36 Kawasaki Disease

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While an acute systemic vasculitis, Kawasaki Disease (KD) morbidity and mortality is related to the development of coronary artery aneurysms. Coronary aneurysms can occur in up to 25% of those who are not treated within the first 10 days of illness, so prompt recognition and appropriate therapy are essential.

The definitive etiology of KD is unknown. However, the current prevailing theory is that there is an inciting trigger (possibly a viral or bacterial infection, or exposure to some environmental agent) that provokes an autoimmune response in genetically susceptible individuals. The most common age for children to have KD is between 2 and 8 years, although cases in children as young as 1 month and as old as 18 years have been reported.

Clinical Presentation and Diagnosis

In 2017, the AHA published the updated Scientific Statement on the Diagnosis, Treatment, and Long-Term Management of Kawasaki Disease (McCrindle et al. 2017). This statement provides much of the foundation for the care outlined in this chapter. The diagnosis of KD is based on clinical criteria.

Table 36-1 lists the criteria for diagnosis of complete and incomplete KD. For patients who do not meet the criteria for complete KD, incomplete (sometimes referred to as atypical) KD should be considered. Incomplete KD occurs more frequently in very young infants, or those at the older age of the spectrum.

Signs, Symptoms, and Other Infections

Concurrent viral respiratory infections can occur in complete or incomplete KD and do not exclude a diagnosis of KD. If a patient has exudative pharyngitis or exudative conjunctivitis, however, KD is very unlikely. KD can occur in patients with group-A streptococcal infection. KD should be considered if the patient has some principal features of KD, and fever uncharacteristically persists after treatment with appropriate antibiotic therapy. KD should also be considered in infants or children with prolonged fever and unexplained or culture negative shock, or cervical adenitis unresponsive to antibiotic therapy.

While not considered one of the 5 principal clinical features, marked irritability is a hallmark of the ill KD patient. Many other nonspecific symptoms can occur, including but not limited to abdominal pain, vomiting, diarrhea, jaundice, arthralgias, arthritis, or aseptic meningitis. Hydrops of the gallbladder can be seen as well.

KD Shock Syndrome

KD shock should be suspected in patients requiring fluid boluses or inotropic support and those with hypotension and tachycardia in excess of that expected for the degree of fever, presence of a gallop, or hepatomegaly. Decreased ventricular function will usually be demonstrated on echocardiogram. KD shock patients typically have prolonged clinical and laboratory findings of inflammation. They are more prone to be resistant

Table 36-1. Diagnostic criteria for complete and incomplete KD (McCrindle et al. 2017)

Complete KD
Diagnosis of complete KD is made if ≥5 days of fever (counting the day of fever onset as the first day of fever) and at least 4 of the following principal clinical features: • Bilateral bulbar nonexudative conjunctivitis • Rash (maculopapular, diffuse erythroderma, or erythema multiforme-like) • Oral mucous membrane changes (strawberry tongue, dry, cracked lips, erythema of mouth, lips, pharynx) • Extremity changes - Hand and foot erythema and edema (may be painful) - Periungual finger and toe desquamation (occurs in subacute phase, 2-3 weeks after fever onset) • Cervical lymphadenopathy (>1.5 cm, typically unilateral) The diagnosis of KD can be made on the 4th day of fever if ≥4 of these features are present, particularly if the patient has redness and swelling of the hands and feet. It is important to note that the principal clinical features, aside from fever, may not and often do not occur simultaneously or continuously and thus may only be elicited by thorough history of observations by a parent, pediatrician, or other care provider.
Incomplete KD
Children with fever for ≥5 days with 2-3 principal clinical features can be diagnosed with incomplete KD on the basis of supportive labs and/or a positive echocardiogram. In infants <6 months of age with fever for ≥7 days and irritability, KD should be considered even the absence of any other clinical features. • **Supportive laboratory criteria.** Elevated acute-phase reactants (erythrocyte sedimentation rate [ESR] ≥40 mm/hr and C-reactive protein [CRP] ≥3 mg/dl) *and* 3 or more of the following: - Anemia for age - Platelet count ≥450,000 after the 7th day of fever - Hypoalbuminemia of ≥3 g/dL - Elevated ALT - WBC >15,000 /uL - Sterile pyuria: urine with ≥10 WBC/hpf • **Echocardiographic criteria** - Coronary dilation: Z-score of LAD or right coronary artery ≥2.5 - Coronary artery aneurysm - ≥3 other suggestive features ▪ Decreased LV function ▪ MR ▪ Pericardial effusion ▪ Z-scores in LAD or right coronary artery ≥2 but <2.5

to intravenous immunoglobulin (IVIG) and exhibit a higher risk for coronary changes. Echocardiography to assess ventricular function in this scenario is important prior to beginning treatment with IVIG to help determine if the rate of infusion should be decreased.

Table 36-2. Recommended labs for workup and follow-up of KD patients

Recommended labs
• Initial labs: CBC with differential, liver panel, C-reactive protein (CRP), erythrocyte sedimentation rate (ESR), D-dimer, basic metabolic panel, and urinalysis. • Repeat inflammatory markers (CRP, D-dimer, CBC) are recommended prior to discharge in uncomplicated cases to ensure expected improvement and to help determine need for additional therapy. Caveats: ESR will be high for 4-6 weeks post-IVIG and should then not be used to assess for improvement. Platelet counts will be expected to rise after the 7th day and through the 14th day of illness. • Repeat labs early and often if the course is complicated or not standard. • Repeat labs ~1 week from discharge may be necessary if labs are abnormal at discharge. • If lab abnormalities persist after 1 week, discuss with Rheumatology.

Management

The management of patients with KD requires a comprehensive and multidisciplinary approach during workup and follow-up of patients. This approach includes a combination of labs, imaging studies, medications, consultations, and follow-up plan.

Table 36-2 lists recommended labs during workup and follow-up of patients with KD. A baseline ECG should be obtained during the acute illness in the hospital. Subsequently, ECGs will be obtained depending on clinical course. For those with severe or complex coronary involvement, ECGs should be routinely obtained as coronary ischemia or infarct in KD can be silent.

The goal of therapy during the acute phase is to reduce inflammation, thus reducing arterial damage and thrombus formation.

Medications in Uncomplicated KD

IVIG (2 g/kg over 10-12 hours) is the first line therapy for KD and should be administered as soon as the diagnosis is made. It can be administered before an echocardiogram is performed if the patient fulfills clinical criteria. However, even with treatment within the first 10 days of fever, 20% will develop coronary artery changes and a smaller number will still develop aneurysms.

Medium-dose (30-50 mg/kg) or high-dose (80-100 mg/kg) *aspirin* is given until the patient is afebrile for 48 hours. Data does not favor either high or medium dosing for prevention of aneurysms. Subsequently, aspirin dosage is changed to low dose for antiplatelet effect (3-5 mg/kg/day once a day). Low-dose aspirin is continued for 6-8 weeks in uncomplicated cases with an echocardiogram at the end of the subacute phase. Aspirin is continued on if there is significant coronary artery dilation or aneurysms.

Medications in Complicated KD

Clopidogrel (Plavix®) may be considered as an adjunctive antiplatelet agent if platelet count exceeds 1,000,000 /mcL, if there is coronary dilation of ≥6 but <8 mm, if complex coronary artery disease at particularly high risk of stasis and thrombosis, if there is nonocclusive coronary thrombus, or if the individual is an aspirin nonresponder.

Anticoagulation is initiated in the presence of giant aneurysms (≥8 mm or ≥10 Z-scores). *Enoxaparin* (Lovenox®) is the agent of choice to ensure the most stable and

consistent levels of anticoagulation, as there is some evidence to suggest that there is improved coronary remodeling with enoxaparin compared to warfarin. It is important to maintain therapeutic anti-factor Xa levels of 0.8-1.0 IU/mL.

After the second year of illness, patients requiring long-term anticoagulation (i.e., if persistent giant aneurysms or history of thrombosis) will be transitioned to *warfarin*, with a target INR of 2-3.

Additional anti-inflammatory agents (e.g., methylprednisolone, infliximab, etanercept, anakinra, and cyclosporine) will be considered by the Rheumatology service if:

- Recurrent or persistent fevers 36 hours after IVIG completed (a second round of IVIG may also be employed in this situation)
- Ongoing or uptrending markers of inflammation or persistent signs of clinical illness (the primary clinical features or irritability)
- High-risk for development of severe coronary artery disease
- Significant coronary dilation or aneurysms on initial echocardiogram (Z score >4 or size >6 mm)

Statins are considered for use in KD patients >6 years (and younger ages currently under investigation) with severe coronary disease due to their pleotropic (non-lipid lowering) anti-inflammatory properties and positive effects on arterial endothelial function.

Beta-blockers may be employed in those with coronary stenosis, ischemia, or infarction.

Tissue plasminogen activator (tPA) could be considered in consultation with hematology adult cardiology, the cardiac catheterization team, and the ICU in the presence of total or near total coronary artery occlusion, or evidence of significant ischemia (elevated troponin, ST segment changes, segmental function changes).

Echocardiographic Recommendations

Echocardiography provides essential diagnostic information and its findings will often guide therapy in KD patients (Figure 36-1). Multiple views are important to assess the coronaries thoroughly for evolution of dilation or aneurysms, or presence of thrombus. Sedation should be considered in these irritable infants and toddlers, to obtain the high-quality and complete studies necessary. The following are recommended guidelines during diagnosis and management of these patients:

- An initial echocardiogram should be performed within 24 hours of diagnosis. If the patient meets clinical KD criteria, there is no need to delay treatment while waiting for the echocardiogram.
- If the patient responds to IVIG:
  - Schedule the second echocardiogram with a cardiology clinic visit for 14 days after the onset of fever (this marks the beginning of the subacute phase).
  - Schedule the third echocardiogram with a cardiology clinic visit within 6-8 weeks from the onset of fever (this marks the end of the subacute phase and the beginning of the convalescent phase).
- If the patient does not respond to IVIG and requires additional therapy, the patient will require a subsequent echocardiogram within a few days and prior to discharge.
- If the patient has significant coronary abnormalities including aneurysms or dilation >4 Z-scores:

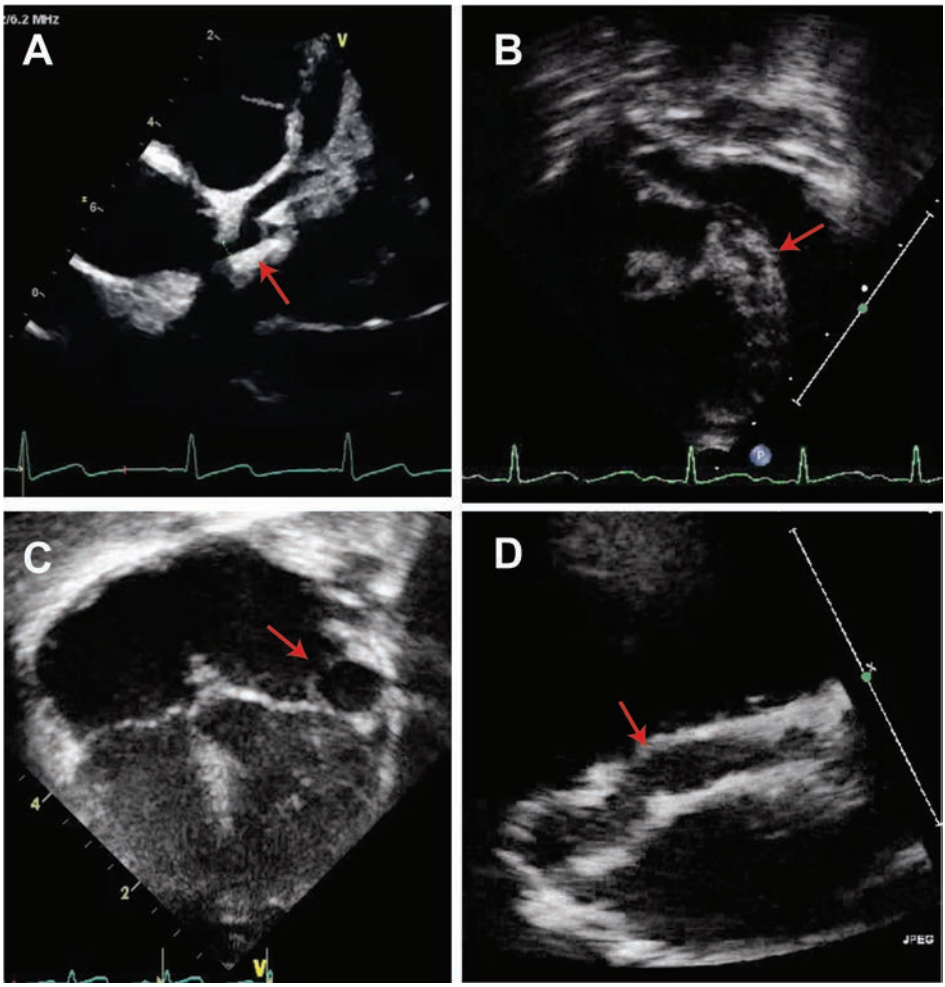

Figure 36-1. Echocardiographic images of patients with Kawasaki disease showing dilation of the proximal left anterior descending artery (A, arrow), mid left anterior descending artery (B, arrow), circumflex artery (C, arrow), and right coronary artery (D, arrow).

- While coronaries may be rapidly expanding, repeat echocardiogram every 2-4 days as guided by Cardiology consult until evidence for coronary artery stabilization and downtrending evidence of inflammation, as well as improvement or resolution of irritability and principal clinical features.
- For those with giant aneurysms, obtain twice weekly echocardiograms as surveillance for thrombus until coronary size is stabilized. Subsequently, these patients require weekly echocardiographic surveillance for at least 1 month, then biweekly for at least another month, monthly for up to 3 months, then at

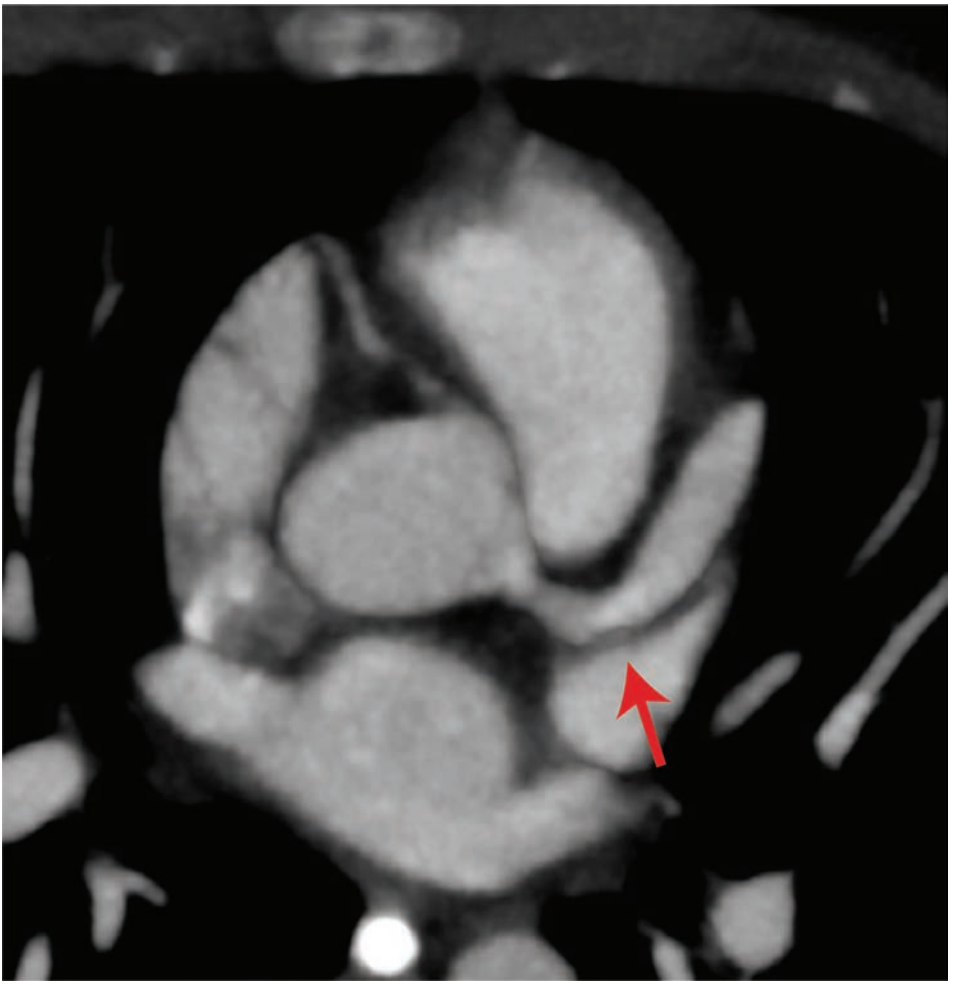

Figure 36-2. CTA of a patient with KD showing significant proximal dilation of the left coronary artery (arrow).

least every 3 months throughout the first year. Color Doppler is essential in the assessment of flow in the coronaries in these patients.

Additional Studies

CTA provides valuable information about the entire coronary distribution (Figure 36-2). Initial CTA is considered in patients with significant proximal coronary involvement. The CTA may also be expanded to include investigation of chest, abdomen, and pelvis to assess for other vascular involvement. Subsequent CTAs are obtained under the guidance of the cardiologist for those with severe or complex coronary artery involvement to assess for changes in coronary size or evolution of coronary stenosis or thrombosis. *Cardiac MRI* is used to assess for perfusion imaging and myocardial scarring in patients

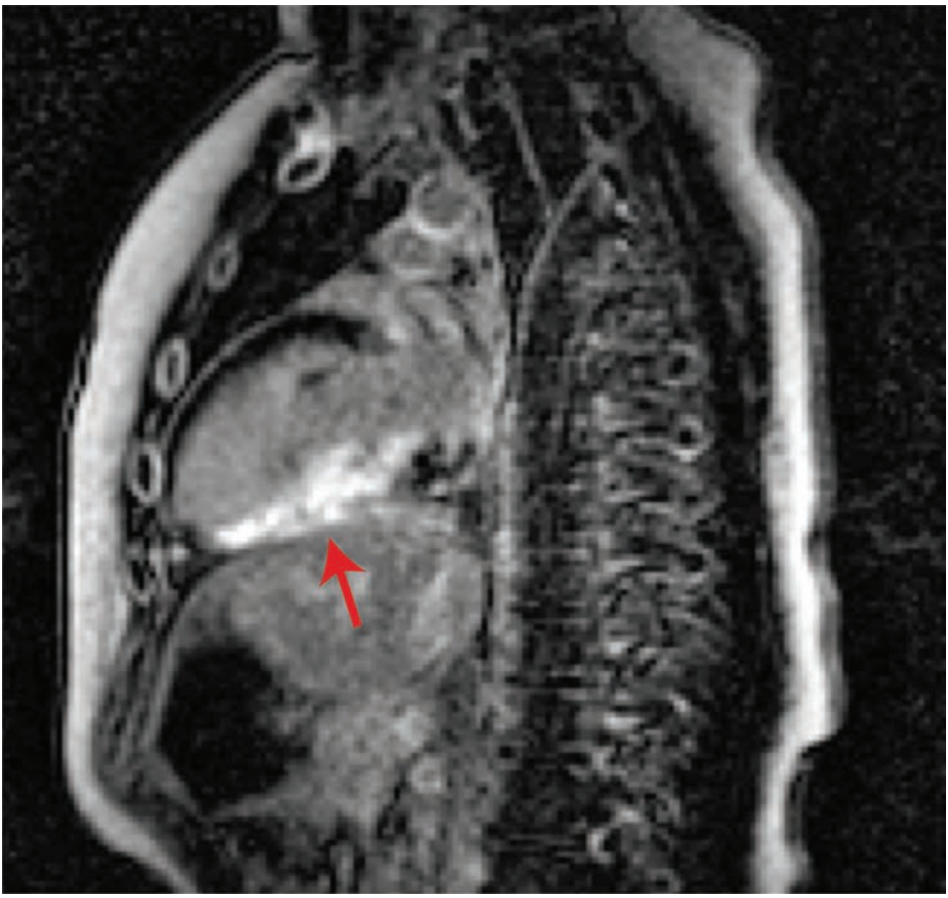

Figure 36-3. Cardiac MRI with late Gadolinium enhancement on a patient with KD showing a diffuse inferior LV infarct (arrow).

being followed with persistent or history of previous significant dilation or aneurysms. Pharmacologic stress MRI may be used to assess for inducible myocardial ischemia (Figure 36-3).

Once a child is old enough to cooperate, *nuclear or echocardiographic stress tests* can be added as additional methods of assessing at-risk myocardium or scarring. These have the benefit of being "real exercise" and thus demonstrating a more physiologic response. The need for *invasive angiography* (Figure 36-4) is guided by symptoms suggestive of ischemia or the findings of ischemia or significant coronary stenosis on CTA, MRI, or other stress tests. Cath is still better than any other imaging test to assess collateral supply. Assessment of functional flow reserve (FFR) can help determine hemodynamic significance of coronary stenoses.

Hospital Consults

Cardiology should be consulted in the following scenarios:

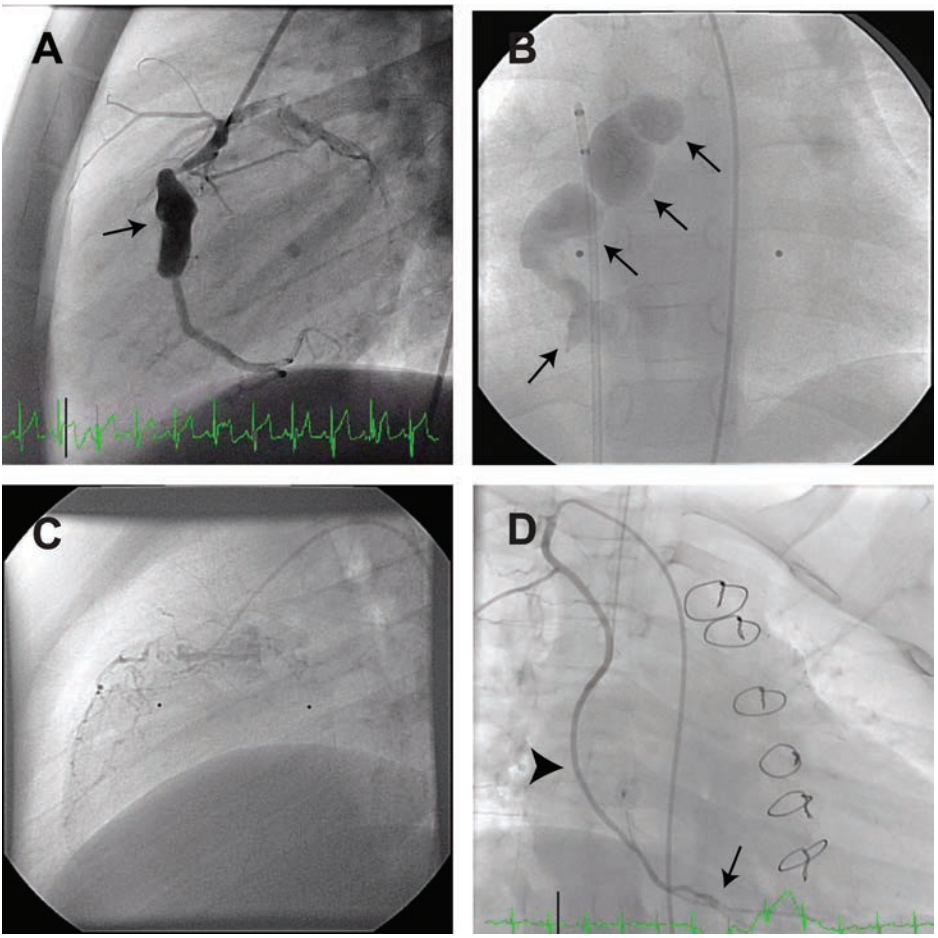

Figure 36-4. Cardiac catheterization images in patients with KD. A) Patient with a large aneurysm of the right coronary artery (arrow). B) Patient with complex aneurysms of the right coronary artery (arrows). C) Patient with occluded right coronary artery and multiple collateral vessels around the area of obstruction. D) Patent right internal mammary coronary bypass graft (arrowhead) providing supply to the distal right coronary circulation (arrow).

- All children with KD or suspicion of KD <1 year of age
- Abnormalities noted on initial or subsequent echocardiograms (including coronary artery dilation or aneurysm, thrombus, ventricular dysfunction or change in function, pericardial effusion, valvulitis)
- Concern regarding echocardiographic read
- Prolonged fever (≥10 days on presentation)
- Atypical clinical course (e.g., recurrence or persistence of fever, repeat dose of IVIG, use of adjunctive anti-inflammatory therapy)
- Help with diagnosis or treatment questions including if enoxaparin or clopidogrel is needed

Table 36-3. Important family counseling tips for patients with KD

Family counseling tips
• Coronary artery disease can worsen over the first 8 weeks of illness – a normal first echocardiogram does not ensure normal coronaries throughout the course of the disease. • Children CAN get KD again, usually in the first 2 years after initial diagnosis. • Siblings are at a slightly increased risk of getting KD as are children of parents who have had KD. • Follow-up with Cardiology is at least childhood-long but infrequent if the coronary arteries are normal throughout. • Signs and symptoms of KD typically do not occur simultaneously. Therefore, patients are frequently seen by healthcare providers several times prior to obtaining the diagnosis. • There is a slight increase in risk of autoimmune/inflammatory disease in adults who have had KD.

- KD shock syndrome

Other consulting services may include Rheumatology (for infants <6 months of age, an atypical clinical course, prolonged fever on presentation, KD shock syndrome, or significant coronary abnormalities), Hematology (to help with anticoagulation), and Infectious Disease.

Follow-Up

All patients are seen in the Cardiology clinic within 1-2 weeks after hospital discharge (depending upon clinical course and coronary involvement), 6-8 weeks after initial fevers, and then at least at 1 year from onset of illness. KD patients with history of persistent or regressed aneurysms require continued follow-up indefinitely. Table 36-3 lists some important family counseling tips.

It is important to track the largest diameters of coronary dilation or aneurysm and corresponding Z-scores, as these have important implications for long-term outcomes. Patients with KD and moderate or larger aneurysms/dilation are at risk for a continued vasculopathy ongoing for years. This can lead to coronary stenosis, thrombosis, ischemia, infarct, ventricular dysfunction, arrhythmias, and need for eventual intervention.

Long-term prognosis for those who never develop aneurysms or significant dilation, and for those with aneurysms/dilation that have regressed significantly or resolved, is generally excellent.

In all cases, providers must engage in regular counseling on healthy lifestyle, including maintaining a healthy weight, normal BP, a healthy diet, and normal cholesterol levels to avoid other risk factors for coronary artery disease. Avoidance of tobacco product use and participation in regular active play or exercise are also essential.

Intervention is generally restricted to those with documented ischemia or at-risk myocardium by FFR or stress imaging, or those with coronary stenoses and concerning symptoms for ischemia. Coronary bypass grafting with an internal mammary artery can provide long-term benefit in children as young as 2 years of age. However, this depends upon having an adequate size distal target for the bypass anastomosis. Catheter based intervention, including ballooning or stenting of narrowings, may rarely be considered when vessels are not amenable to bypass or other intervention

in the post-KD setting. However, need for frequent reintervention should be expected. KD patients may also develop collateral flow around or through thrombosed vessels and significantly contribute to myocardial perfusion.

Suggested Readings

Giglia TM, Massicotte MP, Tweddell JS, et al. Prevention and treatment of thrombosis in pediastric and congenital heart disease: A scientific statement from the AHA. Circulation 2013;128:2622-2703.

Manlihot C, Brnadao LR, Somji Z, et al. Long-term anticoagulation in Kawasaki disease: initial use of low molecular weight heparin is a viable option for patients with severe coronary artery abnormalities. Pediatr Cardiol 2010;31:834-842.

McCrindle BW, Rowley AH, Newburger JW, et al. Diagnosis, Treatment, and Long-Term Management of Kawasaki Disease: A Scientific Statement for Health Professionals From the American Heart Association. Circulation. 2017;135:e927-e999.