 healthy children, aortic diameter was measured at both minimum diastolic pressure and maximum systolic pressure by 2D echocardiography; this study found that aortic distensibility varies with age in normal children.[290] It was low in infants, increased gradually to peak during the ages 10 to 15 years, and decreased with age thereafter. For KD patients, aortic stiffness was increased during the acute illness and was normal during convalescence. In a more recent study, Oyamada et al[291] demonstrated that the aortas in 75 patients with a history of KD had altered elastic properties compared with 57 control subjects. Specifically, LV mass index and aortic stiffness were significantly higher, whereas aortic distensibility and strain were lower at 5 to 10 years of follow-up in KD patients. Another study confirmed that in a KD cohort, aortic stiffness and elasticity were increased in 57 patients with KD >1 year after onset of illness, of whom 12 had coronary artery sequelae.[292] Both groups had altered elasticity and stiffness of the aorta.

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An unusual finding during the acute KD illness is the presence of retrograde holodiastolic flow in the abdominal aorta in the absence of AR. Mori et al[293] described this finding in 15 of 21 children at the time of their acute KD episode, which resolved by 1 month. The abnormal flow pattern may be attributable to an increase in the distensibility of the descending aorta, which is associated with the acute inflammation. Additionally, it was proposed that this pattern may represent diastolic runoff into dilated and dysfunctional peripheral arteries affected by the vasculitis.

An aspect of the vasculitis/inflammation noted during KD may lead to aortic root dilation. Ravekes et al[125] evaluated 100 children with history of KD from 1993 to 1997 and noted that patients had a greater normalized aortic root dimension that persisted at least to 1-year follow-up. In addition, 4% of these patients also had AR, although this was not evident on auscultation in any patient. A study of 198 children with acute KD noted that aortic root dilatation was present in 8%, remained constant at 1 and 5 weeks after diagnosis, and was associated with larger coronary artery size at diagnosis[111]; however, aortic root size had little association with inflammatory markers. The long-term implications of these alterations in aortic size and properties are unknown.

Myocardial Abnormalities

Although myocarditis is common during the acute illness, complete resolution is expected. Early biopsy studies suggested the presence of myocardial abnormalities, but the relationship to the acute illness and coronary artery abnormalities was unclear.[294–296] In a more recent study of 16 patients with giant aneurysms, initial biopsy samples showed myocyte degeneration, hypertrophy, and inflammatory cell infiltration, whereas follow-up biopsy specimens showed myocyte disarray, interstitial fibrosis, and ongoing inflammatory cell infiltration.[297] The pathogenesis of the abnormalities was not clear, but the sites of the aneurysms were not related to the biopsy findings. Subsequent studies of myocardial characterization and function have reported variable findings.[298–300] Long-term myocardial dysfunction, resulting from primary myocardial insult at the time of acute KD and which is independent of long-term coronary artery abnormalities, may very rarely occur, although evidence-based reports are few. Whether the myocarditis that occurs with the acute illness leads to long-term myocardial pathology, such as fibrosis and myocyte dropout, independent of coronary artery abnormalities is not clear. Clinical experience indicates that myocardial function is normal, except among patients with ischemic heart disease from coronary artery stenoses.[153,236]

Arrhythmias

Generally, the development of important rhythm changes in KD has been documented primarily in those patients manifesting more severe forms of myocardial dysfunction, including those patients with overt myocardial ischemia or infarction. Premature ventricular contractions and ventricular tachycardia have been taken as clinical markers of underlying myocardial damage and as potential predictors of long-term consequences, including late sudden death.[272,301] In particular, after MI, the incidence of ventricular tachycardia can be increased. Patients who have sustained severe myocardial injury or infarction may benefit from extended rhythm surveillance (Holter or other long-term electrocardiographic monitoring) to best assess the need for specific antiarrhythmic therapy. However, other recent studies have demonstrated an electrophysiological impact from KD even in the absence of important ventricular dysfunction or of any coronary artery abnormalities. Ghelani et al[302] found increased QT interval dispersion, indicating inhomogenous ventricular repolarization, in a group of KD patients from North India. Kuriki et al[303] similarly described elevations in the QT variability index during acute KD that was correlated with serum inflammatory markers and that normalized as the disease regressed.

Although conduction abnormalities have not been characteristic of KD, sinus node and atrioventricular node dysfunction have been demonstrated in patients with moderate to severe coronary artery abnormalities, although only 1 patient among the 40 studied developed evidence of atrioventricular block.[112]

Risk Stratification

Clinical experience with KD has taught us that it is reasonable to stratify patients according to their relative risk of myocardial ischemia, either related to coronary artery thrombosis or stenoses/occlusions. This stratification allows for patient long-term management to be individualized regarding the frequency of clinical follow-up and diagnostic testing, cardiovascular risk factor assessment and management, medical therapy, thromboprophylaxis, physical activity, and reproductive counseling. With careful clinical follow-up 10 to 20 years after the onset of KD, patients with no coronary artery luminal changes at any stage of the illness appear to demonstrate a risk for clinical cardiac events that is similar to that in the population without KD.[263] For long-term prognostication and management, the severity of coronary artery luminal abnormalities defines the risk category. The extent of maximal involvement, together with its evolution over time, determines the risk of myocardial ischemia related to thrombosis and stenosis. The long-term management algorithm is applied after acute management is completed, and generally when coronary artery luminal *Z* scores are stable and no longer enlarging. If the patient's *Z* scores are still increasing after the end of the convalescent phase, then recommendations for assessment and follow-up for evolving coronary artery

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Table 8. Risk Classification of Coronary Artery Abnormalities During Follow-up

Classification	Description
1	No involvement at any timepoint (*Z* score always <2)
2	Dilation only (*Z* score 2 to <2.5)
3	Small aneurysm (*Z* score ≥2.5 to <5)
3.1	Current or persistent
3.2	Decreased to dilation only or normal luminal dimension
4	Medium aneurysm (*Z* score ≥5 to <10, and absolute dimension <8 mm)
4.1	Current or persistent
4.2	Decreased to small aneurysm
4.3	Decreased to dilation only or normal luminal dimension
5	Large and giant aneurysm (*Z* score ≥10, or absolute dimension ≥8 mm)
5.1	Current or persistent
5.2	Decreased to medium aneurysm
5.3	Decreased to small aneurysm
5.4	Decreased to dilation only or normal luminal dimension

involvement should be followed, as outlined at the end of the Diagnosis section.

Echocardiography is the primary modality used to assess coronary artery luminal dimensions, which are converted to *Z* scores adjusted for BSA as outlined in the Diagnosis section. The risk stratification first rests on the patient's maximal *Z* score at any time point and in any branch. The risk stratification is further modified by the maximal *Z* score in any branch at the time of current assessment (Table 8). This allows clinicians to incorporate different risk levels based on the past and current coronary artery involvement, with changes in the risk of thrombosis and stenosis. Coronary artery involvement based on *Z* scores from echocardiographic assessment of luminal dimensions is classified into 5 categories as outlined in the section Diagnosis, Echocardiography, Classification of Coronary Artery Abnormalities. The current guidelines diverge from previous guidelines, which primarily classified coronary artery involvement based on absolute dimensions, with little to no adjustment for body size.

Although the risk stratification scheme primarily rests on maximal and current coronary artery *Z* scores derived from echocardiography, other features of the coronary arteries and other noncoronary artery cardiac complications could also influence decisions regarding risk specification (Table 9). These additional features may further be derived from other imaging modalities.

Table 9. Additional Clinical Features That May Increase the Long-Term Risk of Myocardial Ischemia

Greater length and distal location of aneurysms that increase the risk of flow stasis
Greater total number of aneurysms
Greater number of branches affected
Presence of luminal irregularities
Abnormal characterization of the vessel wall (calcification, luminal myofibroblastic proliferation)
Presence of functional abnormalities (impaired vasodilation, impaired flow reserve)
Absence or poor quality of collateral vessels
Previous revascularization performed
Previous coronary artery thrombosis
Previous myocardial infarction
Presence of ventricular dysfunction

Recommendations for Risk Stratification of Coronary Artery Abnormalities

1. **It is reasonable to use echocardiographic coronary artery luminal dimensions converted to BSA-adjusted *Z* scores to determine risk stratification *(Class IIa; Level of Evidence B)*.**
2. **It is reasonable to incorporate both maximal and current coronary artery involvement in risk stratification (as per Table 8) *(Class IIa; Level of Evidence C)*.**
3. **It is reasonable to incorporate the presence of additional features other than coronary artery luminal dimensions into decisions regarding risk stratification (as per Table 9) *(Class IIa; Level of Evidence C)*.**

Long-Term Management of Coronary Artery Abnormalities

On the basis of the risk stratification scheme, specific recommendations are made regarding surveillance, cardiovascular risk factor assessment and management, medical therapy, thromboprophylaxis, physical activity, and reproductive counseling for each category of past and current coronary artery involvement. The algorithm is depicted in Tables 10 and 11. The rationale for recommendations in the algorithm is provided in the sections after the recommendation statements.

Risk-Stratified Recommendations for Long-Term Evaluation and Management

Note: Long-term status is taken to be when the patient is stable after the acute illness and the coronary artery luminal dimensions are not increasing, usually at 4 to 6

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Table 10. Long-Term Assessment and Counseling Algorithm

Risk Level	Frequency of Cardiology Assessment*	Assessment for Inducible Myocardial Ischemia†	Type and Frequency of Additional Cardiology Assessment	Cardiovascular Risk Factor Assessment and Management‡	Physical Activity Counseling§	Reproductive Counseling
1: No involvement	May discharge between 4 wk and 12 mo	None	None	Assess at 1 y	Promotion counseling at every visit	Age-appropriate counseling without modification
2: Dilation only	If decreased to normal, discharge between 4 wk to 12 mo; if persistent dilation, reassess every 2–5 y	None	None	Assess at 1 y	Promotion counseling at every visit	Age-appropriate counseling without modification
3.1: Small aneurysm, current or persistent	Assess at 6 mo, then yearly	Assess every 2–3 y	May consider every 3–5 y	Assess at 1 y	Promotion counseling at every visit; restrict contact	Age-appropriate counseling without modification
3.2: Small aneurysm, regressed to normal or dilation only	Assess every 1–3 y (may omit echocardiography)	Assess every 3–5 y	May consider if there is inducible ischemia or ventricular dysfunction	Assess at 1 y, then every 2 y	Promotion counseling at every visit	Age-appropriate counseling without modification
4.1: Medium aneurysm, current or persistent	Assess at 3, 6, and 12 mo, then every 6–12 mo	Assess every 1–3 y	May consider every 2–5 y	Assess at 1 y	Promotion counseling at every visit; restrict contact; self-limit	Precautions for contraception and pregnancy
4.2: Medium aneurysm, regressed to small aneurysm	Assess yearly	Assess every 2–3 y	May consider every 3–5 y	Assess yearly	Promotion counseling at every visit; restrict contact; self-limit	Precautions for contraception and pregnancy
4.3: Medium aneurysm, regressed to normal or dilation only	Assess every 1–2 y (may omit echocardiography)	Assess every 2–5 y	May consider if there is inducible ischemia or ventricular dysfunction	Assess every 2 y	Promotion counseling at every visit; restrict contact; self-limit	Precautions for contraception and pregnancy
5.1: Large or giant aneurysm, current or persistent	Assess at 3, 6, 9, and 12 mo, then every 3–6 mo	Assess every 6–12 mo	Baseline within first year; may consider every 1–5 y	Assess every 6–12 mo	Promotion counseling at every visit; restrict contact; self-limit	Precautions for contraception and pregnancy
5.2: Large or giant aneurysms, regressed to medium aneurysm	Assess every 6–12 mo	Assess yearly	May consider every 2–5 y	Assess yearly	Promotion counseling at every visit; restrict contact; self-limit	Precautions for contraception and pregnancy
5.3: Large or giant aneurysm, regressed to small aneurysm	Assess every 6–12 mo	Assess every 1–2 y	May consider every 2–5 y	Assess yearly	Promotion counseling at every visit; restrict contact; self-limit	Precautions for contraception and pregnancy
5.4: Large or giant aneurysm, regressed to normal or dilation only	Assess every 1–2 y (may omit echocardiography)	Assess every 2–5 y	May consider every 2–5 y	Assess every 2 y	Promotion counseling at every visit; restrict contact; self-limit	Precautions for contraception and pregnancy

Yellow indicates a Class IIa recommendation (it is reasonable to perform); orange indicates a Class IIb recommendation (may be considered).

*To include history and physical examination, echocardiography, and electrocardiography.

†May include stress echocardiography, stress electrocardiography, stress with magnetic resonance perfusion imaging, and stress with nuclear medicine perfusion imaging.

‡General healthy lifestyle counseling should be provided at every visit (may be performed by primary care provider).

§Restrictions for contact apply to patients on anticoagulation or dual antiplatelet therapy; self-limit refers to allowing patients to participate to their reasonable abilities without coercion or pressure to perform or overexert (self, parents, coaches).

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Table 11. Long-Term Thromboprophylaxis and Medical Therapy Algorithm

Risk Level	Low-Dose ASA	Anticoagulation (Warfarin or LMWH)	Dual Antiplatelet Therapy (ASA+Clopidogrel)	β-Blocker	Statin
1: No involvement	4-6 wk then discontinue	Not indicated	Not indicated	Not indicated	Not indicated
2: Dilation only	Indicated until regression to normal	Not indicated	Not indicated	Not indicated	Not indicated
3.1: Small aneurysm, current or persistent	Indicated	Not indicated	Not indicated	Not indicated	May be considered
3.2: Small aneurysm, regressed to normal or dilation only	May be considered	Not indicated	Not indicated	Not indicated	May be considered
4.1: Medium aneurysm, current or persistent	Indicated	Not indicated	May be considered	Not indicated	May be considered
4.2: Medium aneurysm, regressed to small aneurysm	Indicated	Not indicated	May be considered	Not indicated	May be considered
4.3: Medium aneurysm, regressed to normal or dilation only	Reasonably indicated	Not indicated	Not recommended except in the presence of inducible myocardial ischemia	Not indicated	May be considered
5.1: Large and giant aneurysm, current or persistent	Indicated	Reasonably indicated	May be considered in addition to anticoagulation*	May be considered	May be considered
5.2: Large or giant aneurysm, regressed to medium aneurysm	Indicated	Not indicated	Reasonably indicated	May be considered	May be considered
5.3: Large or giant aneurysm, regressed to small aneurysm	Indicated	Not indicated	Not indicated	May be considered	May be considered
5.4: Large or giant aneurysm, regressed to normal or dilation only	Reasonably indicated	Not indicated	Not indicated	Not indicated	May be considered

ASA indicates acetylsalicylic acid or aspirin; and LMWH, low-molecular-weight heparin. Green indicates a Class I recommendation (should be performed); yellow indicates a Class IIa recommendation (it is reasonable to perform); orange indicates a Class IIb recommendation (may be considered); and red indicates a Class III recommendation (should not be performed).

*May be considered in addition to anticoagulation in the setting of very extensive or distal coronary artery aneurysms, or if history of coronary artery thrombosis.

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weeks after the onset of fever. Until this point, patients should be managed in accordance with the recommendations in the Acute Treatment section.

No Involvement (Z Score Always <2)

Frequency of cardiology assessment (to include history and physical examination, echocardiography, electrocardiography):

1. **It is reasonable to discharge patients from cardiology care at 4 to 6 weeks after KD onset, although ongoing follow-up to 12 months may be considered. Ongoing cardiology follow-up is not indicated. Patients and families should be advised to remember that having had KD is part of the patient's permanent medical history *(Class IIa; Level of Evidence C)*.**

Type and frequency of additional cardiology assessment (other cardiology testing):

1. **It is reasonable that no additional cardiology assessment be performed *(Class IIa; Level of Evidence C)*.**

Cardiovascular risk factor assessment and management:

1. **It is reasonable to provide general counseling regarding healthy lifestyle and activity promotion at every visit; this may be provided by the primary care provider *(Class IIa; Level of Evidence C)*.**
2. **It is reasonable to assess blood pressure, fasting lipid profile, body mass index (and plot),**

waist circumference, dietary and activity assessment, and smoking at least once and ideally at least 1 year from the episode of acute KD; this may be performed by the primary care provider *(Class IIa; Level of Evidence C)*.

Medical therapy (β-blockers, angiotensin-converting enzyme inhibitor [ACEI], statin):

1. **No additional medical therapy should be given *(Class III; Level of Evidence C)*.**

Thromboprophylaxis:

1. **It is reasonable to give low-dose ASA for up to 4 to 6 weeks after the episode of acute KD, which should be discontinued thereafter. *(Class IIa; Level of Evidence C)*.**

Physical activity:

1. **It is reasonable to provide physical activity counseling at every visit with no restrictions or precautions at any time *(Class IIa; Level of Evidence B)*.**

Reproductive counseling:

1. **It is reasonable to provide age-appropriate counseling regarding contraception and pregnancy without modification *(Class IIa; Level of Evidence B)*.**

Dilation Only (Z Score ≥2 but <2.5, or a Decrease in Z Score During Follow-up ≥1)†

Frequency of cardiology assessment (to include history and physical examination, echocardiography, electrocardiography):

1. **If luminal dimensions have returned to normal by 4 to 6 weeks after KD onset, it is reasonable to discharge the patient from cardiology care, although ongoing follow-up to 12 months may be considered *(Class IIa; Level of Evidence C)*.**
2. **If dilation remains present at 4 to 6 weeks after KD onset, then it is reasonable to continue follow-up to 12 months. If the luminal dimensions return to normal before then, it is reasonable to discharge the patient from ongoing cardiology care *(Class IIa; Level of Evidence C)*.**
3. **Resolution is expected within 1 year. If dilation persists at 1 year, consider whether this represents a dominant branch. If this is a probable explanation, then it is reasonable to discharge the patient from ongoing cardiology care, although ongoing follow-up every 2 to 5 years is reasonable. Patients and families should be advised to remember that having had KD is part of the patient's permanent medical history *(Class IIa; Level of Evidence C)*.**

Type and frequency of additional cardiology assessment (other cardiology testing):

1. **It is reasonable that no additional cardiology assessment be performed *(Class IIa; Level of Evidence C)*.**

Cardiovascular risk factor assessment and management:

1. **It is reasonable to provide general counseling regarding healthy lifestyle and activity promotion at every visit; this may be provided by the primary care provider *(Class IIa; Level of Evidence C)*.**
2. **It is reasonable to assess blood pressure, fasting lipid profile, body mass index (and plot), waist circumference, dietary and activity assessment, and smoking at least once and ideally at least 1 year from the episode of acute KD; this may be performed by the primary care provider *(Class IIa; Level of Evidence C)*.**

Medical therapy (β-blockers, ACEI, statin):

1. **No additional medical therapy should be given *(Class III; Level of Evidence C)*.**

Thromboprophylaxis:

1. **It is reasonable to give low-dose ASA until 4 to 6 weeks after the acute episode, and then to discontinue. If dilation is still present at 4 to 6 weeks, it is reasonable to continue low-dose ASA until the dilation resolves. *(Class IIa; Level of Evidence C)*.**

Physical activity:

1. **It is reasonable to provide physical activity counseling at every visit with no restrictions or precautions at any time *(Class IIa; Level of Evidence B)*.**

Reproductive counseling:

1. **It is reasonable to provide age-appropriate counseling regarding contraception and pregnancy without modification *(Class IIa; Level of Evidence B)*.**

Small Aneurysms (Z Score ≥2.5 to <5)

Current or Persistent Small Aneurysms

Frequency of cardiology assessment (to include history and physical examination, echocardiography, electrocardiography):

1. **Patients should be seen at 4 to 6 weeks after the acute KD episode, then it is reasonable to assess after 6 months and 1 year. Ongoing follow-up assessment every year thereafter is reasonable (Class *IIa; Level of Evidence B)*.**

Type and frequency of additional cardiology assessment (other cardiology testing):

1. **It is reasonable to assess for inducible myocardial ischemia (stress echocardiography, stress with magnetic resonance imaging [MRI],**

†Dilation has also been defined as an increased absolute luminal dimension up to 1.5 times the dimension of an adjacent segment and in those with a *Z* score <2 but who during follow-up demonstrate a decrease in *Z* score of ≥1.

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stress nuclear medicine [NM], positron emission tomography [PET]) every 2 to 3 years or if the patient has symptoms suggestive of ischemia or signs suggestive of ventricular dysfunction *(Class IIa; Level of Evidence B)*.
2. **Further imaging with angiography (CT, MRI, invasive) may be considered for periodic surveillance every 3 to 5 years *(Class IIb; Level of Evidence C)*.**

Cardiovascular risk factor assessment and management:
1. **It is reasonable to provide general counseling regarding healthy lifestyle and activity promotion at every visit; this may additionally be provided by the primary care provider *(Class IIa; Level of Evidence C)*.**
2. **It is reasonable to assess blood pressure, fasting lipid profile, body mass index (and plot), waist circumference, dietary and activity assessment, and smoking at least once and ideally at least 1 year from the episode of acute KD; this may be performed by the primary care provider. It is reasonable to obtain a follow-up fasting lipid profile as per the Expert Panel guidelines[304] *(Class IIa; Level of Evidence C)*.**

Medical therapy (β-blockers, ACEI, statin):
1. **Empirical statin therapy for non–lipid-lowering (pleiotropic) effects may be considered *(Class IIb; Level of Evidence C)*.**
2. **Empirical treatment with β-blockers is not indicated *(Class III; Level of Evidence C)*.**

Thromboprophylaxis:
1. **Patients should be treated with low-dose ASA *(Class I; Level of Evidence C)*.**
2. **Use of an alternative antiplatelet agent (eg, a thienopyridine such as clopidogrel) instead of ASA is reasonable if the patient is intolerant or resistant to ASA *(Class IIa; Level of Evidence C)*.**
3. **Anticoagulation or treatment with dual-antiplatelet therapy is not indicated *(Class III; Level of Evidence C)*.**

Physical activity:
1. **It is reasonable to provide physical activity counseling at every visit with no restrictions or precautions at any time *(Class IIa; Level of Evidence C)*.**

Reproductive counseling:
1. **It is reasonable to provide age-appropriate counseling regarding contraception and pregnancy without modification *(Class IIa; Level of Evidence B)*.**

Decreased to Normal Z Score or Dilation Only

Frequency of cardiology assessment (to include history and physical examination, echocardiography, electrocardiography):
1. **It is reasonable to assess every 1 to 3 years. It is reasonable not to perform echocardiography unless there is evidence for inducible myocardial ischemia or the patient has symptoms suggestive of ischemia or signs suggestive of ventricular dysfunction *(Class IIa; Level of Evidence B)*.**

Type and frequency of additional cardiology assessment (other cardiology testing):
1. **It is reasonable to assess for inducible myocardial ischemia (stress echocardiography, stress with MRI, stress NM perfusion imaging, PET) every 3 to 5 years or if the patient has symptoms suggestive of ischemia or signs suggestive of ventricular dysfunction *(Class IIa; Level of Evidence B)*.**
2. **Further imaging with angiography (CT, MRI, invasive) may be considered only if there is evidence for inducible myocardial ischemia or ventricular dysfunction *(Class IIb; Level of Evidence C)*.**

Cardiovascular risk factor assessment and management:
1. **It is reasonable to provide general counseling regarding healthy lifestyle and activity promotion at every visit; this may additionally be provided by the primary care provider *(Class IIa; Level of Evidence C)*.**
2. **It is reasonable to assess blood pressure, fasting lipid profile, body mass index (and plot), waist circumference, dietary and activity assessment, and smoking every 2 years; this may be performed by the primary care provider. It is reasonable to obtain a follow-up fasting lipid profile *(Class IIa; Level of Evidence C)*.**

Medical therapy (β-blockers, ACEI, statin):
1. **Empirical statin therapy for non–lipid-lowering (pleiotropic) effects may be considered *(Class IIb; Level of Evidence C)*.**
2. **Empirical treatment with β-blockers is not indicated *(Class III; Level of Evidence C)*.**

Thromboprophylaxis:
1. **Ongoing treatment with low-dose ASA may be considered, although it is reasonable to discontinue *(Class IIb; Level of Evidence C)*.**
2. **Use of an alternative antiplatelet agent (eg, a thienopyridine such as clopidogrel) instead of ASA is reasonable if the patient is intolerant or resistant to ASA *(Class IIa; Level of Evidence C)*.**

Physical activity:
1. **It is reasonable to provide physical activity counseling at every visit with no restrictions or precautions at any time *(Class IIa; Level of Evidence C)*.**

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Reproductive counseling:

1. **It is reasonable to provide age-appropriate counseling regarding contraception and pregnancy without modification *(Class IIa; Level of Evidence B)*.**

Medium Aneurysms (Z Score ≥5 to <10, With an Absolute Luminal Dimension <8 mm)

Current or Persistent Medium Aneurysms

Frequency of cardiology assessment (to include history and physical examination, echocardiography, electrocardiography):

1. **Patients should be seen at 4 to 6 weeks after the acute KD episode; then it is reasonable to assess after 3 months, 6 months, and 1 year. Ongoing follow-up assessment every 6 to 12 months thereafter is reasonable *(Class IIa; Level of Evidence B)*.**

Type and frequency of additional cardiology assessment (other cardiology testing):

1. **It is reasonable to assess for inducible myocardial ischemia (stress echocardiography, stress with MRI, stress NM perfusion imaging, PET) every 1 to 3 years or if the patient has symptoms suggestive of ischemia or signs suggestive of ventricular dysfunction *(Class IIa; Level of Evidence B)*.**
2. **Further imaging with angiography (CT, MRI, invasive) may be considered for periodic surveillance every 2 to 5 years *(Class IIb; Level of Evidence C)*.**

Cardiovascular risk factor assessment and management:

1. **It is reasonable to provide general counseling regarding healthy lifestyle and activity promotion at every visit; this may additionally be provided by the primary care provider *(Class IIa; Level of Evidence C)*.**
2. **It is reasonable to assess blood pressure, fasting lipid profile, body mass index (and plot), waist circumference, dietary and activity assessment, and smoking at least once and ideally at least 1 year from the episode of acute KD; this may be performed by the primary care provider. It is reasonable to obtain a follow-up fasting lipid profile *(Class IIa; Level of Evidence C)*.**

Medical therapy (β-blockers, ACEI, statin):

1. **Empirical statin therapy for non–lipid-lowering (pleiotropic) effects may be considered *(Class IIb; Level of Evidence C)*.**
2. **Empirical treatment with β-blockers is not indicated *(Class III; Level of Evidence C)*.**

Thromboprophylaxis:

1. **Patients should be treated with low-dose ASA *(Class I; Level of Evidence C)*.**
2. **Use of an alternative antiplatelet agent (eg, a thienopyridine such as clopidogrel) instead of ASA is reasonable if the patient is intolerant or resistant to ASA *(Class IIa; Level of Evidence C)*.**
3. **Additional patient and coronary artery characteristics (Table 9) may be considered in decision making regarding intensification of thromboprophylaxis *(Class IIb; Level of Evidence C)*.**
4. **Dual-antiplatelet therapy with an additional antiplatelet agent (eg, a thienopyridine such as clopidogrel) may be considered *(Class IIb; Level of Evidence C)*.**
5. **Use of anticoagulation (warfarin, LMWH) is not indicated *(Class III; Level of Evidence C)*.**

Physical activity:

1. **It is reasonable to provide physical activity counseling at every visit without restrictions or precautions. Participation in competitive sports or high-intensity activities should be guided by results from testing for inducible myocardial ischemia or exercise-induced arrhythmias *(Class IIa; Level of Evidence C)*.**
2. **For patients taking dual-antiplatelet therapy, activities involving a risk of bodily contact, trauma, or injury should be restricted or modified *(Class I; Level of Evidence B)*.**

Reproductive counseling:

1. **It is reasonable to discourage use of oral contraceptive drugs that increase thrombosis risk, to recommend that pregnancy be supervised by a multidisciplinary team including a cardiologist, and to alter thromboprophylaxis management during pregnancy and delivery *(Class IIa; Level of Evidence B)*.**

Decreased to Small Aneurysms

Frequency of cardiology assessment (to include history and physical examination, echocardiography, electrocardiography):

1. **Ongoing follow-up assessment every year is reasonable *(Class IIa; Level of Evidence B)*.**

Type and frequency of additional cardiology assessment (other cardiology testing):

1. **It is reasonable to assess for inducible myocardial ischemia (stress echocardiography, stress with MRI, stress NM perfusion imaging, PET) every 2 to 3 years or if the patient has symptoms suggestive of ischemia or signs suggestive of ventricular dysfunction *(Class IIa; Level of Evidence B)*.**
2. **Further imaging with angiography (CT, MRI, invasive) may be considered for periodic surveillance every 3 to 5 years *(Class IIb; Level of Evidence C)*.**

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Cardiovascular risk factor assessment and management:

1. **It is reasonable to provide general counseling regarding healthy lifestyle and activity promotion at every visit; this may additionally be provided by the primary care provider *(Class IIa; Level of Evidence C)*.**
2. **It is reasonable to assess blood pressure, fasting lipid profile, body mass index (and plot), waist circumference, dietary and activity assessment, and smoking every year; this may be performed by the primary care provider. It is reasonable to obtain a follow-up fasting lipid profile *(Class IIa; Level of Evidence C)*.**

Medical therapy (β-blockers, ACEI, statin):

1. **Empirical statin therapy for non–lipid-lowering (pleiotropic) effects may be considered *(Class IIb; Level of Evidence C)*.**
2. **Empirical treatment with β-blockers is not indicated *(Class III; Level of Evidence C)*.**

Thromboprophylaxis:

1. **Patients should be treated with low-dose ASA *(Class I; Level of Evidence C)*.**
2. **Use of an alternative antiplatelet agent (eg, a thienopyridine such as clopidogrel) instead of ASA is reasonable if the patient is intolerant or resistant to ASA *(Class IIa; Level of Evidence C)*.**
3. **Dual-antiplatelet therapy with an additional antiplatelet agent (eg, a thienopyridine such as clopidogrel) may be considered *(Class IIb; Level of Evidence C)*.**
4. **Use of anticoagulation is not indicated *(Class III; Level of Evidence C)*.**
5. **Additional patient and coronary artery characteristics (Table 9) may be considered in decision making regarding intensification or discontinuation of thromboprophylaxis *(Class IIb; Level of Evidence C)*.**

Physical activity:

1. **It is reasonable to provide physical activity counseling at every visit without restrictions or precautions. Participation in competitive sports or high-intensity activities should be guided by results from testing for inducible myocardial ischemia or exercise-induced arrhythmias *(Class IIa; Level of Evidence C)*.**
2. **For patients taking dual-antiplatelet therapy, activities involving a risk of bodily contact, trauma, or injury should be restricted or modified *(Class I; Level of Evidence B)*.**

Reproductive counseling:

1. **It is reasonable to discourage use of oral contraceptive drugs that increase thrombosis risk, to recommend that pregnancy be supervised by a multidisciplinary team including a cardiologist, and to alter thromboprophylaxis management during pregnancy and delivery *(Class IIa; Level of Evidence B)*.**

Decreased to Normal Z Score or Dilation Only

Frequency of cardiology assessment (to include history and physical examination, echocardiography, electrocardiography):

1. **Ongoing follow-up assessment every 1 to 2 years is reasonable. Not performing routine 2D echocardiography may be considered unless there is evidence for inducible myocardial ischemia or the patient has symptoms suggestive of ischemia or signs suggestive of ventricular dysfunction *(Class IIb; Level of Evidence B)*.**

Type and frequency of additional cardiology assessment (other cardiology testing):

1. **It is reasonable to assess for inducible myocardial ischemia (stress echocardiography, stress with MRI, stress NM perfusion imaging, PET) every 2 to 5 years or if the patient has symptoms suggestive of ischemia or signs suggestive of ventricular dysfunction *(Class IIa; Level of Evidence B)*.**
2. **It is reasonable to perform no further imaging with angiography (CT, MRI, invasive) in the absence of evidence of inducible myocardial ischemia *(Class IIa; Level of Evidence C)*.**

Cardiovascular risk factor assessment and management:

1. **It is reasonable to provide general counseling regarding healthy lifestyle and activity promotion at every visit; this may additionally be provided by the primary care provider *(Class IIa; Level of Evidence C)*.**
2. **It is reasonable to assess blood pressure, fasting lipid profile, body mass index (and plot), waist circumference, dietary and activity assessment, and smoking every 2 years; this may be performed by the primary care provider. It is reasonable to obtain a follow-up fasting lipid profile *(Class IIa; Level of Evidence C)*.**

Medical therapy (β-blockers, statin):

1. **Empirical statin therapy for non–lipid-lowering (pleiotropic) effects may be considered *(Class IIb; Level of Evidence C)*.**
2. **Empirical treatment with β-blockers is not indicated *(Class III; Level of Evidence C)*.**

Thromboprophylaxis:

1. **It is reasonable to continue treatment with low-dose ASA *(Class IIa; Level of Evidence C)*.**
2. **Use of an alternative antiplatelet agent (eg, a thienopyridine such as clopidogrel) instead**

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of ASA is reasonable if the patient is intolerant or resistant to ASA *(Class IIa; Level of Evidence C)*.

3. **Use of anticoagulation (warfarin/LMWH) is not indicated *(Class III; Level of Evidence C)*.**
4. **Use of an additional antiplatelet agent (eg, a thienopyridine such as clopidogrel) is not recommended except in the presence of inducible myocardial ischemia *(Class IIb; Level of Evidence C)*.**
5. **Additional patient and coronary artery characteristics (Table 9) may be considered in decision making regarding intensification or discontinuation of thromboprophylaxis *(Class IIb; Level of Evidence C)*.**

Physical activity:

1. **It is reasonable to provide physical activity counseling at every visit without restrictions or precautions. Participation in competitive sports or high-intensity activities should be guided by results from testing for inducible myocardial ischemia or exercise-induced arrhythmias *(Class IIa; Level of Evidence C)*.**

Reproductive counseling:

1. **It is reasonable to provide age-appropriate counseling regarding contraception and pregnancy without modification *(Class IIa; Level of Evidence B)*.**

Large and Giant Aneurysms (Z Score ≥10 or Absolute Dimension ≥8 mm)

Note: Long-term status is taken to be when the patient is stable after the acute illness and the coronary artery luminal dimensions are not increasing or progressing (usually within 15 to 45 days). Until this point, patients should be managed in accordance with the recommendations in the Acute Treatment section. Failure to follow up closely and to escalate thromboprophylaxis with progressing coronary artery aneurysms is a major contributor to unexpected morbidity and mortality.

Current or Persistent Large and Giant Aneurysms

Frequency of cardiology assessment (to include history and physical examination, echocardiography, electrocardiography):

1. **It is reasonable to assess patients at 3, 6, 9, and 12 months after the episode of acute KD in the first year and every 3 to 6 months thereafter *(Class IIa; Level of Evidence C)*.**

Type and frequency of additional cardiology assessment (other cardiology testing):

1. **It is reasonable to assess for inducible myocardial ischemia (stress echocardiography, stress with MRI, stress NM perfusion imaging, PET) every 6 to 12 months or if the patient has symptoms suggestive of ischemia or signs suggestive of ventricular dysfunction *(Class IIa; Level of Evidence B)*.**
2. **Further imaging with angiography (CT, MRI, invasive) may be considered for diagnostic and prognostic purposes during the first year and may be considered for periodic surveillance every 1 to 5 years thereafter *(Class IIb; Level of Evidence C)*.**

Cardiovascular risk factor assessment and management:

1. **It is reasonable to provide general counseling regarding healthy lifestyle and activity promotion at every visit; this may additionally be provided by the primary care provider *(Class IIa; Level of Evidence C)*.**
2. **It is reasonable to assess blood pressure, body mass index (and plot), waist circumference, dietary and activity assessment, and smoking every 6 to 12 months; this may be performed by the primary care provider. It is reasonable to obtain a fasting lipid profile during follow-up *(Class IIa; Level of Evidence C)*.**

Medical therapy (β-blockers, ACEI, statin):

1. **Empirical statin therapy for non–lipid-lowering (pleiotropic) effects may be considered *(Class IIb; Level of Evidence C)*.**
2. **Empirical treatment with β-blockers may be considered *(Class IIb; Level of Evidence C)*.**

Thromboprophylaxis:

1. **Patients should be treated with low-dose ASA *(Class I; Level of Evidence C)*.**
2. **Use of an alternative antiplatelet agent (eg, a thienopyridine such as clopidogrel) instead of ASA is reasonable if the patient is intolerant or resistant to ASA *(Class IIa; Level of Evidence C)*.**
3. **Use of warfarin to achieve a target international normalized ratio of 2 to 3 is reasonable *(Class IIa; Level of Evidence B)*.**
4. **Use of LMWH to achieve target anti-factor Xa levels of 0.5 to 1.0 U/mL is reasonable as an alternative to warfarin *(Class IIa; Level of Evidence C)*.**
5. **Use of an additional antiplatelet agent (eg, a thienopyridine such as clopidogrel) may be considered together with ASA and warfarin/LMWH (triple therapy) for thromboprophylaxis in the setting of very extensive or distal coronary artery aneurysms, or if there is a history of coronary artery thrombosis (Table 9) *(Class IIb; Level of Evidence C)*.**
6. **Additional patient and coronary artery characteristics (Table 9) may be considered in decision making regarding adjustments to strategy for thromboprophylaxis *(Class IIb; Level of Evidence C)*.**

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Physical activity:

1. **It is reasonable to provide physical activity counseling at every visit without restrictions or precautions. Participation in competitive sports or high-intensity activities should be guided by results from testing for inducible myocardial ischemia or exercise-induced arrhythmias *(Class IIa; Level of Evidence C)*.**
2. **Activities involving a risk of bodily contact, trauma, or injury should be restricted or modified if the patient is on dual-antiplatelet or anticoagulation therapy *(Class I; Level of Evidence B)*.**

Reproductive counseling:

1. **It is reasonable to discourage use of oral contraceptive drugs that increase thrombosis risk, to recommend that pregnancy be supervised by a multidisciplinary team including a cardiologist, and to alter thromboprophylaxis management during pregnancy and delivery *(Class IIa; Level of Evidence B)*.**

Decreased to Medium Aneurysms

Frequency of cardiology assessment (to include history and physical examination, echocardiography, electrocardiography):

1. **It is reasonable to assess the patient every 6 to 12 months *(Class IIa; Level of Evidence C)*.**

Type and frequency of additional cardiology assessment (other cardiology testing):

1. **It is reasonable to assess for inducible myocardial ischemia (stress echocardiography, stress with MRI, stress NM perfusion imaging, PET) every year or if the patient has symptoms suggestive of ischemia or signs suggestive of ventricular dysfunction *(Class IIa; Level of Evidence B)*.**
2. **Further imaging with angiography (CT, MRI, invasive) may be considered for periodic surveillance every 2 to 5 years *(Class IIb; Level of Evidence C)*.**

Cardiovascular risk factor assessment and management:

1. **It is reasonable to provide general counseling regarding healthy lifestyle and activity promotion at every visit; this may additionally be provided by the primary care provider *(Class IIa; Level of Evidence C)*.**
2. **It is reasonable to assess blood pressure, body mass index (and plot), waist circumference, dietary and activity assessment, and smoking every year; this may be performed by the primary care provider. It is reasonable to obtain a follow-up fasting lipid profile *(Class IIa; Level of Evidence C)*.**

Medical therapy (β-blockers, ACEI, statin):

1. **Empirical statin therapy for non–lipid-lowering (pleiotropic) effects may be considered *(Class IIb; Level of Evidence C)*.**
2. **Empirical treatment with β-blockers may be considered *(Class IIb; Level of Evidence C)*.**

Thromboprophylaxis:

1. **Patients should be treated with low-dose ASA *(Class I; Level of Evidence C)*.**
2. **Use of an alternative antiplatelet agent (eg, a thienopyridine such as clopidogrel) instead of ASA is reasonable if the patient is intolerant or resistant to ASA *(Class IIa; Level of Evidence C)*.**
3. **Use of anticoagulation (warfarin, LMWH) is not indicated *(Class III; Level of Evidence C)*.**
4. **Discontinuation of anticoagulation (warfarin/LMWH) and substitution with an additional antiplatelet agent (eg, a thienopyridine such as clopidogrel) is reasonable *(Class IIa; Level of Evidence C)*.**
5. **Additional patient and coronary artery characteristics (Table 9) may be considered in decision making regarding adjustments to strategy for thromboprophylaxis *(Class IIb; Level of Evidence C)*.**

Physical activity:

1. **It is reasonable to provide physical activity counseling at every visit without restrictions or precautions. Participation in competitive sports or high-intensity activities should be guided by results from testing for inducible myocardial ischemia or exercise-induced arrhythmias *(Class IIa; Level of Evidence C)*.**
2. **Activities involving a risk of bodily contact, trauma, or injury should be restricted or modified for patients on dual-antiplatelet or anticoagulation therapy *(Class I; Level of Evidence B)*.**

Reproductive counseling:

1. **It is reasonable to discourage use of oral contraceptive drugs that increase thrombosis risk, to recommend that pregnancy be supervised by a multidisciplinary team including a cardiologist, and to alter thromboprophylaxis management during pregnancy and delivery *(Class IIa; Level of Evidence B)*.**

Decreased to Small Aneurysms

Frequency of cardiology assessment (to include history and physical examination, echocardiography, electrocardiography):

1. **It is reasonable to assess the patient every 6 to 12 months *(Class IIa; Level of Evidence C)*.**

Type and frequency of additional cardiology assessment (other cardiology testing):

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1. **It is reasonable to assess for inducible myocardial ischemia (stress echocardiography, stress with MRI, stress NM perfusion imaging, PET) every 1 to 2 years or if the patient has symptoms suggestive of ischemia or signs suggestive of ventricular dysfunction *(Class IIa; Level of Evidence B)*.**
2. **Further imaging with angiography (CT, MRI, invasive) may be considered for periodic surveillance every 2 to 5 years *(Class IIb; Level of Evidence C)*.**

Cardiovascular risk factor assessment and management:

1. **It is reasonable to provide general counseling regarding healthy lifestyle and activity promotion at every visit; this may additionally be provided by the primary care provider *(Class IIa; Level of Evidence C)*.**
2. **It is reasonable to assess blood pressure, body mass index (and plot), waist circumference, dietary and activity assessment, and smoking every year; this may be performed by the primary care provider. It is reasonable to obtain a follow-up fasting lipid profile *(Class IIa; Level of Evidence C)*.**

Medical therapy (β-blockers, ACEI, statin):

1. **Empirical statin therapy for non–lipid-lowering (pleiotropic) effects may be considered *(Class IIb; Level of Evidence C)*.**
2. **Empirical treatment with β-blockers may be considered *(Class IIb; Level of Evidence C)*.**

Thromboprophylaxis:

1. **Patients should be treated with low-dose ASA *(Class I; Level of Evidence C)*.**
2. **Use of an alternative antiplatelet agent (eg, a thienopyridine such as clopidogrel) instead of ASA is reasonable if the patient is intolerant or resistant to ASA *(Class IIa; Level of Evidence C)*.**
3. **Anticoagulation or dual-antiplatelet therapy is not indicated *(Class III; Level of Evidence C)*.**
4. **Additional patient and coronary artery characteristics (Table 9) may be considered in decision making regarding adjustments to strategy for thromboprophylaxis *(Class IIb; Level of Evidence C)*.**

Physical activity:

1. **It is reasonable to provide physical activity counseling at every visit without restrictions or precautions. Participation in competitive sports or high-intensity activities should be guided by results from testing for inducible myocardial ischemia or exercise-induced arrhythmias *(Class IIa; Level of Evidence C)*.**
2. **For patients on anticoagulation or dual-antiplatelet therapy, activities involving a risk of bodily contact, trauma, or injury should be restricted or modified *(Class I; Level of Evidence B)*.**

Reproductive counseling:

1. **It is reasonable to provide age-appropriate counseling regarding contraception. It is reasonable to recommend that pregnancy be supervised by a multidisciplinary team including a cardiologist and to alter thromboprophylaxis management during pregnancy and delivery *(Class IIa; Level of Evidence B)*.**

Decreased to Normal Z Score or Dilation Only

Frequency of cardiology assessment (to include history and physical examination, echocardiography, electrocardiography):

1. **It is reasonable to assess the patient every 1 to 2 years. Not performing routine 2D echocardiography may be considered unless there is evidence for inducible myocardial ischemia or the patient has symptoms suggestive of ischemia or signs suggestive of ventricular dysfunction *(Class IIa; Level of Evidence C)*.**

Type and frequency of additional cardiology assessment (other cardiology testing)"

1. **It is reasonable to assess for inducible myocardial ischemia (stress echocardiography, stress with MRI, stress NM perfusion imaging, PET) every 2 to 5 years or if the patient has symptoms suggestive of ischemia or signs suggestive of ventricular dysfunction *(Class IIa; Level of Evidence B)*.**
2. **Further imaging with angiography (CT, MRI, invasive) may be considered for periodic surveillance every 2 to 5 years *(Class IIb; Level of Evidence C)*.**

Cardiovascular risk factor assessment and management:

1. **It is reasonable to provide general counseling regarding healthy lifestyle and activity promotion at every visit; this may additionally be provided by the primary care provider *(Class IIa; Level of Evidence C)*.**
2. **It is reasonable to assess blood pressure, body mass index (and plot), waist circumference, dietary and activity assessment, and smoking every 2 years; this may be performed by the primary care provider. It is reasonable to obtain a follow-up fasting lipid profile as per the Expert Panel guidelines.[304] Evaluation and management of identified abnormalities should follow the Expert Panel guidelines[304] *(Class IIa; Level of Evidence C)*.**

Medical therapy (β-blockers, ACEI, statin):

1. **Empirical statin therapy for non–lipid-lowering (pleiotropic) effects may be considered *(Class IIb; Level of Evidence C)*.**

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2. **Empirical treatment with β-blockers is not indicated *(Class III; Level of Evidence C)*.**

Thromboprophylaxis:

1. **It is reasonable to continue treatment with low-dose ASA *(Class IIa; Level of Evidence C)*.**
2. **Use of an alternative antiplatelet agent (eg, a thienopyridine such as clopidogrel) instead of ASA is reasonable if the patient is intolerant or resistant to ASA *(Class IIa; Level of Evidence C)*.**
3. **Use of anticoagulation (warfarin/LMWH) or dual-antiplatelet therapy is not indicated *(Class III; Level of Evidence C)*.**
4. **Additional patient and coronary artery characteristics (Table 9) may be considered in decision making regarding intensification or discontinuation of thromboprophylaxis *(Class IIb; Level of Evidence C)*.**

Physical activity:

1. **It is reasonable to provide physical activity counseling at every visit without restrictions or precautions. Participation in competitive sports or high-intensity activities should be guided by results from testing for inducible myocardial ischemia or exercise-induced arrhythmias *(Class IIa; Level of Evidence C)*.**
2. **For patients on anticoagulation or dual-antiplatelet therapy, activities involving a risk of bodily contact, trauma, or injury should be restricted or modified *(Class I; Level of Evidence B)*.**

Reproductive counseling:

1. **It is reasonable to provide age-appropriate counseling regarding contraception. It is reasonable to recommend that pregnancy be supervised by a multidisciplinary team including a cardiologist and to alter thromboprophylaxis management during pregnancy and delivery *(Class IIa; Level of Evidence B)*.**

Surveillance

Long-term management of sequelae of KD requires an approach to surveillance calibrated to the presence and severity of past and current coronary artery involvement. Surveillance is aimed at defining changes in coronary artery involvement that either increase or decrease the risk of thrombosis, stenoses/obstructions, and myocardial ischemia, particularly those that require changes in surveillance or therapy. Surveillance also aims to detect and define changes in valvular function and myocardial abnormalities, particularly function, perfusion, and scar/fibrosis.

Frequency of Assessment

Standard assessment includes history and physical examination, electrocardiography, and echocardiography as previously outlined. For patients whose coronary arteries have consistently remained with a maximal *Z* score <2 and who are therefore defined as having no involvement, discharge from cardiology care is reasonable at between 4 weeks and 12 months, provided that the recommended echocardiograms have been obtained at diagnosis and 1 and 4 to 6 weeks after acute treatment.[305] Previous studies have shown that if there are no echocardiographic abnormalities at a 4- to 6-week assessment, further follow-up is not cost-effective, and these patients are not at risk for new onset of abnormalities.[306–308] Likewise, it is reasonable to discharge patients classified as having dilation only with *Z* score <2.5 if the *Z* score is documented to have decreased to <2 by the 4- to 6-week assessment. Otherwise, a further follow-up assessment is reasonable after 6 months to 1 year, or until the measurements are normal or an alternative explanation (dominant coronary artery branch) is evident. Although systematic long-term data are not available, evidence suggests that these patients are not at increased risk of late mortality attributable to CVD compared with the general population.[309–313] The association with late events is limited to rare case reports.[314,315]

For patients defined as having an aneurysm of any size noted at any assessment, ongoing cardiology follow-up is recommended. The frequency depends on the degree of maximal and current involvement, which can be modified by other characteristics (Table 9). For patients with small or medium aneurysms, the pathological progression toward normal luminal dimensions occurs most quickly during the first year after acute treatment, whereas for patients with large or giant aneurysms, this occurs at a slower and constant rate over a longer period of time, with far fewer patients ever achieving a normal luminal dimension. The frequency of follow-up is informed by the rate of change and risk. It is also noted that the initial degree of involvement influences the frequency of follow-up based on current involvement. For example, a patient with a persistent small aneurysm would be considered at lower risk of myocardial ischemia than a patient with a large or giant aneurysm that evolved to the size of a small aneurysm, and this is reflected in the recommended frequency of follow-up. Ranges of recommended follow-up frequency represent the need to individualize follow-up, taking into account other factors as previously outlined that would increase risk.

For patients with aneurysms whose coronary artery luminal dimensions have reduced to normal or dilation only, it is reasonable to omit imaging of the coronary arteries with 2D echocardiography, although ongoing assessments for inducible myocardial ischemia are valuable.

Assessment for Inducible Ischemia

For patients with coronary artery aneurysms, the pathological progression toward normal luminal dimension

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(thrombosis, luminal myofibroblastic proliferation) increases the risk of stenoses and obstructions. Hence, periodic surveillance for inducible myocardial ischemia is recommended, with timing of the first assessment and the subsequent testing frequency calibrated to the severity of maximal and current coronary artery abnormalities. In addition, patients with symptoms suggestive of myocardial ischemia should be evaluated for inducible ischemia in a timely manner. If inducible ischemia is present, further imaging is suggested, usually with invasive angiography, to determine the presence of coronary artery stenoses and occlusions. Historically, patients with significant residual coronary artery abnormalities were followed by myocardial perfusion imaging (MPI) and serial coronary angiography; however, angiography is invasive, and both modalities expose the patient to repeated radiation, which is an important issue in children. Although MPI is useful, limitations include modest specificity, lengthy acquisition time, and necessity for sedation in young children, and other modalities have gained preference. The selection of modality for surveillance for inducible myocardial ischemia should take into account the expertise of the institution, with preference for physiological stress with exercise over pharmacological stress, and minimizing the cumulative radiation dose and risks to the patient.

NM Scintigraphic Stress Imaging

MPI is used to detect myocardial ischemia in KD patients, particularly in those with abnormal coronary artery morphology.[316,317] The presence of reversible perfusion defects on dipyridamole-stress MPI has been shown to be a powerful predictor for cardiac events in patients using thallium 201–based and technetium (^{99m}Tc)-based radiopharmaceuticals.[318] Kashyap et al[319] reported a longitudinal study of 84 children with KD who underwent MPI, 20 of whom had coronary artery aneurysms or dilatation on echocardiography. There were 12 patients with abnormal MPI; however, only 2 of these patients had coronary artery abnormalities. These investigators concluded that perfusion deficits in patients with normal-appearing coronary arteries might be attributable to endothelial dysfunction. Because of the challenges in performing treadmill exercise testing in small children, pharmacological stress (coronary vasodilators and cardiac inotropic agents) is preferred by some clinicians to assess the presence of myocardial ischemia during stress MPI. However, exercise stress may be more suitable for evaluation of older patients. With MPI, there may be a high positive rate in patients who have anatomically normal coronary arteries.

Positron Emission Tomography

PET can detect the attenuation of myocardial flow reserve and endothelial function and is therefore another potential tool to detect myocardial ischemia in KD patients.[279] In the late follow-up of patients with a history of KD, myocardial flow reserve and endothelial function might still be impaired in regressed aneurysmal regions, despite coronary angiography demonstrating smooth, normal-appearing arteries.[279,320] Although no perfusion deficits were found in patients with normal coronary arteries and a history of KD 4 to 15 years before PET study, myocardial flow reserve was decreased and coronary resistance was increased compared with a normal control group, which confirmed that these patients had abnormal coronary flow reserve.[280] A recent study that used this tool to monitor treatment demonstrated that statins reduced persistent coronary arterial inflammation as evaluated by serial fluorodeoxyglucose (^{18}F) PET imaging long after KD.[281]

Stress Echocardiography

Both dobutamine and exercise stress echocardiography have been used in children diagnosed with coronary artery abnormalities secondary to KD.[321–324] Pahl et al[321] performed treadmill exercise stress echocardiographic studies in 28 children aged 6 to 16 years with a history of KD 1 to 10 years before the study and coronary artery abnormalities. They concluded that exercise stress echocardiography is a safe, noninvasive procedure and may identify children with myocardial ischemia that was not detected with exercise stress electrocardiographic testing alone. However, a major limitation to exercise stress echocardiography is rapid return of heart rates to normal in children, thus necessitating rapid imaging. Also, young children cannot perform on treadmills; thus, alternatives such as dobutamine stress echocardiography (DSE) may be used instead.

Zilberman et al[322] studied 47 patients after KD and found that DSE was useful to distinguish high-risk patients from other lower-risk categories. They concluded that DSE might have more sensitivity for perfusion abnormality detection than standard exercise stress electrocardiographic testing, and they found positive wall-motion abnormalities in 2 of 4 patients with coronary artery stenoses; all others were negative. In an early large experience from Japan, Noto et al[323] reported DSE using doses limited to 30 $\mu g \cdot kg^{-1} \cdot min^{-1}$ in 50 patients, of whom 26 had residual coronary artery abnormalities. Although only 40% of patients reached an ideal rate pressure product of 20 000, they found new wall-motion abnormalities in 19 of 21 patients and did not find wall-motion abnormalities in the 24 patients with normal coronary arteries; the sensitivity and specificity were 90% and 100%, respectively. This same group recently reported a long-term study of DSE with 15-year follow-up of these patients in which they found that DSE provided independent prognostic information in adolescent KD survivors.[324]

Cardiac MRI

In adults, adenosine stress CMRI has been used in patients with coronary artery stenosis for risk stratification of major cardiac events. This tool could have potential

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applications for patients with a history of KD; however, data are limited. In a case series of 14 asymptomatic patients with a history of KD and coronary involvement (5 residual coronary artery abnormalities), subjects underwent adenosine-stress CMRI, with gadolinium also used to assess for fibrosis.[325] Notably, 8 patients had anesthesia for this study. The authors demonstrated an inducible perfusion defect in 1 patient and a myocardial scar in another. Notably, the mean myocardial perfusion reserve was impaired in all patients compared with historical control subjects, which suggests the presence of microvascular dysfunction. A second study in the Netherlands, which used comprehensive MRI both for anatomic imaging and stress, applied CMRI during follow-up of 63 patients with KD using adenosine.[326] They identified 23 aneurysms in 15 patients, ischemia in 4, and scar in 5. In 6 of the 15 patients with aneurysms, the coronary artery abnormalities were not visualized with echocardiography, which suggests that comprehensive CMRI is a superior, noninvasive, and radiation-free imaging modality for long-term surveillance of these patients.

In summary, patients with a history of KD and coronary artery abnormalities warrant risk stratification and surveillance for inducible ischemia and long-term follow-up. Testing should include anatomic imaging of the coronary arteries, as well as functional testing with exercise or pharmacological stress testing with echocardiography or MPI, depending on institutional expertise and age of the child. Treadmill stress electrocardiographic testing alone is not adequate to assess for inducible ischemia. PET has also been used with less conclusive data to detect perfusion defects, and myocardial stress CMRI is a promising new technique with limited published data in the KD cohort.

Recommendations for Testing for Inducible Ischemia

1. **It is reasonable to use stress echocardiography or CMRI, NM MPI, or PET for assessment of inducible myocardial ischemia *(Class IIa; Level of Evidence B)*. Note: The general principle is to minimize risk to the patient, particularly cumulative radiation dose, and this should guide selection of testing modality based on patient and institutional characteristics.**
2. **Exercise treadmill electrocardiographic testing alone should not be used for assessment for inducible myocardial ischemia *(Class III; Level of Evidence C)*.**

Recommendation for Assessment of Patients With Inducible Myocardial Ischemia

1. **Patients with evidence of inducible myocardial ischemia on testing should undergo invasive coronary angiography *(Class I; Level of Evidence B)*.**

The management of patients with evidence of inducible ischemia on testing who are noted to have important coronary artery stenoses or occlusions on advanced imaging is outlined in the Catheter and Surgical Coronary Artery Interventions sections.

Role of Advanced Cardiovascular Imaging and Functional Assessment

The long-term cardiovascular impact of KD may manifest not only in distortion of coronary artery luminal geometry but also in changes in the structure and function of the arterial endothelium and wall, as well as the myocardium. Advanced imaging methods can be applied to characterize vascular remodeling, flow reserve, endothelial dysfunction, and myocardial fibrosis, any of which can influence the prognosis and risks of selected patients with important coronary artery involvement. In the convalescent KD patient with coronary artery aneurysms, long-term specialized follow-up is recommended.[311]

Invasive Angiography

The "gold standard" for coronary artery assessment, particularly in the adult patient, is invasive angiography. It provides a detailed image of the coronary artery lumen and is very useful in defining regional flow-limiting stenoses and assessing them for potential intervention. Fractional flow reserve, measured during angiography, is a common method for determining the ischemia-causing potential of atherosclerotic stenoses. Discrete coronary artery stenosis in KD can also be assessed, with similar cut points as in adults with atherosclerosis.[327] An additional insight from fractional flow reserve (FFR) in KD relates to the impact of coronary artery aneurysms on the arterial pressure. Turbulence-related pressure loss at dilated segments may create a drop in pressure along the artery, but FFR assessed in a small series of KD-associated aneurysms documented pressure drops that were smaller than threshold values used to predict pathophysiological importance.[328]

Intravascular Assessment

A more detailed assessment of the KD-related arterial wall abnormalities can be obtained with intravascular imaging. IVUS has been used to demonstrate vascular pathology at the sites where coronary artery abnormalities were documented during the acute phase of KD. Anatomic and functional vessel wall changes can be identified in patients with both current and regressed coronary artery aneurysms. Using IVUS-based "virtual histology" in convalescent KD patients, Mitani et al[275] showed dense calcium, necrotic core, and fibrofatty areas at sites of important coronary artery stenosis compared with normal regions or sites of regressed aneurysms. Iemura et al[274] found ongoing functional abnormalities in cases of

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regressed coronary artery aneurysms using IVUS plus acetylcholine infusion.

OCT is an invasive angiographic modality that uses light rather than ultrasound to provide high-resolution intravascular imaging of arterial wall abnormalities, which have been detected even when the coronary artery lumen is not distorted. The spatial resolution of OCT is higher than IVUS because of the shorter wavelengths, but the depth of penetration into the wall is less (2–3 mm versus 4–8 mm with IVUS). OCT has mostly been applied in adults. In a small series of children with a history of KD and angiographically normal luminal dimensions after regression of aneurysms, OCT was able to demonstrate important arterial wall abnormalities in all, including intimal thickening, distortion of wall layers, thrombus, calcification, and neovascularization with destruction of the internal elastic lamina.[329]

These invasive intravascular assessments can define the extent of coronary artery thrombus, calcification, and eccentricity; however, their utility for serial follow-up of KD patients is currently limited by their invasive nature. Likewise, the routine use of invasive angiography is additionally limited by patient exposure to contrast agents and radiation.

Noninvasive Modalities

Less invasive approaches to visualization of the coronary arteries have proven useful in the follow-up of KD patients. CMRI or magnetic resonance angiography studies, multislice spiral CT, and rapid CTA have become established as preferred methodologies for surveillance.

CMRI is useful for the assessment of many aspects of KD patients in the long term and has the advantage of avoiding radiation exposure.[330] Compared with CMRI angiography for aneurysm detection, CTA may be more sensitive to abnormalities in distal vessels and to the presence of thrombus.[331] These differences may be minimized as increasing field strength and spatial resolution continue to improve coronary artery visualization with magnetic resonance angiography. CMRI also affords assessment of ventricular function, myocardial perfusion, and scarring. CMRI of 60 patients at an average interval of 11.6 years after acute KD did not demonstrate differences in right ventricular or LV sizes or function compared with control subjects.[153] Delayed gadolinium enhancement, in a pattern consistent with MI, was identified in only 2 patients with persistent giant coronary artery aneurysms. Quantitative myocardial perfusion with CMRI identified abnormal perfusion reserve in KD convalescent patients that was independent of coronary artery status. This could make it a tool for identification of coronary microvascular dysfunction in KD patients.[325] Finally, CMRI can be used to detect myocardial edema with quantitative T2 mapping, scarring with delayed gadolinium enhancement, and fibrosis with T1 mapping.[332] Whether these multimodal features in isolation or combination will correlate with outcomes or modify therapy remains to be determined.

CTA can provide 3-dimensional visualization of the coronary arterial tree and may identify regions of stenoses more optimally than current cardiac magnetic resonance techniques; however, the radiation involved, when serial studies are likely, could limit its use. Newer systems with lower levels of radiation exposure could increase the utility and safety of this modality.

Low-dose, noncontrast CT calcium scoring also has been demonstrated to be useful in KD patients to guide selection for further evaluation with coronary angiography. In a series of patients with a history of KD (average time from acute illness, 14 years), coronary artery calcification was not identified in convalescent KD patients who had never had coronary artery abnormalities. In contrast, coronary artery calcium was demonstrated in most subjects with a persistent aneurysm.[333] This could be useful in guiding further evaluation of adults with prior KD when information about prior coronary artery abnormalities cannot be obtained.

CT performed in combination with PET can identify the presence of ongoing inflammation of the coronary artery, but insufficient data are available to define a role for this approach at present.[334] In addition, this is associated with important radiation exposure.

Lifestyle and Cardiovascular Risk Factors

There continues to be debate about whether the long-term pathological vascular process in the arteries of patients after KD represents a distinct vasculopathy or has common features of atherosclerosis.[335] Pathology suggests a distinct process characterized by thrombosis, chronic inflammation, and luminal myofibroblastic proliferation. However, studies in patients have variably noted the presence of endothelial dysfunction, increased intima-media thickness, and arterial stiffness. It is unknown whether atherosclerosis and atherosclerosis risk factors could influence the chronic processes of KD vasculopathy.

Nonetheless, KD patients have been classified as being at risk for CVD and targeted for evaluation and management of atherosclerotic CVD risk factors. In an AHA scientific statement on "Cardiovascular Risk Reduction in High-Risk Pediatric Patients" published in 2006, KD was classified as a risk condition, with patients having current coronary artery aneurysms believed to be at high risk, those with regressed aneurysms at moderate risk, and those without detected coronary artery involvement at low risk.[336] This classification was incorporated into the 2011 National Heart, Lung, and Blood Institute–commissioned Expert Panel Integrated "Guidelines for Cardiovascular Health and Risk Reduction in Children and Adolescents," with patients having current aneurysms being designated as having a high-risk condition and those with regressed aneurysms as having a moderate-risk condi-

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tion.[304] The reader is referred to these guidelines for detailed recommendations regarding lifestyle management and detection and management of specific CVD risk factors applicable to both the general population and those after KD. Given that these patients already have CAD, it is important that CVD risk factors are assessed and managed.

Risk Factors in KD Patients

KD patients might have a different pattern or susceptibility to CVD risk factors than the general population. Several reports have documented that high-density lipoprotein (HDL) cholesterol levels are decreased acutely after KD, sometimes together with increases in triglycerides and reduced levels of apolipoproteins AI and AII, with a variable relation to the extent of coronary artery involvement or inflammatory markers.[337–340] Qualitative changes in HDL particles have also been noted and thought to be related to acute levels of serum amyloid A.[341] Although they are improved after convalescence, lower HDL cholesterol levels can persist, particularly in those patients with severe and ongoing coronary artery aneurysms.[338,342,343] HDL and inflammation are known to be interrelated, and chronic changes may reflect this relationship. Nuclear magnetic resonance lipoprotein particle analysis suggests that pediatric and adult patients with KD, regardless of their aneurysm status, are no more likely than age-similar, healthy control subjects to have lipid patterns associated with increased risk of atherosclerosis.[344] Differences in blood pressure have been equivocal, with one study that used ambulatory blood pressure reporting reduced nighttime dipping[345] and others reporting no alterations in blood pressure regulation.[342,346–348] KD patients may be predisposed to adiposity, most likely related to lifestyle factors, particularly reduced levels of physical activity.[349–351] A single study noted elevation of glycosylated hemoglobin relative to normal control subjects.[345] It would appear that KD patients do not differ significantly from the general population with regard to CVD risk factors; however, their increased risk based on the presence of CAD merits careful attention and more aggressive management of lifestyle and CVD risk factors.

Medical Therapy

Infective Endocarditis Prophylaxis

Guidelines from the AHA have provided recommendations for prevention of infective endocarditis.[352] Patients with KD do not require antibiotic prophylaxis, regardless of the degree of past or current coronary artery involvement, coronary artery revascularization including stent placement, or the presence of valvular regurgitation.

Medical Therapy for Myocardial Protection

Patients with coronary artery aneurysms after KD may merit medical therapy to minimize the risk for and the degree of myocardial ischemia. Myocardial ischemia in patients after KD may result from structural abnormalities, including coronary artery stenoses or obstructions, and extreme sluggishness of flow through capacious aneurysms, particularly those in distal segments.[328] It may also arise from functional abnormalities, including vasospasm, endothelial dysfunction, and impaired myocardial flow reserve. KD patients with CAD may be asymptomatic or may have stable symptoms of ischemic heart disease, such as exertional chest pain or dyspnea. In addition to compromised coronary artery perfusion, some KD patients may also have ventricular dysfunction resulting from prior MI, which increases their potential for myocardial ischemia, symptoms, and progression and can modify the choices of therapy.

The evidence base specific to KD patients is sparse, but data acquired from extensive experience with atherosclerotic disease in adults identifies several effective approaches to myocardial protection in the setting of coronary obstruction. These interventions have been addressed in recent adult guidelines for the management of stable ischemic heart disease.[353] Medical interventions can be considered in 2 roles: first, of avoiding MI and death, and second, of controlling chest pain and other ischemic symptoms.

β-Blockers

β-Blockade decreases the risk of MI and death by reducing myocardial oxygen demand. For atherosclerotic disease, β-blockers are a critical part of management, and their effects should extend to the pathophysiology of KD coronary disease as well. Use of β-blockade is a Class I indication for all adult patients who have had MI or ACS for the 3 years after the event, irrespective of LV function (*Level of Evidence B*), and indefinitely in patients with LV systolic dysfunction (LV ejection fraction <40%) with heart failure or prior MI, unless a contraindication exists (*Level of Evidence A*). β-Blockers may be considered for KD patients of all ages, particularly those at high risk of myocardial ischemia because of large or giant coronary artery aneurysms. Carvedilol, metoprolol succinate, or bisoprolol are the β-blocking agents that have been shown to reduce risk of death. The consideration of β-blocking agents has been incorporated into the long-term management algorithm for KD patients with large or giant aneurysms that persist.

Angiotensin-Converting Enzyme Inhibitors

Renin-angiotensin-aldosterone blocker therapy has also been shown to be protective against MI and death in atherosclerotic CVD, and similar protection may be anticipated in KD patients with reduced ventricular function, although this has not been proven. ACEIs are recommended in all adult patients with atherosclerosis and stable ischemic heart disease who have the incremental risks of hypertension, diabetes mellitus, LV ejection fraction ≤40%, or chronic kidney disease. In patients who

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are intolerant of ACEIs, angiotensin receptor blockers are recommended.

Medical Therapy for Symptoms of Ischemia

For relief of symptoms of ischemia, β-blockers should be used as initial therapy (*Class I, Level of Evidence B* for atherosclerotic patients); if these are inadequate for symptom control, calcium channel blockers or long-acting nitrates should be added or used instead of β-blockers in intolerant patients. Sublingual nitroglycerine or nitroglycerine spray is recommended for immediate control of angina.

Empirical Use of Statins

Hydroxymethylglutaryl coenzyme-A reductase inhibitors (statins) are a cornerstone of therapy for the primary and secondary prevention of atherosclerotic cardiovascular events in adults.[354] In addition to lowering low-density lipoprotein cholesterol, statins have potentially beneficial pleiotropic effects on inflammation, endothelial function, oxidative stress, platelet aggregation, coagulation, and fibrinolysis. Although controversy continues concerning whether the vascular pathology of KD may have features of atherosclerosis, statins could have a role in the long-term management. KD patients have been variably shown to have chronic inflammation and reduced HDL-cholesterol levels. In addition, endothelial dysfunction, increased vascular stiffness, and intima-media thickening have been noted in both affected coronary arteries and in systemic arteries. In the setting of familial hypercholesterolemia, children and adolescents treated with statins showed normalized endothelial function and regression of carotid intima-media thickening.[355,356] To date, these studies have included patients as young as 6 years. Short-term small studies in KD patients with aneurysms treated with statins have shown reductions in high-sensitivity CRP and improved endothelial function.[357–359] A review of empirical statin use in 20 KD patients as young as 8 months with aneurysms who were treated for a median of 2.5 years showed only transient laboratory abnormalities and no effect on growth.[360] Given this discussion, empirical treatment with low-dose statin may be considered for KD patients with past or current aneurysms, regardless of age or sex.

Thromboprophylaxis

Patients with important coronary artery aneurysms remain at chronic risk of thrombosis. Nonocclusive organized thrombus and recanalized occlusive thrombus both contribute to chronic pathological changes in the arterial wall and may be superimposed on chronic inflammation and luminal myofibroblastic proliferation. These changes may contribute not only to a reduction or normalization of luminal dimensions but also to the development of stenoses. The chronic risk of thrombosis is greatest in those with giant aneurysms and is attributable to reduced shear stress and flow disturbances (stagnation) as noted in rheological studies[361,362] and flow simulations.[363,364] Other patient and aneurysm characteristics can also increase thrombosis risk (Table 9). The degree to which both local and systemic endothelial dysfunction and inflammation contribute to thrombosis risk is not completely known. Albisetti et al[365] showed that patients with aneurysms had a decreased fibrinolytic response to venous occlusion as a marker of systemic endothelial dysfunction.

Prevention of thrombosis is therefore an important component of long-term management. Given that arterial thrombi are believed to initiate with platelet activation, antiplatelet therapy is the mainstay of initial therapy. However, for patients with large or giant aneurysms, in which flow stasis is a prominent feature, activation of the clotting system may be an initiating factor, and hence, anticoagulation is added. For some patients with medium aneurysms, or giant aneurysms that have reduced in size, dual-antiplatelet therapy may be considered as an alternative to the addition of an anticoagulant. The risk is largely driven by the size of the aneurysm and is highest in those with giant aneurysms. Also, flow stasis may increase in more distal aneurysms, particularly those distal to large proximal aneurysms. The relationship with luminal dimension in the chronic phase is largely driven by the current degree of involvement, although the presence of previous thrombosis also increases the risk. Hence, an approach to thromboprophylaxis must take into account both maximal and current luminal dimensions, as well as other factors that could increase the risk of thrombosis.

For antiplatelet effects, low-dose ASA remains the mainstay. For those with resistance to ASA or ASA intolerance or allergy, an alternative antiplatelet agent is used. For anticoagulation, warfarin continues to be the drug of choice in most circumstances. The use of anticoagulation has been shown to reduce MI in those with giant aneurysms, to 1 of 19 patients treated with warfarin and ASA versus 16 of 49 patients treated with ASA alone (with 7 sudden deaths in the ASA-only group).[245] A further multicenter study of 83 patients with giant aneurysms, most of whom were treated with ASA and warfarin, showed a 10-year freedom from cardiac events of 91%, or 2.9% per patient-year of follow-up, with a rate of hemorrhagic complications of 1.7% per patient-year.[366] However, particularly for patients in whom dosing and maintenance of warfarin are problematic and achievement of a stable level of anticoagulation is essential, such as in young patients and in those early in the course of their disease, LMWH may be a useful alternative.[367] LMWH has been shown to provide a similar freedom from thrombosis, with more minor but fewer major bleeding complications than with warfarin. In addition, a greater time spent in the therapeutic target range has been noted, with some evidence of increased normalization of luminal dimensions.

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The use of direct oral anticoagulant drugs has not been studied in children, or in patients with KD, although they do hold promise.

Physical Activity

Regular physical activity is important for healthy physical and psychosocial development for children and adolescents. Conversely, there are important health risks associated with inactivity. However, little is known of the activity levels of patients after KD, and there is no evidence to support aggressive activity restrictions. KD patients, regardless of the extent of coronary artery abnormalities, have been shown to be <50% as active as their healthy peers, and this was associated with lower self-efficacy for physical activity and lower physical functioning.[351] Exercise capacity has been shown to be normal regardless of the extent of coronary artery involvement, even in the presence of inducible myocardial ischemia.[368–370] KD has been recognized as a high-risk cardiovascular condition, and physical activity should be promoted for everyone within the parameters defined by the risk of myocardial ischemia, arrhythmia, and bleeding associated with thromboprophylaxis.[336]

Guidelines exist regarding physical activity and exercise for patients with congenital heart disease and can be adapted for the KD patient.[371] In addition, the 36th Bethesda Conference regarding competitive athletes with cardiovascular abnormalities provides recommendations specific to KD.[372] These recommendations regarding participation in competitive sports emphasize the need for guidance based on testing for inducible myocardial ischemia or arrhythmia for those with past or current aneurysms, with a preference for lower-intensity competitive sports for those with persistent aneurysms.

Physical activity should be discussed and encouraged at every visit. If a precaution is indicated, the reason for the precaution should be discussed in detail and provided in writing to the patient and the patient's providers. Failure to do so has been shown to result in uncertainties for patients and families, which leads to lack of participation and inactivity.[373] Patients taking thromboprophylaxis that includes dual-antiplatelet or anticoagulation therapy are restricted from activities involving a risk of bodily contact, trauma, or injury. If the risk can be effectively mitigated, such as with appropriate supervision and the use of a helmet and protective gear, participation may be considered. Patients at risk for myocardial ischemia or exercised-induced arrhythmia are restricted from activities with a high dynamic or static component, and decisions should be guided by stress echocardiography or MPI, as well as the presence of exercise-induced arrhythmias or symptoms. Patients should be instructed regarding symptoms and signs of myocardial ischemia and guidance for safe participation (lack of coercion, adequate supervision, permission to self-limit, safe environment, and availability of a defibrillator and people capable of performing cardiopulmonary resuscitation). A 2013 AHA scientific statement provides healthcare providers with best practices regarding physical activity promotion.[374] Additionally, the 2010 KD guidelines from Japan provide a school activity management table that gives clear direction to patients and schools regarding specific recommended activities and participation levels.[137]

Some KD patients at risk for myocardial ischemia or who have exercise intolerance and deconditioning could benefit from participation in a rehabilitation program. Rehabilitation programs are recognized as an important part of the care for adults with CVD[375–377] and are beginning to be conceptualized and adapted for children.[378] Most emerging programs have focused on exercise training interventions for patients with congenital heart disease that require important resources. Home-based activity programs might be a better option for children and families. The benefits of such programs have yet to be broadly studied. A small study of KD patients with an occluded coronary artery and stress-induced myocardial ischemia showed improved perfusion to collateral-dependent areas after a 10-day exercise training program with heparin pretreatment.[379] This further supports the concept that all KD patients should be allowed to benefit from physical activity within the context of any restrictions.

Reproductive Counseling

For female patients, reproductive counseling in terms of contraception and risks of pregnancy are part of long-term management. Although specific recommendations for patients with KD are not available, guidelines are available for adults with congenital heart disease.[380] Counseling should be age appropriate and begin at approximately the age of 10 years, and they should be incorporated into general health counseling. For those patients with important CAD, the issue of increasing thrombosis risk with certain types of oral contraceptive agents should be considered. In such circumstances, low-estrogen or progesterone-only oral contraceptives would be preferred. Appropriate referral or consultation with a specialist might be needed. For patients considering pregnancy or who have become pregnant, appropriate assessment of their current cardiac status is essential, including the risk of ischemia, deterioration in functional status, heart failure, arrhythmia, and thrombosis. Ideally, at-risk women who are considering pregnancy should be referred to a high-risk obstetric service for appropriate counseling before pregnancy. Comanagement of pregnancy with a high-risk obstetric service, including a maternal-fetal medicine specialist, and an adult cardiologist is needed. Thromboprophylaxis strategy might need to be adjusted during pregnancy (warfarin should be discontinued; heparin or dual-antiplatelet therapy may be a suitable al-

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ternative) and delivery. Warfarin must be avoided during the first trimester because of its teratogenic effect. In addition, statins and ACEIs should be discontinued.

Outcomes of pregnancy have been reported in KD patients. Two patients with giant aneurysms had successful pregnancy and delivery after switching their warfarin to low-dose ASA and unfractionated heparin.[381] A series of 21 pregnancies in 10 women (6 normal, 4 with coronary artery aneurysms) showed no cardiovascular complications (although 2 of the 21 progeny subsequently developed KD).[382] A study in Japan of 46 pregnancies in 30 women also showed no cardiac events.[383,384]

Catheter and Surgical Coronary Artery Interventions

The recommendations outlined in this section are based on limited data and mostly reflect available observational data and consensus opinion from experts in the field. Decisions regarding the need for revascularization and the optimal mode of revascularization are often difficult and tailored to the patient's clinical status, candidacy for different forms of revascularization, and preference. It is important to consult an adult interventional cardiologist and adult cardiothoracic surgeon with experience in revascularization of patients with KD when revascularization is considered.

Acute Coronary Syndromes

ACS includes ST-segment elevation MI (STEMI), non–STEMI, and unstable angina. Patients with KD may present with STEMI in the setting of complete thrombosis of an aneurysm during the acute/subacute phase of the illness, thrombosis of a residual giant aneurysm later in the illness, or rupture of an atherosclerotic plaque that may have formed independently in an adult with a remote history of KD. STEMI is a medical emergency and requires an attempt at prompt restoration of anterograde flow through the vessel.

In young patients in the acute/subacute phase of the illness, the optimal means of achieving restoration of coronary flow is not known. In this setting, there is little experience with mechanical revascularization techniques, either with catheter-based techniques or with coronary artery bypass grafting (CABG) surgery. Systemic thrombolytic or intravenous antiplatelet therapy (ie, abciximab) may be the best option for these patients in potentially reducing thrombus burden and allowing for rapid recanalization of the acutely occluded vessel. Systemic and intracoronary thrombolytic therapy has been used successfully to reduce aneurysmal thrombus burden in patients with more stable presentation.[385,386] CABG should not be considered because of inherent delays in restoring anterograde flow into the occluded vessel. Percutaneous coronary interventions (PCIs) can be considered, although there may be difficulties in successfully passing a coronary guidewire through an acutely occluded aneurysm. If PCI is pursued, consideration should be given to the use of thrombectomy catheters to remove thrombus burden. Balloon angioplasty may not yield a durable result, and it is unlikely that a stent could be deployed in a stable fashion within an acutely occluded aneurysm with thrombus.

The adult with a known remote history of KD presenting with STEMI should be referred for emergency coronary angiography and determination of the best mode of revascularization. Unlike the patient in the acute/subacute phase of KD presenting with STEMI, the adult presenting with STEMI may have typical atherosclerotic disease as the cause of their STEMI, and standard PCI techniques may be appropriate. If the patient is found to have an acutely thrombosed aneurysm, then a judgment decision will need to be made by the interventional cardiologist as to whether PCI should be attempted or a pharmacological strategy should be used.

Management of ACS in adult patients with remote KD can be particularly complicated when the initial diagnosis was missed in childhood or was not followed up after the transition to adult care. Given the high incidence of ACS in the general population, such patients can surprise the adult interventional cardiologist and should be recognized as a clinical challenge unique from conventional atherosclerotic disease, and suspicion of prior KD, particularly in young adults presenting with ACS and in the setting of unanticipated aneurysmal changes, should be maintained. A recent series in a US-based population underscores the particular challenges of acute percutaneous interventions in this population, relating to the presence of coronary calcification and the potential for underestimation of true luminal dimensions and the potential to miss underlying aneurysmal distortion.[387] These factors emphasize the importance of IVUS to demonstrate true luminal dimensions, improve stent deployment, and inform potential modifications to postprocedural anticoagulation. Clinical follow-up strategies in the patient after an ACS episode will include the previously listed recommendations for surveillance and management of CAD in adult KD patients.

Urgency for revascularization is less for patients with other forms of ACS (non-STEMI and unstable angina) provided the patient is stable from an ischemic and hemodynamic standpoint. KD patients with non-STEMI/unstable angina may present because of nonocclusive thrombosis of coronary aneurysms with distal embolization or progression of calcified stenoses later in the disease. Coronary CTA or CMRI may be helpful to understand the pathophysiology of the presentation and determine the appropriate next steps. For patients who present because of thrombosis of an aneurysm, consideration may be given to thrombolytic therapy and institution of long-term anticoagulation. Mechanical revascularization is not likely to be of marginal benefit in these patients. For pa-

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tients presenting with progression of calcified stenoses as the cause of their presentation, cardiac catheterization should be considered, and revascularization can be considered as discussed below.

KD patients with stable angina typically present well after the initial presentation with KD and often will present in early adulthood. They generally have predictable angina with exertion. Symptoms tend to develop gradually, not suddenly as is typically seen with ACS. Stable angina is usually attributable to demand ischemia caused by progressive stenoses located at the inlet or outflow of coronary artery aneurysms that have mostly regressed and stabilized. Unlike typical atherosclerotic plaques seen in CAD, these stenoses tend to be circumferential rather than eccentric and are often heavily calcified.

KD patients with stable angina should undergo revascularization for left main coronary artery involvement, lifestyle-limiting angina despite maximal medical therapy, or high-risk features on noninvasive ischemia assessment. This practice would be in keeping with guidelines for adult patients with typical atherosclerotic CAD.[388]

Left main CAD, or disease that is equivalent to left main disease (ie, ostial/proximal LAD involvement and left circumflex involvement), represents anatomy that confers a high ischemic burden with activity. According to revascularization guidelines in adults with CAD, a left main stenosis of ≥50% should be considered for revascularization in a patient with symptoms and documentation of ischemia. CABG is the mode of revascularization of choice, although PCI can be considered in selected patients.

There is growing evidence that patients with angina and without high-risk coronary artery anatomy can be safely managed with medical therapy without conferring an increased risk of long-term mortality or MI. Although data are limited, this likely is true for KD patients with stable angina attributable to fixed obstructions within the coronary arteries. Therapies should be aimed at relieving angina, and this can be achieved with β-blockers, calcium channel blockers, and nitrates. However, if the angina cannot be successfully managed to the point of being acceptable for the patient, or the side effects of the antianginal medications cannot be tolerated, consideration should be given to revascularization.

Symptomatic KD patients with high-risk features on noninvasive imaging should also be considered for revascularization. High-risk features include an early positive testing for inducible myocardial ischemia or exercise-induced arrhythmias, or poor exercise tolerance (<3 MET [metabolic equivalent of task] units) because of symptoms (angina and dyspnea). The COURAGE (Clinical Outcomes Utilizing Revascularization and Aggressive Drug Evaluation) study randomized adult patients with stable atherosclerotic coronary disease to receive optimal medical therapy versus revascularization with PCI and optimal medical therapy.[389] Patients in the revascularization group fared no better than patients in the optimal medical therapy group in terms of death and MI at follow-up. However, the nuclear substudy suggested a potential mortality benefit in patients who underwent revascularization for CAD that resulted in ≥10% of the myocardial muscle mass becoming ischemic.[390] Therefore, in symptomatic KD patients with this threshold of ischemic muscle mass, revascularization may be reasonable.

Prior reports have suggested that symptomatic KD patients with coronary stenoses estimated to be ≥70% on coronary angiography should be considered for revascularization independent of physiological assessment of the lesion. However, revascularization based on lesion severity alone (the "oculostenotic reflex") in stable patients has not proven to be of benefit. It would be reasonable to consider revascularization in patients if ischemia testing demonstrates ischemia in the myocardial territory subtended by the lesion. In patients referred for cardiac catheterization without prior noninvasive testing, measurement of FFR in the catheterization laboratory should be considered as a risk-stratification tool to determine need for revascularization. Patients with FFR >0.80 can safely be managed medically without an increased risk of death, MI, or delayed need for target-vessel revascularization. However, based on the results of the recent FAME II (Fractional Flow Reserve versus Angiography for Multivessel Evaluation 2) study, patients with FFR ≤0.80 may be at increased risk for urgent readmission for unstable angina and need for target-vessel revascularization.[391] These patients may be considered for revascularization after FFR assessment.

Patients with silent ischemia (documented ischemia on noninvasive testing or FFR assessment in the absence of symptoms) represent a difficult subset of patients to manage because the optimal management of these patients is not certain. This holds true for patients with KD as well. Patients with silent ischemia are believed to have an altered warning system and do not sense angina in a typical fashion. In stable patients with obstructive coronary lesions, angina relief is the major benefit of coronary revascularization; however, whether revascularization positively affects outcomes of patients with silent ischemia is not well understood at this time. Revascularization should certainly be considered in KD patients with silent ischemia who have left main coronary artery involvement (or left main equivalent involvement) or who have high-risk features on noninvasive assessments for ischemia. It would be reasonable to consider revascularization in KD patients with silent ischemia who have ≥10% of myocardial muscle mass that is ischemic on MPI. It would also be reasonable to consider revascularization in patients with FFR ≤0.80.

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Recommendations for Indications for Mechanical Revascularization

1. **Revascularization should be avoided in KD patients in the acute/subacute phase of the illness with STEMI attributable to acute thrombotic occlusion of an aneurysm *(Class III; Level of Evidence C)*.**
2. **Adult patients with remote history of KD presenting with STEMI should be referred emergently for coronary angiography for determination of best means of flow restoration in the culprit artery *(Class I; Level of Evidence C)*.**
3. **Revascularization should be performed in KD patients with stable angina and high-risk coronary anatomy including left main CAD, multivessel coronary disease with reduction in LV function, multivessel coronary disease with diabetes mellitus, or high-risk noninvasive ischemia testing *(Class I; Level of Evidence C)*.**
4. **Revascularization should be performed for patients with non–ST-segment elevation and coronary anatomy amenable to revascularization on coronary angiography *(Class I; Level of Evidence C)*.**
5. **Revascularization for patients with stable angina and symptoms refractory to maximal medical therapy is reasonable *(Class IIa; Level of Evidence C)*.**
6. **Revascularization for KD patients with silent ischemia and ischemia involving >10% of LV mass may be considered *(Class IIb; Level of Evidence C)*.**

Coronary Artery Bypass Grafting

Once the decision to proceed with revascularization is made, the decision between CABG and PCI can often be difficult, and the risks and benefits of both procedures have to be weighed carefully before a route is selected.

There are several factors favoring CABG surgery over PCI. Patients with left main coronary involvement or multivessel coronary artery involvement will be better treated with CABG. It is likely that more complete revascularization can be achieved with CABG, particularly if there is the presence of ≥1 chronic total occlusions. Patients with multivessel coronary artery involvement and reduced LV function (because of either prior MI or chronic ischemia) may also benefit more from CABG, again because of the greater likelihood for complete revascularization. A third subset of patients who may fare better with CABG are diabetic patients. The recently published FREEDOM trial (Future Revascularization Evaluation in Patients With Diabetes Mellitus: Optimal Management of Multivessel Disease) showed a survival benefit for diabetic patients treated with CABG versus multivessel PCI.[392] Although these were all patients with typical atherosclerotic CAD, whether these findings would apply in a clinical trial of KD patients with diabetes mellitus is unknown. It stands to reason, however, that the conclusions would be similar. Patients with single-vessel disease requiring revascularization but for whom prior PCI attempts have failed or for whom PCI is deemed unfeasible should also be considered for CABG. Finally, age plays an important role in the decision for CABG versus PCI. CABG is favored in older children and younger adults, although children in the first decade of life have been treated with CABG.

If CABG is deemed the optimal revascularization strategy, every effort should be made to use both mammary arteries for conduits. Unlike saphenous vein grafts, the length and diameter of mammary artery grafts continues to grow as children grow. Furthermore, the patency of mammary artery grafts over the long-term is superior to that of saphenous vein grafts. In a Japanese survey of KD patients who underwent CABG since 1975 (the largest published series to date of KD patients who have undergone surgery), the patency rates for mammary artery grafts at 1, 5, and 15 years were 95%, 91%, and 91%, respectively, when the operation was performed at >12 years of age.[393] In patients for whom the operative age was ≤12 years, the patency rates were less at 93%, 73%, and 65% at the same respective time points. The overall patency of saphenous vein grafts was 65%, 53%, and 48%, respectively, at 5, 10, and 15 years after CABG in all patients. There are no published data regarding the patency of radial artery or gastroepiploic artery grafts in patients with KD.

Although graft failure of mammary artery grafts is uncommon, particularly in older children, it is important to ensure that a mammary artery is used as a bypass conduit only for arteries with physiological stenoses. Mammary artery grafts for angiographically borderline lesions may fail to mature because of significant competitive flow from the native circulation. If prior ischemia testing has failed to show ischemia in the territory supplied by the lesion, strong consideration should be given to FFR assessment in the catheterization laboratory before grafting of the vessel with a mammary artery is considered.

Complications from CABG for KD are no different than for CABG for patients with CAD and include an aggregate risk of 1% to 2% for major complications, including death, MI, major bleeding, stroke, and renal failure. Patients with KD tend to be much younger than patients with CAD and do not have the diffuse atherosclerosis that contributes to major complications from CABG in adults.

The long-term clinical outcome of KD patients treated with CABG appears to be favorable. In the 244 patients who were included in the survey, there were 15 deaths (1 operative death, 12 late deaths, and 2 noncardiac deaths).[393] Fourteen patients required re-

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peat CABG operations, and another 17 patients required PCI for graft stenoses. As would be expected, patients with normal LV function experienced better long-term survival.

Percutaneous Coronary Intervention

The factors that tend to favor PCI as the optimal revascularization strategy include single-vessel disease, multivessel disease with focal and easily treated lesions, normal LV function, and absence of diabetes mellitus. Patients with coronary artery anatomy severe enough to warrant CABG but with significant medical comorbidities that make CABG too high of a risk can also be considered for PCI provided the lesions are technically amenable to PCI and the risk of PCI is acceptable. Finally, patients who refuse CABG can be considered for PCI as well, provided the risks and benefits of PCI compared with CABG are carefully discussed and the patients are aware of the potential long-term consequences of their decisions. Patients may wish to take the less invasive route to minimize the recovery time required, and in most cases, this would not preclude CABG in the future should it become necessary.

Most of the experience with PCI has been accumulated in Japan, and at this time, there are very few large-scale data to evaluate the long-term efficacy of PCI in patients with KD. PCI techniques that can be used to treat stenotic lesions in patients with KD include balloon angioplasty, with or without coronary stenting, and rotational atherectomy (RA) with or without coronary stenting.

Balloon angioplasty is a poor stand-alone technique for the treatment of stenotic lesions in KD. In the years after the acute illness, these lesions become heavily fibrotic and calcified, which renders them extremely difficult to expand with balloon angioplasty alone. If the lesion can be expanded, there is often significant recoil that limits the acute result. Furthermore, the high pressures required to expand these lesions have been associated with the development of neoaneurysms at the site of dilation. There are no data or reports of the use of plaque-incising balloons in calcified stenotic lesions in KD, although their use can be considered.

For patients in whom moderate balloon inflations fail to expand the lesion, or in whom there is clear evidence of heavy calcification at the lesion, consideration should be given to RA to debride the calcium and increase the compliance of the lesion. RA has been used successfully to treat calcified lesions in KD[394]; however, the short-term and long-term outcomes have not been studied in a systematic fashion. RA also poses unique considerations in KD patients. For instance, it is likely the RA burr will need to traverse an aneurysm to address the stenotic lesion. It is conceivable that high-speed rotation of the burr in an aneurysm that is not completely thrombosed could lead to liberation and embolization of thrombotic material, although this complication has not been reported.

Regardless of whether balloon angioplasty or RA is used for lesion modification, coronary stents should be used. Stenting after balloon angioplasty will reduce the impact of recoil on restenosis, a major limitation in densely fibrotic lesions. The largest routinely used RA burr is 2 mm in diameter. Although a burr this size would be sufficient to favorably alter the compliance of the lesion, the residual lumen of 2 mm may still be too small to allow for relief of ischemia under demand conditions. Coronary artery stenting provides a means of restoring lumen dimensions that are congruent with the native vessel. RA followed by stenting has a success rate of >90% in a published Japanese series.[395]

When a stent is chosen for PCI, the choice of a bare-metal stent versus a drug-eluting stent (DES) is an important consideration. In patients with atherosclerotic CAD, numerous studies have shown that bare-metal stents are limited by a higher risk of in-stent restenosis than DESs; however, DESs may require longer to achieve complete endothelial coverage, and therefore, the time period of risk for stent thrombosis may be longer. At the present time, guidelines suggest that patients receiving bare-metal stents remain on dual-antiplatelet therapy (ASA and a thienopyridine agent) for a minimum of 30 days, whereas patients receiving DESs should remain on dual-antiplatelet therapy for a minimum of 1 year. The choice of stent will be highly individualized on the basis of the patient's ability to take multiple antiplatelet/antithrombin agents if they require warfarin for prophylaxis in the setting of giant coronary aneurysm. The bleeding risk of 1 year of "triple therapy" may be excessive for some patients; however, if an anticoagulant is not required, a DES may be the better choice. At the present time, there are no reports regarding the long-term performance of DESs in patients with KD.

Concurrent use of intravascular imaging may be helpful in planning PCI procedures in patients with KD. IVUS is the imaging modality of choice and will provide qualitative information regarding the extent of calcification of the lesion, as well as potentially providing information regarding the composition of any aneurysms. Quantitative information that can be obtained includes reference vessel diameter, which would be helpful in the selection of appropriate stent sizes. There have been a few reports describing the use of OCT in KD patients, although this technology may be limited in patients with coronary artery aneurysms, and there are difficulties in adequately displacing the blood pool during imaging.

Recommendations for Modes of Revascularization

1. **CABG is preferred to PCI in KD patients with left main CAD, multivessel CAD with reduced LV function, multivessel CAD with lesions not amenable to PCI, and multivessel CAD in diabetic patients *(Class I; Level of Evidence B).***

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2. **CABG is preferred to PCI in older children and adults with KD and multivessel involvement *(Class I; Level of Evidence C)*.**
3. **CABG should be performed with bilateral internal thoracic arterial grafts where possible *(Class I; Level of Evidence B)*.**
4. **PCI is preferred in patients with single-vessel or focal multivessel disease amenable to PCI *(Class I; Level of Evidence C)*.**
5. **RA and stents should be used in PCI of calcified lesions *(Class I; Level of Evidence C)*.**
6. **The use of multivessel PCI is reasonable for KD patients with focal lesions amenable to PCI *(Class IIa; Level of Evidence C)*.**
7. **The use of DESs during PCI is reasonable for KD patients who do not require long-term anticoagulation *(Class IIa; Level of Evidence C)*.**
8. **The use of IVUS is reasonably indicated during PCI in KD patients to ensure adequate stent sizing and deployment *(Class IIa; Level of Evidence C)*.**
9. **Multivessel PCI may be considered for patients who are acceptable CABG candidates but prefer to avoid CABG, provided the risks and benefits of both approaches are discussed with and understood by the patient *(Class IIb; Level of Evidence C)*.**
10. **The use of DESs during PCI may be considered for KD patients who require anticoagulation, provided the bleeding risk of the patient is acceptable *(Class IIb; Level of Evidence C)*.**
11. **Stand-alone balloon angioplasty should not be used for PCI in KD patients with coronary obstructions *(Class III; Level of Evidence C)*.**

Cardiac Transplantation

A small number of pediatric and adult patients with KD have undergone cardiac transplantation for severe myocardial dysfunction, severe ventricular arrhythmias, or severe coronary arterial lesions for which interventional catheterization or coronary artery bypass procedures were not feasible. The timing of transplantation after acute KD has ranged from a few weeks to as long as 19 years, and it has been performed in pediatric as well as adult patients. A review performed in 1997 from transplant registries and KD investigators documented that almost half of transplant patients had undergone previous bypass grafting procedures.[396] Reported cases include patients who developed severe heart failure after extensive MI from thrombosis of aneurysms but also from in-stent thrombosis after percutaneous coronary stenting.[397,398] Individual case reports of transplantation outcomes are insufficient to determine whether posttransplantation vasculopathy or rejection risk is higher in transplant patients with KD. Advanced pretransplantation care with ventricular assist devices used as a bridge to subsequent cardiac transplantation has been successfully achieved in a child.[399]

Recommendation for Cardiac Transplantation

1. **It is reasonable to consider cardiac transplantation for patients with severe, irreversible myocardial dysfunction and coronary artery lesions for which interventional catheterization procedures or CABG are not feasible *(Class IIa; Level of Evidence C)*.**

Psychosocial Issues

After KD, nearly all children return to their usual baseline state of functional health. Reports of overall psychosocial well-being provide reassurance that KD does not affect long-term health-related quality of life in the majority of patients. Similarly, KD has not been shown to have long-term effects on cognitive development or academic performance.[400,401] Patients with a history of KD have similar or better scores on physical and psychosocial health when questionnaires are completed by their parents.[402,403] The association of KD with behavior problems is controversial, with some studies describing increased behavioral concerns[400,404,405] and others finding no evidence of heightened behavior problems.[401,405] Importantly, several studies have suggested that parents continue to worry long-term about their child's health after KD regardless of their child's coronary artery status.[402,406,407]

Healthcare providers should provide accurate education to families throughout the illness course. Patients and families face similar stressors during the acute illness, including hospitalization, medical procedures, and uncertainty about long-term outcome.[406] Children who have coronary artery aneurysms face the challenges of adapting to a chronic, potentially important health condition that requires continued medical testing and medications and, for those on anticoagulation or with myocardial ischemia or arrhythmias, precautions about physical activity. Additionally, both the patient and the patient's family may have challenges coping with the uncertainty of the long-term prognosis.[406] Caregivers should determine on an individual basis whether a patient or family would benefit from the support of a psychologist or social worker.

Transition to Adult Care

The earliest patients with KD are now in their middle adult years, and many more patients reach adulthood every year. The ultimate goal of transition is to prevent lapses in care during and after transfer, which for KD patients with aneurysms can put them at increased risk of morbidity and mortality. Transition programs should be in place to

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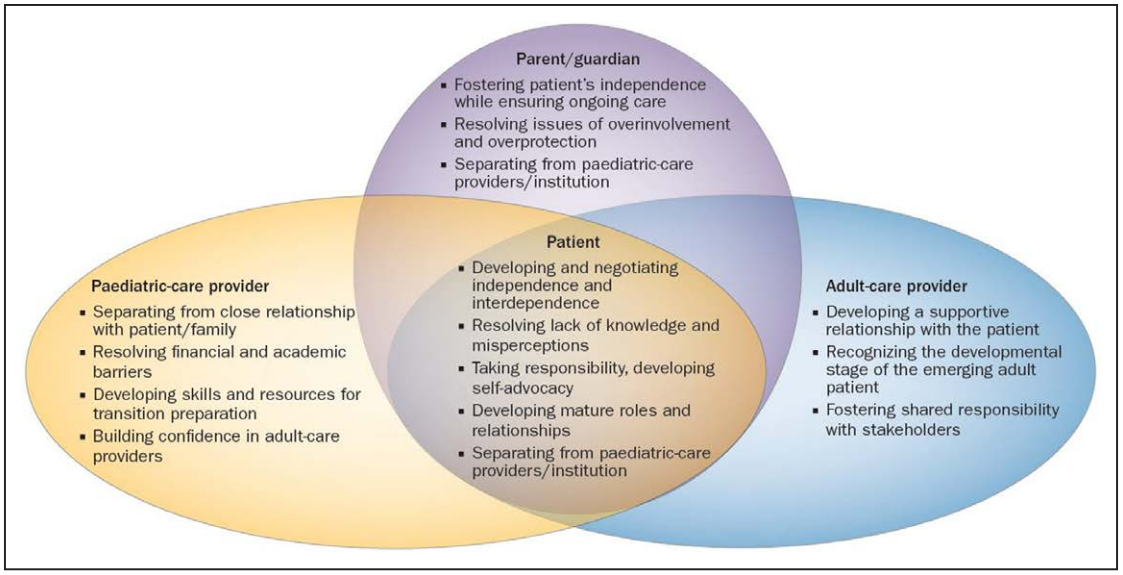

Figure 5. Stakeholder perspectives regarding transition from pediatric to adult cardiac care.
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prepare these patients for transfer of care to adult cardiology teams with expertise in the unique issues related to KD. Best practices have been developed regarding education, assessment of readiness for transition, and skills development for effective communication, self-advocacy, decision making, and self-care for patients with congenital and acquired heart disease.[408,409] Therefore, transition encompasses more than the transfer of care to an appropriate and knowledgeable adult cardiology provider. Transition should be purposeful and planned, with the needs of the adolescent or young adult at the center while taking into account the perspectives of the families and care providers (Figure 5).

For patients who have never had coronary artery aneurysms, long-term cardiology care is not recommended, and hence, transition is not required. These patients can continue to receive health maintenance from their primary care providers. However, for patients with aneurysms, either persistent or decreased to a normal luminal dimension, lifetime cardiology follow-up is recommended. Adult KD patients would best be served by joint programs consisting of a selected group of adult cardiology providers who are experts in CAD in consultation with pediatric cardiac teams who have expertise in the unique issues related to KD. At some centers, experts in adult congenital heart disease may have the appropriate combined training to follow these patients. Transfer from pediatric to adult cardiology care is recommended, with a flexible age of 18 to 21 years, and mechanisms should be in place to ensure uninterrupted financial coverage of care together with collaboration with an adult cardiology care team knowledgeable in KD. Flexibility in the age of transfer may reflect the fact that some patients may not be ready for or in a situation to facilitate transition. Some patients in this age group may be in living situations that are less permanent (attending college).

Because KD is an illness that typically occurs in young childhood, most of the early education is aimed at parents. However, as the child becomes older, it is important to educate him or her about the particular coronary artery or cardiac issues, starting as early as age 12 years. Knowledge goals should include the following[408]:

- Specifics of KD history and complications, including cardiac events and procedures with dates or ages
- Importance of uninterrupted life-long cardiology care
- Names, doses, and reasons for taking all medications; requirements for monitoring
- Names and reasons for tests performed
- Specific symptoms or signs that warrant immediate medical attention
- Recommendations regarding physical activity
- Considerations regarding contraception, pregnancy, and recurrence of KD in offspring
- Expectations regarding long-term prognosis and health
- Importance of and strategies to achieve healthy lifestyle behaviors

Risk behaviors, such as the use of alcohol and its potential interactions with medications such as warfarin, should be discussed beginning in adolescent years. The use of illicit drugs should also be assessed at each visit, because certain drugs, such as cocaine, can be particularly dangerous for patients with CAD.

In addition to education, it is important that the transitioning patient assume increasing responsibility for their decision making and management in accordance with their readiness for transition. There are several tools and algorithms designed to assist in the assessment

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of readiness of a particular patient that can be used to guide skills development.[408,410] Self-management skills that should be evident at the time of transfer include the following:

- Ability to contact healthcare providers; scheduling and attending appointments and tests; knowing when and how to access emergency care; understanding when and how to access mental health services
- Creating and using a portable health summary; maintaining health records
- Adhering to a medication regimen, including requesting prescription refills
- Communicating independently and effectively with healthcare providers

Recognizing the requirements for education and skills development in addition to the need for effective processes for achieving and tracking transfer of care, both the pediatric and the adult cardiology program should collaborate to create an effective transition program. Programs should have a designated transition champion who partners with each patient and creates a planned and individualized process. The transition process and documented plan should also be shared with the patient's primary care provider. The program should benefit from shared best practices and resources with other centers. The prevention and prompt detection of lapses in care will ensure that the possibility exists to optimize long-term outcomes for these vulnerable patients.

SUMMARY

This statement provides updated discussion and recommendations for the diagnosis, acute treatment, and long-term management of KD. The ultimate goal is the prevention of important coronary artery abnormalities. However, young adult patients continue to present with CAD or sudden death presumed to be secondary to complications of a remote episode of KD during childhood. Although the development of this statement relied on best-available evidence and expert opinion, important evidence gaps were identified. Until the cause and pathogenesis are defined, an exact diagnostic test remains elusive, and acute treatment remains somewhat empirical. In addition, we have no means to prevent KD. Despite best available empirical therapy, to which some patients do not respond, a small percentage of patients either present with or develop coronary artery aneurysms. The distinctive nature of KD-related vasculopathy is beginning to be understood, but it has yet to completely inform strategies aimed at risk stratification and prevention of thromboses, occlusions, and stenoses, as well as their effective long-term management, in young patients. Given the young age at the acute illness and the long-term and unpredictable consequences for those with aneurysms across the life span, effective care strategies to address psychosocial concerns and to ensure transition to uninterrupted expert adult cardiology care are essential to optimize health-related quality of life. It is hoped that the evidence gaps can be addressed in future iterations of this statement.

FOOTNOTES

The American Heart Association makes every effort to avoid any actual or potential conflicts of interest that may arise as a result of an outside relationship or a personal, professional, or business interest of a member of the writing panel. Specifically, all members of the writing group are required to complete and submit a Disclosure Questionnaire showing all such relationships that might be perceived as real or potential conflicts of interest.

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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. A relationship is considered to be "significant" if (a) the person receives $10 000 or more during any 12-month period, or 5% or more of the person's gross income; or (b) the person owns 5% or more of the voting stock or share of the entity, or owns $10 000 or more of the fair market value of the entity. A relationship is considered to be "modest" if it is less than "significant" under the preceding definition.

*Modest.

†Significant.

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Gerard R. Martin	Children's National Medical Center	None	None	None	None	None	None	None
Stanford T. Shulman	Lurie Children's Hospital, Children's Memorial Hospital, Northwestern University Medical School	None	None	None	None	None	None	None
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