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AHA SCIENTIFIC STATEMENT

Update on Diagnosis and Management of Kawasaki Disease: A Scientific Statement From the American Heart Association

Pei-Ni Jone, MD, FAHA, Chair; Adriana Tremoulet, MD, MAS, FAHA; Nadine Choueiter, MD, FAHA;
Samuel R. Dominguez, MD, PhD, FAHA; Ashraf S. Harahsheh, MD, FAHA; Yoshihide Mitani, MD, PhD, FAHA;
Meghan Zimmerman, MD, MPH, FAHA; Ming-Tai Lin, MD, PhD; Kevin G. Friedman, MD, FAHA, Vice Chair; on behalf of the
American Heart Association Rheumatic Fever, Endocarditis, and Kawasaki Disease Committee of the Council on Lifelong
Congenital Heart Disease and Heart Health in the Young; Council on Cardiovascular and Stroke Nursing; Council on
Cardiovascular Radiology and Intervention; and Council on Clinical Cardiology

ABSTRACT: Kawasaki disease (KD), an acute self-limited febrile illness that primarily affects children <5 years old, is the leading cause of acquired heart disease in developed countries, with the potential of leading to coronary artery dilation and coronary artery aneurysms in 25% of untreated patients. This update summarizes relevant clinical data published since the 2017 American Heart Association scientific statement on KD related to diagnosis, cardiac imaging in acute KD treatment, and long-term management. Criteria defining North American patients at high risk for developing coronary artery aneurysms who may benefit from more intensive initial treatment have been published. Advances in cardiovascular imaging have improved the ability to identify coronary artery stenosis in patients with KD, yet knowledge gaps remain regarding optimal frequency of serial imaging and the best imaging modality to identify those at risk for inducible myocardial ischemia. Recent data have advanced the understanding of safety and dosing for several anti-inflammatory therapies in KD. New anticoagulation medication, myocardial infarction management, transition of health care for patients with KD, and future directions in research are discussed.

Key Words: AHA Scientific Statements ■ coronary aneurysm ■ diagnosis ■ heart disease ■ immunoglobulins, intravenous ■ mucocutaneous lymph node syndrome ■ thrombosis ■ vasculitis

Kawasaki disease (KD) is an acute febrile illness that primarily affects children <5 years old and is the leading cause of acquired heart disease in children in developed countries. Without treatment, ≈25% of patients develop coronary artery (CA) dilation or CA aneurysms (CAAs).[1] The incidence of KD in the United States is 18 to 25 per 100 000 in children <5 years old; the incidence is 10 to 30 times higher in northeast Asian countries, including Japan, South Korea, China, and Taiwan.[1,2] The pathogenesis of KD remains unknown and the diagnosis is based on established clinical criteria.[1]

This update highlights key points about KD and summarizes relevant clinical data published since the 2017 American Heart Association (AHA) scientific statement on KD related to diagnosis, cardiac imaging in acute KD treatment, and long-term management.[1] Although the

diagnostic criteria have not changed since the last statement, early diagnosis of KD remains crucial to reduce the risk of CAA. Criteria defining North American patients at high risk for developing CAA who may benefit from more intensive initial treatment have been published.[3] Advances in cardiovascular imaging have improved the ability to identify CA stenosis in patients with KD, but knowledge gaps remain regarding optimal frequency of serial imaging and the best imaging modality to identify those at risk for inducible myocardial ischemia.[4–7] Recent data have advanced the understanding of safety and dosing for several anti-inflammatory therapies in KD. Several studies have suggested that acute intensification of primary anti-inflammatory therapy in high-risk patients may improve CA outcomes.[8–10] Large cohort studies and international registries have provided data on outcomes and

risk factors for adverse cardiac events, including findings that children with transient CA dilation or small CAA (CA Z score <5) are at minimal risk for adverse cardiac events and almost universally have remodeling of CAA to normal internal lumen diameter.[11–14] There remains a substantial gap in transition of care for adults with KD and management of women with KD and giant aneurysms receiving long-term anticoagulation who plan on becoming pregnant. Future directions in research on diagnosis and management of patients with KD are discussed.

DIAGNOSIS

KD remains a clinical diagnosis characterized by fever, unilateral lymphadenopathy, rash, bilateral nonexudative conjunctival injection, swelling and erythema of the hands and feet, and oropharyngeal findings, including strawberry tongue and erythematous lips.[1] The algorithm for diagnosing complete or incomplete KD, with supportive laboratory features, is shown in Figure 1. In the presence of ≥4 principal clinical features, the diagnosis of KD can be made with 4 days of fever.[1] Experienced clinicians may establish the diagnosis earlier, at 3 days of fever.[1,15] Other pediatric febrile illnesses that share clinical features with KD need to be considered when evaluating infants and children for suspected KD. Certain clinical findings, including oral ulcerations, exudative pharyngitis, exudative or unilateral conjunctivitis, and vesicular rash, are not characteristic of KD.

KD shock syndrome is a rare but severe form of the illness in which patients present with vasodilatory shock, hypotension, and poor perfusion, with or without myocardial dysfunction.[16] Because there is no pathognomonic test for KD, KD and its associated shock syndrome can be difficult to distinguish clinically from other hyperinflammatory disorders. For example, in 2020, with the emergence of SARS-CoV-2 and subsequent recognition of multisystem inflammatory syndrome in children (MIS-C), this new condition became part of the differential diagnosis of KD.[17–19] MIS-C and KD have clinical similarities, but it has become increasingly clear over the course of the COVID-19 pandemic that they are distinct illnesses. Certain clinical characteristics (eg, prominent gastrointestinal symptoms [abdominal pain, vomiting, diarrhea], headache), laboratory findings (eg, thrombocytopenia, lymphopenia, elevated troponin or BNP [B-type natriuretic peptide] levels), and cardiac findings (eg, decreased left ventricular systolic function, pericardial effusion) are more prominent in patients with MIS-C.[17–22] Rash, conjunctival injection, oral mucosal changes, and CA abnormalities are more common in patients with KD. The incidence of MIS-C has decreased substantially since 2022, potentially because of widespread immunity to SARS-CoV-2 or decreased ability of newer variants of SARS-CoV-2 to cause MIS-C.[23] Machine learning algorithms have been developed that may help clinicians distinguish between KD and MIS-C.[24]

It is imperative to diagnose KD within 10 days of fever onset, ideally at 4 to 5 days of illness for patients with complete KD, and as soon as possible and within 10 days of fever onset for patients with a possible diagnosis of incomplete KD. Treatment within 10 days of fever onset is strongly associated with a lower risk of CA dilation or aneurysms. Identification of patients at high risk for developing CAA at the time of diagnosis allows for intensification of primary anti-inflammatory therapy, which may improve CA outcomes. Although identification of all children with KD at risk of developing CAA in a multiethnic population remains a challenge, some criteria for North American patients have been published. These include age <6 months and CA Z score ≥2.5 on the initial echocardiogram.[25,26] Children <1 year of age are at higher risk of developing CAA than older patients, as documented in the prevalence of CAAs in patients between 6 and 12 months of age (40%) and those <6 months of age (68%).[27] Studies have shown that infants <6 months of age are at a particularly high risk for development of CAAs, with nearly 50% of these infants having a baseline echocardiogram with CA Z score ≥2.5.[25,26] Son et al[3] established risk score criteria in the North American population comprising age <6 months, Asian race, CA Z score >2 on initial echocardiogram, and C-reactive protein >13 mg/dL (each with 1 point assigned, with the exception of 2 points assigned to CA). A risk score ≥3 points is strongly predictive of CAA by 8 weeks after acute illness. Whereas this risk score emphasizes the higher risk of age <6 months, high-risk criteria in Japan include age <12 months. Criteria for defining patients at high risk for CAAs are important; recent data suggest that high-risk patients may benefit from intensification of primary anti-inflammatory therapy, as discussed in KD Treatment.

Key Points

1. KD remains a clinical diagnosis without a pathognomonic diagnostic test.
2. In the presence of ≥4 principal clinical features, the diagnosis of complete KD can be made with 4 days of fever.
3. Diagnostic criteria for incomplete KD remain unchanged, although clinicians are encouraged to diagnose KD early to prevent CA dilation and aneurysms.
4. MIS-C should be added to the differential diagnosis of KD, although the prevalence of this condition has decreased markedly since 2022.
5. Although it remains difficult to identify all children with KD at risk for developing CAA in multiethnic populations, substantial data indicate that right CA or left anterior descending Z score ≥2.5 at diagnosis and age <6 months are high-risk features in multiple racial and ethnic groups, and these patients should be considered for intensification of primary therapy.
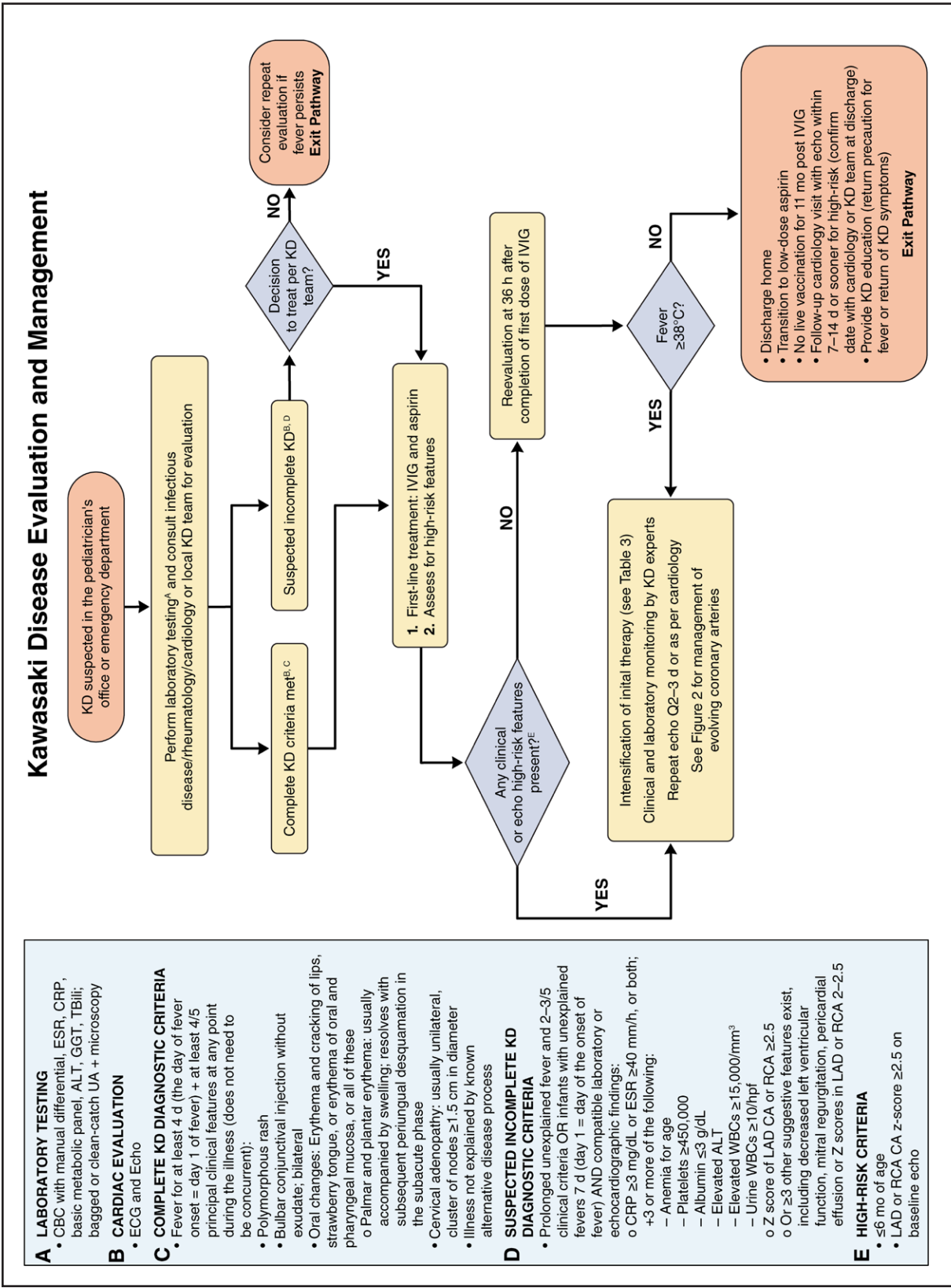
Kawasaki Disease Evaluation and Management

A LABORATORY TESTING
- CBC with manual differential, ESR, CRP, basic metabolic panel, ALT, GGT, TBili; bagged or clean-catch UA + microscopy

B CARDIAC EVALUATION
- ECG and Echo

C COMPLETE KD DIAGNOSTIC CRITERIA
- Fever for at least 4 d (the day of fever onset = day 1 of fever) + at least 4/5 principal clinical features at any point during the illness (does not need to be concurrent):
  - Polymorphous rash
  - Bulbar conjunctival injection without exudate; bilateral
  - Oral changes: Erythema and cracking of lips, strawberry tongue, or erythema of oral and pharyngeal mucosa, or all of these
    - o Palmar and plantar erythema: usually accompanied by swelling; resolves with subsequent periungual desquamation in the subacute phase
  - Cervical adenopathy: usually unilateral, cluster of nodes ≥1.5 cm in diameter
  - Illness not explained by known alternative disease process

D SUSPECTED INCOMPLETE KD DIAGNOSTIC CRITERIA
- Prolonged unexplained fever and 2–3/5 clinical criteria OR infants with unexplained fevers 7 d (day 1 = day of the onset of fever) AND compatible laboratory or echocardiographic findings:
  - o CRP ≥3 mg/dL or ESR ≥40 mm/h, or both; +3 or more of the following:
    - Anemia for age
    - Platelets ≥450,000
    - Albumin ≤3 g/dL
    - Elevated ALT
    - Elevated WBCs ≥15,000/mm^3
    - Urine WBCs ≥10/hpf
  - o Z score of LAD CA or RCA ≥2.5
  - o Or ≥3 other suggestive features exist, including decreased left ventricular function, mitral regurgitation, pericardial effusion or Z scores in LAD or RCA 2–2.5

E HIGH-RISK CRITERIA
- ≤6 mo of age
- LAD or RCA CA z-score ≥2.5 on baseline echo

Figure 1. Diagnostic algorithm for diagnosis and management of Kawasaki disease.
ALT indicates alanine aminotransferase; CA, coronary artery; CBC, complete blood count; CRP, C-reactive protein; ESR, erythrocyte sedimentation rate; GGT, gamma-glutamyl transferase; IgG, immunoglobulin G; KD, Kawasaki disease; LAD, left anterior descending; RCA, right coronary artery; UA, urinalysis; and WBC, white blood cell.

CARDIAC IMAGING IN ACUTE KD
Echocardiography

Echocardiography is the primary imaging modality in KD. It is noninvasive and has high spatial and temporal resolution, allowing rapid visualization of proximal CA abnormalities. Imaging standards for echocardiography in patient preparation, technical standards of evaluating coronaries, and quantitative assessments of cardiac findings are described in Table 1. The proximal left anterior descending artery and the proximal right CA are the most frequent locations of CAA, and the posterior descending artery is the least common.[1,28] The left main CA rarely has CAA in the absence of CAA in the left anterior descending or left circumflex artery. Measurements of CA luminal dimension are normalized to body surface area using Z scores. The 2017 AHA statement adopted a Z score–based classification for CAAs.[1] The 2020 Japanese guidelines also adopted a Z score–based classification for CAAs.[29,30] Routine use of CA Z scores has brought a level of standardization to quantification of CA size, but challenges remain. A small error in measurement of the CA dimension can translate into a significant difference in Z scores, changing the CA classification, particularly in young patients. Accurate weight and height measurements are necessary for accurate body surface area calculation to avoid errors in measurements that may lead to over- or underestimation of CA Z scores. There are several published CA Z score

Table 1. Echocardiographic Imaging Standards for Patients With Kawasaki Disease

Patient preparation	Coronary artery technical evaluations	Qualitative assessment	Quantitative assessment
Equipment 1. Highest-frequency transducer possible 2. Dynamic video or digital cine recording	LMCA: 1. PSAX at level of AoV 2. PLAX of LV (superior tangential) 3. Subcostal ventricular long axis	Presence of coronary artery aneurysms or thrombus	Coronary artery lesions Z score, normalization to BSA 1. No involvement: always Z<2 2. Dilation only: 2 to <2.5 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 It is reasonable to repeat the echocardiogram in the acute phase more frequently in patients with CA involvement until CA dimensions stabilize or before discharge in those with high-risk clinical features (age <6 mo or with coronary Z scores ≥2.5 at baseline)
Sedation might be considered in: 1. Age <3 y 2. Uncooperative or irritable children	LAD: 1. PSAX at level of AoV and LV, distal LAD (courses anterior to the PV) 2. PLAX of LV (superior tangential)	Regional wall motion abnormalities	Ventricular function 1. LV ejection fraction or M-mode (LV dysfunction seen in 20% at presentation associated with CA lesions[33]) 2. LV end diastolic volume or dimensions 3. LV end systolic volume or dimensions 4. LV/RV diastolic function 5. LV strain
	Left circumflex branch: 1. PSAX at level of AoV 2. Apical 4-chamber (inferior) in left AV groove		Presence or degree of AV regurgitation
	RCA, proximal segment: 1. PSAX at level of AoV 2. PLAX (inferior tangential) of LV 3. Subcostal coronal projection of RVOT 4. Subcostal SAX at level of AV groove		Presence and size of pericardial effusion
	RCA, middle segment: 1. PLAX of LV (inferior tangential) 2. Apical 4-chamber 3. Subcostal LV long axis 4. Subcostal SAX at level of AV groove		Size of the aortic root (>10% of patients with KD have an aortic Z score >2)
	RCA, distal segment: 1. Apical 4-chamber (inferior) 2. Subcostal atrial long axis (inferior)		
	Posterior descending coronary artery: 1. Apical 4-chamber (inferior) 2. Subcostal atrial long axis (inferior) 3. PLAX (inferior tangential) 4. Posterior interventricular groove		

AoV indicates aortic valve; AV, atrioventricular; BSA, body surface area; KD, Kawasaki disease; LAD, left anterior descending; LMCA, left main coronary artery; LV, left ventricle; PLAX, parasternal long axis; PSAX, parasternal short axis; PV, pulmonary valve; RCA, right coronary artery; RV, right ventricle; RVOT, right ventricular outflow tract; and SAX, short axis.

systems.[30–34] A standard CA Z score system has not been established, resulting in variability of which system is used across studies. Studies have shown that when comparing the different Z score systems, the CA risk level classification may change.[35–37] Thus, it is important for centers to use the same Z score equation for comparisons over time in patients with KD. The CA risk stratification adopted in the 2017 AHA scientific statement[1] and the current scientific statement are based on formulas provided in the study from the National Heart, Lung, and Blood Institute Pediatric Heart Network.[32]

Obtaining an echocardiogram should not delay the initiation of therapy, and normal results do not exclude KD diagnosis.[1,38] When results are abnormal, the echocardiogram is a useful adjunct to diagnosis. Normal baseline echocardiogram results in the first week of illness do not exclude the possibility of later development of a CAA. An echocardiogram should be repeated during hospitalization and before discharge in patients with high-risk clinical features or IV immunoglobulin (IVIg) resistance (defined as a persistent or recrudescent fever ≥36 hours after completion of the initial IVIg infusion). Fever, clinical status, and laboratory findings are monitored closely during hospitalization. Patients with recurrence of fever in the week after discharge need to have an urgent echocardiogram unless there is a clear alternative diagnosis.

In patients with no CA involvement during hospitalization, an echocardiogram is repeated within 1 to 2 weeks after discharge, as a small number of patients will develop coronary enlargement within a week or two after discharge, and earlier detection allows for prompt institution of adjunctive anti-inflammatory therapy. In patients who respond to anti-inflammatory therapy and have normal echocardiogram results at diagnosis and at 1 to 2 weeks after discharge, the likelihood of developing CA changes is extremely low. A recent study showed that in this patient population, 98.6% have normal echocardiogram results at 4 to 6 weeks, suggesting these patients with KD may not need any further cardiac follow-up unless new concerns develop.[39] The rare patients (1.4%) who had evidence of new CA changes at 4- to 6-week follow-up after initially normal echocardiogram results all had CA Z score <5, and CA changes were transient with return to normal CA dimensions in the first year of follow-up. In risk level 2 patients (CA Z score between 2 and 2.5), follow-up is recommended at 1 to 2 weeks after hospital discharge, and a repeat visit at 4 to 6 weeks if echocardiogram results, clinical status, or laboratory values are abnormal at 1 to 2 weeks (Table 2). However, patients in whom coronary arteries were not well imaged or in whom inflammation has not substantially improved require repeat imaging earlier than 4 to 6 weeks. In patients with CA Z score ≥2.5, it is reasonable to repeat the echocardiogram at least twice per week during the hospitalization until the dilation or aneurysms have stopped progressing (Figure 2). The maximum CA Z score reached during the illness is the strongest predictor of outcome and guides AHA risk level classification and ongoing management (Table 2). An echocardiogram at discharge and a follow-up visit with an echocardiogram within 1 week is reasonable for patients with CA Z score ≥2.5. CA dilation does not exclude or confirm that the arterial wall has been damaged, whereas documentation of an anatomic aneurysm does.[40] Z score alone cannot determine the nature of injury to the CAs.

Other cardiac evaluation using echocardiography is listed in Table 1. Myocardial dysfunction with reduced shortening fraction is seen in 20% of patients at diagnosis and is associated with CA dilation or CAA.[41] Deformation imaging, including ventricular and atrial strain, is increasingly used in KD; however, its clinical use and effect on outcome is yet to be determined.[42]

Key Points

1. Echocardiography remains the primary noninvasive imaging method for assessing the CAs, and accurate measurement of the CAs is crucial in patients with KD.
2. Centers should use the same Z score equation for comparison over time in patients with KD; using different Z score equations will change the CA risk classification.
3. Obtaining accurate weight and height can prevent over- or underestimation of CA Z scores.
4. The CAA classifications as defined by the 2017 AHA scientific statement are useful from the epidemiologic perspective. Z score alone cannot determine the nature of injury to the CAs.

KD TREATMENT

Treatment for KD starts with recognizing standard versus high-risk cases at diagnosis. Patients with standard risk can be treated with IVIg and aspirin. Patients with high risk may benefit from intensification of therapy with IVIg plus adjunctive anti-inflammatory therapy to reduce the risk of CAA. This section describes the initial therapy for acute KD, treatment of IVIg resistance, intensification of initial therapy in patients with high risk, and additional therapies for patients with refractory KD.

Initial Therapy in Acute KD

IVIg at 2 g/kg infused over 8 to 12 hours remains the standard of care for patients with acute KD to reduce inflammation. There is variability in the infusion time for IVIg depending on the brand of IVIg that is used in different hospitals. Patients with persistent or recrudescent fever ≥36 hours after the completion of the initial IVIg infusion are defined as IVIg resistant. IVIg is

Table 2. Long-Term Management, Thromboprophylaxis, and Medical Therapy for Kawasaki Disease

Classification of risk level	Description of coronary arteries	Follow-up frequency after the patient has stable coronaries or improved dimensions at discharge from hospital: history; physical examination; ECG; echocardiogram	Assessment for inducible myocardial ischemia* (stress tests)	Advanced coronary imaging	Antiplatelet therapy	Anticoagulation	Physical activity counseling
1 (Z score <2)	No coronary involvement at any point	1–2 wk (consider 4- to 6-wk follow-up if coronary artery imaging is suboptimal or laboratory markers of inflammation are abnormal at 1- to 2-wk follow-up); may discharge between 4 wk and 1 y	None	None	Low-dose aspirin for 6 wk, then discontinue	Not indicated	Promotion counseling at every visit
2 (Z score 2–2.5)	Dilation only, resolves within 6 wk to 1 y	1–2 wk (consider visit at 6 wk if abnormal at 1–2 wk); 1 y; may discharge after 1 y if normal; assess every 2–5 y if persisting	None	None	Low-dose aspirin for 6 wk; if normal coronaries at 6 wk, then discontinue	Not indicated	Promotion counseling at every visit
3 (Z score 2.5–<5)	3.1 Small aneurysm, current or persistent	Within 1 wk (if progressive enlargement, then recommend close follow-up once a wk until stable coronaries); 6 wk; 6 mo; 12 mo; yearly	Assess every 3–5 y	Consider coronary CTA at 1 y as baseline; may consider every 3–5 y	Low-dose aspirin	Not indicated	Promotion counseling at every visit
	3.2 Small aneurysm, regressed to dilation only or normal	Within 1 wk; 6 wk; 1 y; 5 y, may discharge provided stress test and coronary CTA are normal	Assess every 5 y	Consider coronary CTA at 1 y as baseline; may consider if there is inducible ischemia	Low-dose aspirin is continued until normal dimensions	Not indicated	Promotion counseling at every visit
4† (Z score 5–<10 and absolute dimension <8 mm)	4.1: Medium aneurysm, current or persistent	Within 1 wk (if progressive dilation, then recommend close follow-up once a wk until stable coronaries); 6 wk; 3 mo; 6 mo; 12 mo; yearly	Assess every 2–5 y	Consider coronary CTA at 1 y as baseline; may consider every 2–5 y	Low-dose aspirin plus clopidogrel	Not indicated	Promotion counseling at every visit; consider restricting contact; self-limit
	4.2: Medium aneurysm, regressed to small aneurysm	Within 1 wk; 6 wk; 6 mo; 12 mo; yearly	Assess every 3–5 y	Consider coronary CTA at 1 y as baseline; may consider every 3–5 y	Low-dose aspirin	Not indicated	Promotion counseling at every visit
	4.3: Medium aneurysm, regressed to normal or dilation only	Within 1 wk; 6 wk; 6 mo; 12 mo; every 2 y	Assess every 4–5 y	Consider coronary CTA at 1 y as baseline, may consider if there is inducible ischemia	Low-dose aspirin	Not indicated	Promotion counseling at every visit
5† (Z score ≥10 or absolute dimension >8 mm)	5.1: Large or giant aneurysm, current or persistent	Within 1 wk (if progressive dilation, then recommend close follow-up once a wk until stable coronaries); 6 wk; 3 mo; 6 mo; 9 mo; 12 mo, then every 6–12 mo	Assess every 6–12 mo	Consider baseline coronary CTA within 2–6 mo; may consider every 1–5 y, or may consider invasive coronary angiography	Low-dose aspirin; dual antiplatelet therapy with clopidogrel may be considered	Warfarin, LMWH, or DOAC	Promotion counseling at every visit; restrict contact; self-limit
	5.2: Large or giant aneurysm, regressed to medium aneurysm	Within 1 wk (if progressive dilation, then recommend close follow-up once a wk until stable coronaries); 6 wk; 3 mo; 6 mo; 9 mo; 12 mo, then every 6–12 mo	Assess every 2–5 y	Consider coronary CTA at 1 y as baseline; may consider every 2–5 y	Low-dose aspirin; dual antiplatelet therapy with clopidogrel may be considered	Warfarin, LMWH, or DOAC	Promotion counseling at every visit; restrict contact; self-limit
	5.3: Large or giant aneurysm, regressed to small aneurysm	Within 1 wk (if progressive dilation, then recommend close follow-up once a wk until stable coronaries); 6 wk; 3 mo; 6 mo; 9 mo; 12 mo, then yearly	Assess every 3–5 y	Consider coronary CTA at 1 y as baseline, may consider every 3–5 y	Low-dose aspirin; dual antiplatelet therapy with clopidogrel may be considered	Warfarin, LMWH, or DOAC may be considered	Promotion counseling at every visit; restrict contact; self-limit
	5.4: Large or giant aneurysm, regressed to normal or dilation only	Within 1 wk (if progressive dilation, then recommend close follow-up once a wk until stable coronaries); 6 wk; 3 mo; 6 mo; 9 mo; 12 mo, then every 1–2 y	Assess every 3–5 y	Consider coronary CTA at 1 y as baseline, may consider every 3–5 y	Low-dose aspirin	Not indicated	Promotion counseling at every visit; restrict contact; self-limit

CTA indicates CT angiography; DOAC, direct oral anticoagulant; and LMWH, low molecular weight heparin.

*If symptoms, then can perform stress test earlier.

†β-blockers and statins may be considered.

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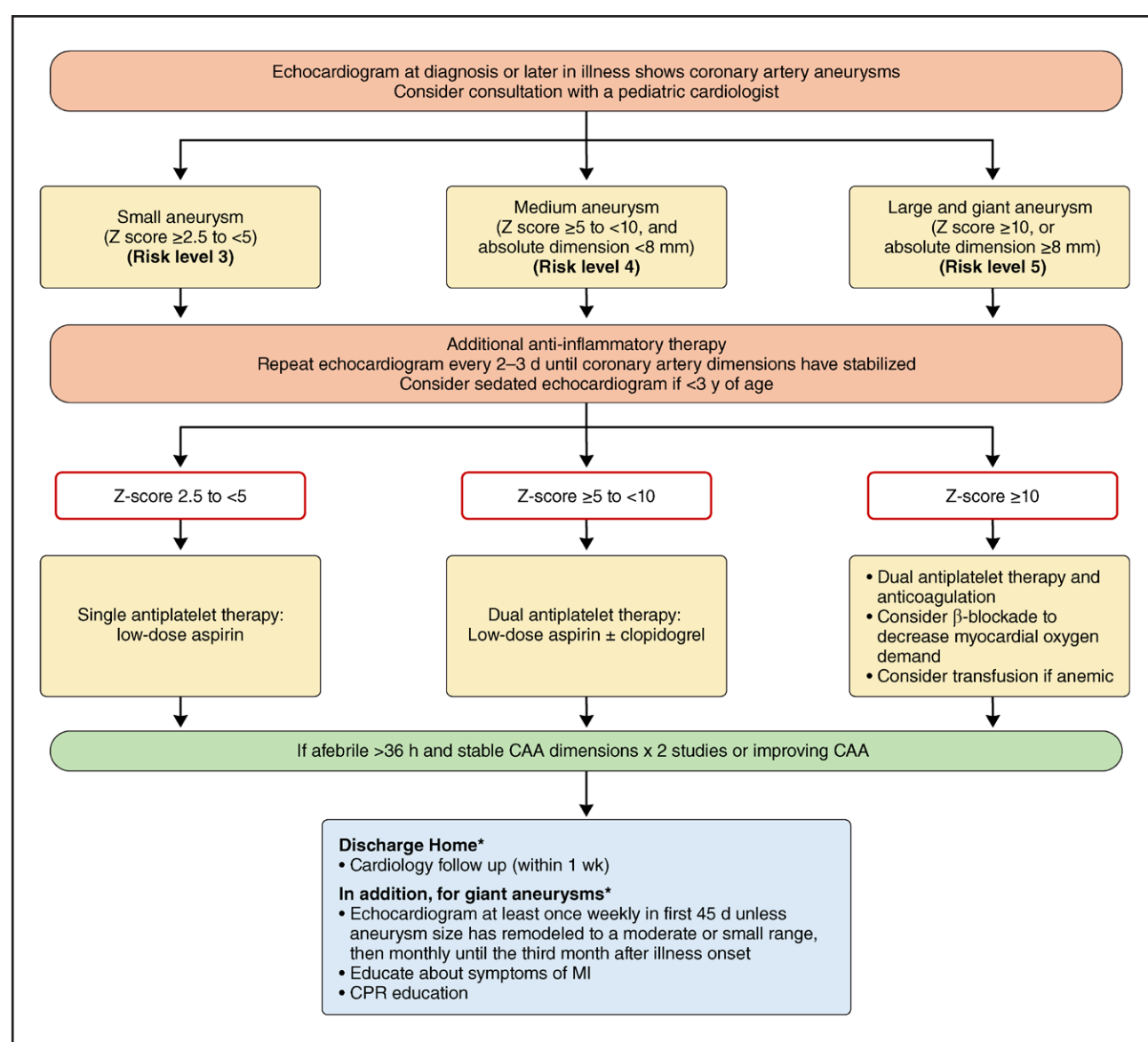
Figure 2. Management of evolving coronary artery aneurysms in Kawasaki disease during the acute phase.
*In addition to items listed in the orange box of Figure 1. CAA indicates coronary artery aneurysm; CPR, cardiopulmonary resuscitation; and MI, myocardial infarction.

generally well tolerated. Hemolytic anemia is a dose-dependent complication of IVIg administration, and more frequently encountered in patients with A, B, or AB blood group type.[43,44] A recent study suggests that dosing for IVIg be based on lean body mass in patients with obesity to reduce the risk of hemolytic anemia.[44] IVIg can also lead to aseptic meningitis, but it is usually transient and without sequelae. All live vaccines, including measles, mumps, rubella, and varicella vaccines, should be deferred for 11 months after IVIg administration, as administered IVIg may reduce efficacy of those live vaccines. The erythrocyte sedimentation rate is increased after IVIg treatment; therefore, erythrocyte sedimentation rate is not a reliable marker of inflammation after IVIg infusion.

Aspirin is given during the acute period of KD, but its activity on platelets is inhibited by nonsteroidal anti-inflammatory drugs. Aspirin traditionally has been administered at a moderate (30–50 mg/kg per day) or high (80–100 mg/kg per day) dose as anti-inflammatory therapy and for its antipyretic effect until the patient is afebrile for 48 to 72 hours.[1] Low-dose aspirin (3–5 mg/kg per day) once a day has been used for its antiplatelet effect after defervescence and is continued until 6 to 8 weeks after onset of illness.[1] There is increasing evidence that medium- or high-dose aspirin in the acute phase is likely not associated with improved CA outcomes. Several retrospective cohort studies show no difference in CAA rate between patients treated with moderate- compared with high-dose aspirin.[45,46] Two retrospective, nonrandomized

cohort studies found no difference in the CAA rate between patients treated with high-dose or low-dose aspirin during the acute period.[47,48] In addition, a retrospective Japanese study found that treatment without aspirin during the acute phase of KD resulted in similar CAA and IVIg resistance rates compared with treatment with medium dose.[49] In 2 meta-analyses, different doses of aspirin were compared, and no significant differences in CAA, IVIg resistance, or hospital length of stay were found.[50,51] A multicenter prospective, randomized, open-label, noninferiority trial is underway to evaluate moderate-dose versus low-dose aspirin with IVIg in acute KD.[52]

For patients who are allergic or resistant to aspirin, clopidogrel or dipyridamole can be used in place of aspirin.[1,53] Dual antiplatelet therapy may be considered in patients with CA Z score ≥5, although the use of aspirin and clopidogrel is extrapolated from adults with atherosclerosis who have undergone stent placement for CA stenosis in the setting of myocardial infarction (MI).[54] Future data will elucidate the appropriate aspirin dosing in the acute illness of patients with KD and randomized trials are needed for dual antiplatelet therapy in patients with CA Z score ≥5.

Treatment of IVIg Resistance

IVIg resistance is defined as persistent or recrudescent fever ≥36 hours after the completion of the initial IVIg infusion.[1] These patients are at increased risk for developing CAA compared with those who respond to IVIg. Multiple anti-inflammatory therapies have been evaluated to varying degrees for treatment resistance, including corticosteroids, tumor necrosis factor α inhibitors (infliximab and etanercept), interleukin-1 inhibition (anakinra), and cyclosporine (Table 3).

Corticosteroids

Scoring systems to predict IVIg-resistant patients have been established in Japan,[55] but these scoring systems have not performed well in North American cohorts.[56] Using the Kobayashi risk score in Japanese patients, RAISE (Randomized Controlled Trial to Assess Immunoglobulin Plus Steroid Efficacy for Kawasaki Disease; https://www.umin.ac.jp/ctr; unique identifier: UMIN000000940) demonstrated that IVIg plus prednisolone (2 mg/kg per day) for 5 days followed by an oral taper resulted in a lower incidence of CA abnormalities than IVIg alone (4 patients [3%] versus 28 patients [23%]; risk difference, 0.20 [95% CI, 0.12−0.28]; $P<0.0001$).[57] The post-RAISE study of 724 patients with KD, predicted to be at high risk for IVIg resistance using the Kobayashi score, also demonstrated that IVIg plus prednisolone therapy reduced the IVIg resistance rate and decreased the incidence of CA abnormalities to 5.9% using the AHA criteria and 3.8% using the Japanese criteria.[58] The RAISE results are compelling, but have not been validated in a non-Japanese population.

Infliximab and Etanercept

The KIDCARE trial (Kawasaki Disease Comparative Effectiveness; https://www.clinicaltrials.gov; unique identifier: NCT03065244) compared infliximab (10 mg/kg IV), a monoclonal antibody against tumor necrosis factor α, with a second IVIg infusion in IVIg-resistant patients. This study showed shorter duration of fever, reduced need for additional therapy, less severe anemia, and shorter hospitalization in the infliximab group.[59] Because this study excluded patients who received primary intensification therapy for CAA, the power of this study to detect differences in CA outcomes was limited.

Etanercept, a soluble tumor necrosis factor α receptor used as adjunctive therapy with IVIg, was studied in a multicenter, double-blind, randomized, placebo-controlled trial to assess efficacy in reducing IVIg resistance.[60] Whereas there was no significant overall difference in IVIg resistance between the 2 arms, in secondary analyses, there was a lower rate of IVIg resistance in the etanercept group in children >1 year of age, and reduced progression of CA enlargement among patients with baseline CA enlargement.

Anakinra

Interleukin-1 pathway genes are markedly upregulated in patients with KD during the acute phase of illness; therefore, interleukin-1 blockers have been used in patients with KD.[61] A phase II open-label study in 16 IVIg-resistant patients with KD demonstrated that anakinra (ranging from 2 to 6 mg/kg per day subcutaneously), a recombinant interleukin-1b receptor antagonist, was well tolerated and associated with cessation of fever.[62]

Cyclosporine

Cyclosporine, a specific T-cell inhibitor that blocks the calcium-driven calcineurin−NFAT (nuclear factor of activated T cells) pathway, has also been explored as a therapeutic option in KD. Polymorphisms in calcium pathway and calcium channel genes are risk factors for KD susceptibility, which underscores the importance of the calcineurin−NFAT pathway.[63] In the randomized, placebo-controlled KAICA (Kawasaki Disease Study to Assess the Efficacy of Immunoglobulin Plus Cyclosporine A; unique identifier: JMA-ILA00174), Japanese patients at high risk for IVIg resistance on the basis of the Kobayashi score were randomly assigned to either IVIg plus cyclosporine (5 mg/kg per day for 5 days) or IVIg.[64] Whereas there was a higher rate of treatment resistance in those treated with cyclosporine, the incidence of CA abnormalities was lower in the IVIg plus cyclosporine group than with IVIg alone at the 2-week time point (although not at the 1- and 4-week time points), and there was no difference in the incidence of adverse events between the groups. There was a higher rate of relapse in the cyclosporine-treated arm, requiring additional therapy. A longer course of cyclosporine is typically used in North America (Table 3). Oral magnesium supplementation (eg, magnesium protein complex) is important during cyclosporine use to reduce the risk of hypomagnesemia, and

Table 3. Initial Therapy, Intensification Therapy for Intravenous Immunoglobulin–Resistant or High-Risk Patients With Kawasaki Disease, and Additional Therapies for Refractory Disease

Agent	Description	Dose	Additional medical precautions
Initial therapy			
IVIg	Pooled polyclonal immunoglobulin	IV, 2 g/kg given over 8–12 h; consider slower infusion in KD shock or myocardial dysfunction; consider lean body mass for dosing in patients with obesity	Risk for hemolytic anemia in patients with obesity unless using ideal lean body weight
Aspirin	Acetylsalicylic acid	PO, 30 to 50 mg/kg per d* divided every 6 h; PO 3–5 mg/kg per d once afebrile for 48–72 h; used in many centers although prospective investigation underway to determine the appropriate dose	Do not administer with NSAIDs as efficacy is reduced
Intensification therapy			
Prednisolone	Corticosteroids as per RAISE	IV, 2 mg/kg per d divided every 8 h for 5 d (maximum 60 mg/d) while hospitalized; then PO prednisolone 2 mg/kg per d divided every 8 h; slow tapering over 15 d (maximum 30 mg/dose) once CRP normalized	Famotidine is given to prevent gastric ulcer
Methylprednisolone	Corticosteroids as per North American studies	IV, 2 mg/kg per d divided every 12 h for 5 d (maximum 60 mg/d) while hospitalized; then PO prednisone 2 mg/kg per d divided every 12 h; once CRP <1 mg/dL, corticosteroids are tapered over 2–4 wk with the dose cut in half every 5 d	Famotidine is given to prevent gastric ulcer
Infliximab	Monoclonal antibody against TNFα	IV, 10 mg/kg given over 2 h	
Etanercept	Soluble receptor that binds TNFα and TNFβ	SC, 0.8 mg/kg weekly ×3 doses	
Additional therapy for refractory disease			
Cyclosporine	Inhibitor of calcineurin–NFAT pathway	PO, 5 mg/kg per d divided every 12 h; check 2 h level after 3rd dose (goal of 300–600 ng/mL); start to taper (by 10% every 3 d) once patient afebrile, clinically improving, and CRP ≤1.0 mg/dL or 10 d of therapy, whichever is longer	Use Neoral (not generic cyclosporine, due to variable absorption); Mg protein complex (133 mg) supplementation must be given once daily while on cyclosporine to prevent hypomagnesemia; should not be administered with statins given both are metabolized by cytochrome P450, which may increase side effects
Anakinra	Recombinant interleukin-1b receptor antagonist	IV/SC, 10 mg/kg per d (IV divided q12 h preferred to SC) while hospitalized; wean once ready for discharge (5 mg/kg per d for 1 d, then stop)	
Second dose of IVIg		IV, 2 g/kg given over 8–12 h	Increased risk of hemolytic anemia with A, B, and AB blood types
Cyclophosphamide	Alkylating agents block DNA replication	IV, 10 mg/kg per d in 1 or 2 doses	Adequate hydration needed; consider rheumatology consult

*Used in many centers though prospective investigation underway to determine the appropriate dose.

CRP indicates C-reactive protein; IV, intravenous; IVIg, intravenous immunoglobulin; KD, Kawasaki disease; NFAT, nuclear factor of activated T cells; NSAID, nonsteroidal anti-inflammatory drug; RAISE, Randomized Controlled Trial to Assess Immunoglobulin Plus Steroid Efficacy for Kawasaki Disease; and TNF, tumor necrosis factor.

the brand of cyclosporine used must be considered, given variable absorption with generic formulations.

Intensification of Initial Therapy for High-Risk Patients

Intensification of initial therapy (dual therapy) may benefit high-risk patients with KD (baseline CAA Z score ≥2.5, infants <6 months, or in high risk category using the Son risk score). Eighteen percent of infants <6 months old who had normal echocardiogram results at diagnosis subsequently developed a Z score ≥2.5 within 8 weeks of diagnosis despite timely treatment with IVIg.[25] These data were corroborated in a large Latin American cohort, in which infants <6 months of age treated with IVIg in the first 10 days of illness were 5 times more likely to develop a Z score ≥2.5 than patients >6 months old.[26] Treatment strategies are shown in Figure 3 for children with evolving CAA during the acute illness. These therapies include corticosteroids, tumor necrosis factor α inhibitors (eg, infliximab and etanercept), interleukin-1 inhibitors (eg, anakinra), and cyclosporine (Table 3).[60,64–67] Despite the existence of short-term safety and pharmacokinetic data for these medications in patients with KD, allowing for more definitive dosing regimens, efficacy data from randomized controlled trials are lacking.

Corticosteroids and Infliximab

Several retrospective studies have compared the progression of CAA in patients receiving IVIg alone compared with
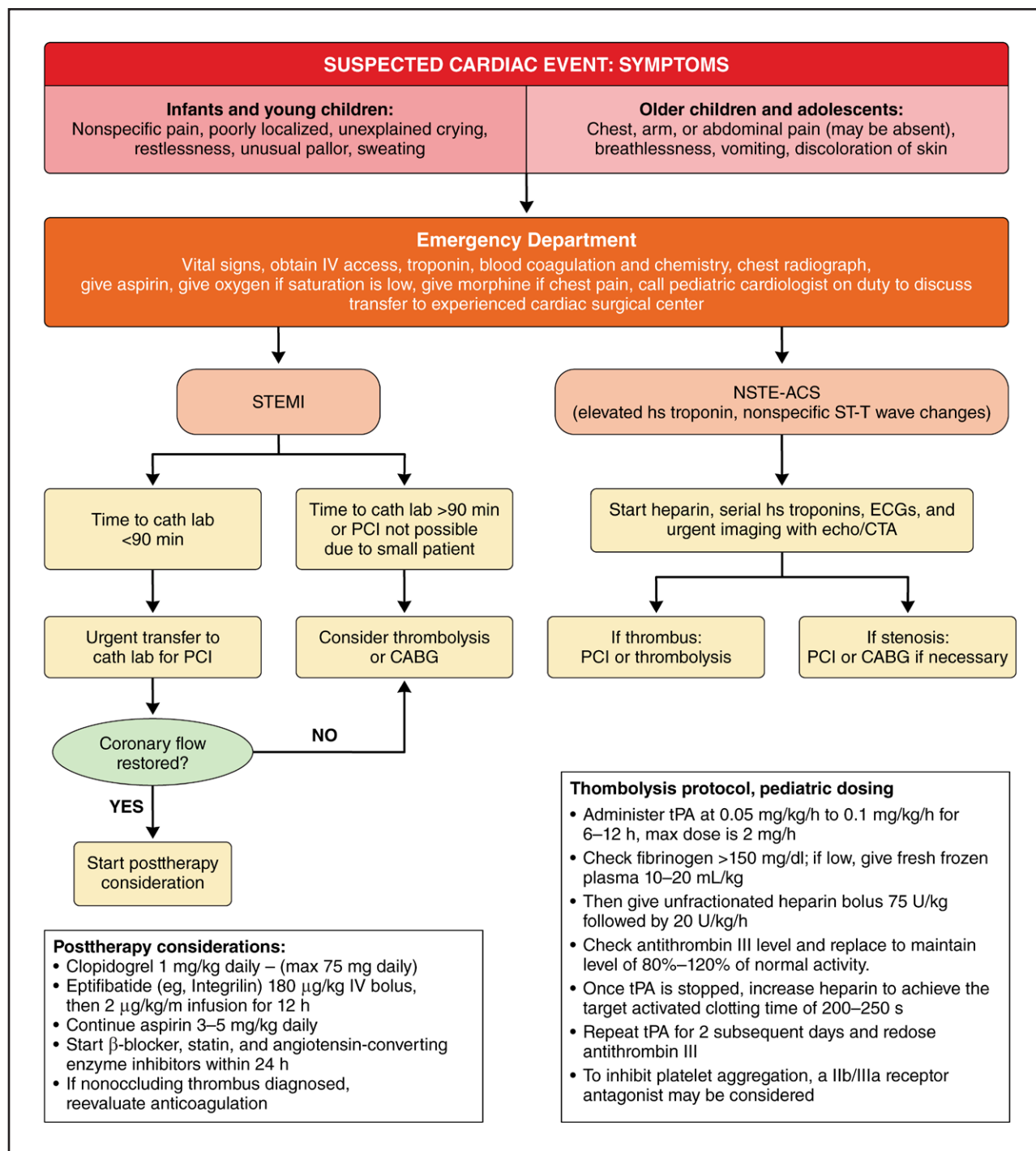
Figure 3. Management flowchart for patients with Kawasaki disease with acute myocardial infarction.
Adapted from Brogan et al.[83] Copyright © 2020 The Authors. Published on behalf of the BMJ Group. This is an open access article under the terms of the Creative Commons Attribution-NonCommercial License, which permits use, distribution and reproduction in any medium, provided the original work is properly cited and is not used for commercial purposes. CABG indicates coronary artery bypass graft; CTA, computed tomography angiography; hs, high sensitivity; IV, intravenous; NSTE-ACS, non–ST-segment–elevation acute coronary syndrome; PCI, percutaneous coronary intervention; STEMI, ST-segment–elevation myocardial infarction; and tPA, tissue-type plasminogen activator.

those receiving dual therapy (IVIg in combination with corticosteroids or infliximab). Among a group of patients with KD with Z score ≥2.5 on baseline echocardiography treated at 3 different centers with varying practices for CAA, those treated with infliximab or corticosteroids in addition to IVIg

had less progression in CAA size (increase in Z score >1 SD unit) compared with those treated with IVIg alone.[10] In addition, 2 other retrospective studies of infliximab (10 mg/kg) or methylprednisolone followed by oral prednisolone in combination with IVIg demonstrated that intensification of

primary therapy is associated with higher likelihood of CAA regression in patients who have CAA (Z score ≥2.5) at diagnosis.[68,69] Given the retrospective nature and small numbers, these studies must be interpreted with caution, and a larger, prospectively randomized study is needed.

Anakinra

A phase I/IIa dose-escalation study of anakinra (2–11 mg/kg per day) in 22 patients with acute KD with CAA demonstrated that both IV and subcutaneous anakinra are safe in infants and children.[66] IV dosing every 8 to 12 hours during the acute hospitalization of patients with KD may result in a sustained concentration while avoiding frequent subcutaneous injections. Although anakinra appears well tolerated and has been proposed as an option for patients with CAA, there are no data regarding efficacy in patients with coronary abnormalities.

Cyclosporine

Cyclosporine has been used in patients with CAA, which seems reasonable because gene expression studies of KD CA autopsy tissues have shown an increase in transcripts related to cytotoxic T cells that can be inhibited by cyclosporine.[70]

KD Shock

KD with signs of low blood pressure, low perfusion, or myocardial dysfunction has been described as KD shock syndrome, and described as more commonly presenting with elevated C-reactive protein, hypoalbuminemia, and thrombocytopenia compared with KD without shock.[16,71,72] Hemodynamic instability generally improves quickly once IVIg therapy is administered. Given the increased risk for IVIg resistance and CA abnormalities, intensification of initial IVIg therapy with a second anti-inflammatory therapy needs to be considered.

Additional Therapies for CAA

Cyclophosphamide

In patients with giant aneurysms that are continuing to progress despite IVIg and other adjunctive anti-inflammatory therapies, cyclophosphamide, an alkylating agent that blocks DNA replication, has been used in patients with KD who are refractory to multiple other therapies.[73] This medication is usually used in consultation with rheumatologists. Patients will need to increase fluid hydration while on this medication.

Statins

Statins have pleotropic antioxidant and anti-inflammatory effects that promote endothelial cell homeostasis and block endothelial to mesenchymal transition, which may be beneficial in acute KD. In a phase I/IIa study of atorvastatin in children at least 2 years old with acute KD and Z score ≥2.5, 34 patients received up to 6 weeks of treatment in a dose-escalation study with 0.125 to 0.75

mg/kg per day of atorvastatin.[74] Atorvastatin was well-tolerated in all patients, and 18 of these patients were treated at the highest dose level with no adverse effects. Gene expression profiling demonstrated that cultured endothelial cells incubated with sera from patients with KD treated with IVIg, infliximab, and atorvastatin showed improved endothelial cell health and decreased inflammation compared with controls treated with only IVIg and infliximab.[75] However, to date, no randomized clinical trial has tested whether statins in the acute phase result in improved outcomes, and thus this is an area that needs more study.

Anticoagulation for CAAs

In patients with large CAAs, there is risk for luminal thrombosis in both the acute and chronic phases. Patients with large CAAs traditionally receive both antiplatelet medication (typically aspirin 81 mg daily or dual antiplatelet [aspirin and clopidogrel] agents) and anticoagulation with either warfarin or low molecular weight heparin (LMWH). In a pragmatic registry trial, warfarin and LMWH had equivalent effectiveness for preventing thrombosis in large CAAs after KD.[76] Whereas efficacy is generally adequate, bleeding complications and ease of administration are concerns. Warfarin is difficult to manage in many children, with international normalized ratios in goal range only two-thirds of the time, and twice daily injections for LMWH can be difficult for children.[77] Direct oral anticoagulants (DOACs) are a potential alternative for thromboprophylaxis, with low rates of clinically relevant bleeding and thrombosis, and the advantages of once or twice daily oral weight-based dosing and infrequent need for monitoring.[78,79] These agents have few drug and food interactions, making them attractive for the pediatric population. In an international randomized 3-month trial (ENNOBLE-ATE [Edoxaban for Prevention of Blood Vessels Being Blocked by Clots (Thrombotic Events) in Children at Risk Because of Cardiac Disease]; https://www.clinicaltrials.gov; unique identifier: NCT03395639), edoxaban was found to cause treatment-emergent adverse events in 46.8% of patients (51 of 109), compared with 41.4% (24 of 58) in the standard of care anticoagulants arm.[78] In a 1-year trial of apixaban (SAXOPHONE [Safety of Apixaban on Pediatric Heart Disease on the Prevention of Embolism]; https://www.clinicaltrials.gov; unique identifier: NCT02981472) in children with cardiac disease, apixaban was found to be safe and well-tolerated, with no thromboembolic events in the patients with KD (14% of 192 patients in the cohort).[80] Reversal agents (prothrombin concentrates) and an antidote (andexanet alfa) are available for cases of severe bleeding.[81] Additional safety and efficacy of DOAC therapy in patients with KD may be available from postmarketing surveillance and will benefit from further studies.

Key Points

1. Intensification of primary therapy with adjunctive anti-inflammatory therapy (dual therapy) may benefit high-risk patients with KD.
2. Patients with large CAAs require antiplatelet and anticoagulation therapy.
3. New DOACs are not as affected by vitamin K intake as warfarin and do not require the therapeutic monitoring challenges of warfarin or LMWH.
4. DOACs may provide a more convenient and safer alternative than warfarin or LMWH.
5. Future studies are needed to establish safety and efficacy of DOAC therapy in patients with KD.

MI MANAGEMENT

The risk of MI in patients with KD with CAA is highest in the first 2 to 3 months after KD onset.[82] Although risk of MI declines beginning 2 years after illness onset, there is persistent ongoing risk of ischemia in patients with large or giant CAA throughout the patient's lifetime.[1,82–85] Acute MI is a medical emergency.[11,82,86,87] Acute MI management is divided into infarction with or without ST-segment elevation. ST-segment–elevation MI (STEMI) occurs with sudden complete occlusion of a CA segment resulting in transmural ischemia associated with myocardial injury or necrosis.[54] Non–ST-segment–elevation acute coronary syndromes include chest pain, elevated troponin levels, and nonspecific ST-T–wave changes. This represents a mismatch between myocardial oxygen demand and blood flow, resulting in myocardial injury with elevated troponin levels, but without the extensive myocardial necrosis associated with STEMI.[54] An urgent and coordinated response from the cardiovascular heart team (eg, pediatric and adult interventionalists, pediatric and adult cardiologists, pediatric and adult cardiac surgeons) is required to manage pediatric patients with KD presenting with new-onset ischemia.[29,54,82,83]

Acute coronary symptoms may present differently in patients with KD compared with the classical presentation of MI in adults with atherosclerosis.[82,83] Infants and young children may present with nonspecific pain, poorly localized pain, unexplained crying, restlessness, unusual pallor, or sweating.[82,83] Older children may present with chest, arm, or abdominal pain, breathlessness, vomiting, or skin discoloration.[82,83] Management strategies listed in Figure 3 are extrapolated from adult guidelines in coronary revascularization and expert consensus.[54,82,83] Overall, in patients who present with STEMI and arrive at a cardiac catheterization laboratory with an experienced interventionalist within 90 minutes, percutaneous coronary intervention can be performed. If an intervention cannot be performed, then medical therapy with thrombolysis is recommended. This is often the case for very young patients with KD, because there are no catheters small enough for infants who present with an acute MI.[29] Non-STEMI can progress to STEMI, particularly in the first few months after KD onset. Antiplatelet and anticoagulation therapy are administered after acute MI. β-blockers, statins, and angiotensin-converting enzyme inhibitors may be considered.[29,54]

Key Points

1. The risk of MI in patients with KD with CAA is highest in the first 2 to 3 months after KD onset.
2. Acute coronary symptoms may present differently in patients with KD compared with the classic presentation of MI in adults with atherosclerosis.
3. Medical centers that follow patients with KD with giant CAA need to have a multidisciplinary heart team and a protocol in place to address major adverse cardiac events.

LONG-TERM MANAGEMENT OF KD

Long-term management is based on the extent of CA involvement, with a maximum CA Z score determined at the acute phase of illness. Patients are risk stratified on the basis of their maximal CA dimensions and associated Z score. The goals of long-term follow-up are to prevent thrombosis and MI and provide counseling for optimal cardiovascular health. CA dilation typically occurs early in the acute phase of illness in KD, with maximal CA dimensions often occurring in the second or third week after illness. In some patients, CA dimensions sometimes continue to increase in diameter up to 6 weeks after illness, and rarely (in especially severe cases) even beyond 2 months. Patients with persistent CAA, defined as Z score ≥2.5 after 6 weeks, are considered to have long-term arterial damage.[1,29] However, the risk of adverse cardiac events and need for follow-up are variable, and require further consideration on the basis of evolving literature. Since the publication of the 2017 AHA KD scientific statement, multiple studies have evaluated the risk of adverse cardiac events and the regression of CAA. Several contemporary studies have shown patients with small CAAs have near universal normalization of CA internal lumen diameter size over follow-up and near zero risk of adverse cardiac events. A large registry study of 1651 patients showed normalization of CA diameter in 99±4% of small CAAs and 92±1% of moderate CAAs over 10 years of follow-up. In addition, no adverse cardiac events occurred in patients with maximal CA Z score <10.[14] In a 2018 multicenter retrospective Japanese cohort study of 1006 patients, the 10-year coronary event-free survival rates for small and medium CAAs were 100% and 94% in male participants and 100% and 100% in female participants, respectively.[12] Multiple other smaller studies in diverse populations have shown similar findings, with regression of small and medium CAAs in the

large majority of patients and exceedingly rare adverse cardiac events.[11] These studies suggest that decreased frequency of visits and frequency of surveillance testing may be warranted in patients with small CAAs (Table 2).[14]

Surveillance Imaging

Surveillance imaging in KD is tailored to the presence and severity of maximal and current CA involvement as well as rate of change in the coronary dimensions and ventricular function. A transthoracic echocardiogram is the primary imaging modality for surveillance in KD. It is less reliable in older children because of poor acoustic windows. Its sensitivity to detect distal CAA is lower compared with computed tomography (CT) angiography.[88] Transesophageal echocardiography can be used in adolescent and adult patients with KD when there are poor transthoracic acoustic windows because of obesity or lung artifact. Advanced CA imaging by coronary CT angiography (CTA), cardiac magnetic resonance (CMR) imaging, or invasive coronary angiography are important tools for surveillance in KD.

Coronary CTA

Coronary CTA allows visualization of all segments of the coronary tree and can reliably assess CAA and thrombosis and detect CA stenosis (≥50%) in KD.[89,90] It has superior spatial resolution compared with CMR imaging for detecting distal CA lesions and thrombus, albeit with radiation exposure. Modern dose-reduction techniques and dual-source CTA technology have successfully reduced exposure levels for some studies to <1 mSv.[89] β blockade may be needed to help lower the heart rate to obtain a gated coronary CTA. Transthoracic echocardiography and coronary CTA demonstrate excellent agreement in coronary vessel and aneurysm measurements when assessing the proximal CA.[91] There are no normative data for coronary diameters derived from CTA data for the pediatric population. Thus, the typical practice is the application of echo Z scores to CTA measurements in the proximal coronaries. Although this practice is not ideal, it is reassuring that there is excellent agreement in the proximal coronary vessels in small cohorts, and that both inter- and intraobserver reliability is high for CTA measurements of coronary aneurysms in KD.[91] Coronary CTA measurements in the distal CA tend to be smaller than in transthoracic echocardiogram but coronary CTA is better at detecting distal CAA than transthoracic echocardiogram.[91,92] Coronary CTA is also used in patients presenting with symptoms of acute MI. CT-derived fractional flow reserve (FFR) is a physiologic simulation technique that models the coronary flow from coronary CTA and is used in adults with CA disease to evaluate for stenotic lesions.[93] This is an active area of research and future studies of CT-derived FFR in patients with KD may

help identify stenotic lesions that may need intervention. In patients with CAA, long-term surveillance imaging using coronary CTA is helpful.

Calcifications in CAA occur late in the course of disease and heavy calcification can obscure coronary measurements from coronary CTA. Tsuji et al[94] demonstrated 10% incidence of aneurysm calcification at 10 years, 38% calcification at 20 years, and 72% calcification at 30 years after initial KD illness in patients with persistent aneurysms. Kahn et al[95] imaged patients with KD using CT to obtain a calcium score and demonstrated that only patients with persistent coronary abnormalities had calcified segments. CA calcium scoring is useful for adult patients with unknown CA status after KD in childhood to screen for calcification as a marker for CAA. In these patients, imaging with coronary CTA is needed to further evaluate CAA. Given the advancements in reduced radiation dose and time in performing coronary CTA, this modality can be used in patients with KD with expanding giant CAA during hospitalization right before discharge to map out the extent of the aneurysms in the short term. Coronary CTA may be helpful at 1 year from diagnosis as a baseline to follow patients with CAA, particularly patients with large or giant aneurysms or those with features that make echocardiographic imaging of CAA difficult, including distal CAA and suboptimal echocardiographic windows (Table 2). It can also be used in long-term serial follow-up if progressive stenosis is suspected, for confirmation of thrombus formation detected by echocardiography, or if acute coronary syndrome is suspected during clinical follow-up and as outlined in Table 2.

CMR Imaging

CMR imaging allows visualization of the CA and evaluation of ventricular function and tissue characterization without the use of radiation. Imaging the CA in children by CMR imaging can be challenging because of high heart rate and small vessel size. CMR imaging requires sedation in children younger than 8 years. Ferumoxytol-enhanced coronary magnetic resonance angiography has been performed in adults and correlated with invasive catheter angiography to diagnose CA stenosis.[96,97] Matsumoto et al[98] showed that 3-dimensional turbo spin echo vessel wall coronary imaging was equivalent to standard vessel wall imaging with 2-dimensional dual inversion recovery turbo spin echo in a small cohort of patients with KD. The Society of CMR 2020 expert consensus statement for acquired pediatric heart disease provides a comprehensive CMR imaging protocol for patients with KD to evaluate the CA walls and lumen, detect myocardial inflammation (T2 mapping), detect fibrosis (T1 mapping and late gadolinium enhancement), and assess for rest and stress perfusion defects.[5] Lower circumferential and longitudinal strain values by CMR are seen in the convalescent phase of KD compared with healthy individuals,

even after recovery of systolic function by conventional imaging measures irrespective of the presence of CAA.[99] Myocardial fibrosis is an ischemic pattern that occurs in a small number of patients with severe CAA and is not restricted to areas of reduced perfusion.[100] Patients who had KD shock syndrome, especially those with myocardial dysfunction, may have an increased long-term risk for myocardial fibrosis, and thus might benefit from CMR imaging later in life.[101] Abnormal myocardial perfusion reserve by CMR imaging is seen in patients with KD with persistent or regressed CAA on follow-up.[102] Stress testing by CMR imaging can be performed using inotropic agents (dobutamine) or coronary vasodilators (adenosine, dipyridamole, or regadenoson). Adenosine stress CMR imaging in patients with KD has shown inducible perfusion defects in those with CAA.[100] Regadenoson, a newer and more selective agent than adenosine, is hemodynamically safe and feasible in children with KD CAA, and may identify those in need for revascularization therapy.[103] The correlation of CMR imaging measures with outcomes remains to be determined.

Invasive Coronary Imaging

Invasive coronary angiography delineates coronary architecture including stenoses, collaterals, and peripheral arterial and internal mammary anatomy. It is generally reserved for patients who are being considered for percutaneous revascularization (ie, because of acute MI, angina, or inducible ischemia stress testing), or in whom advanced imaging modalities (eg, CT, magnetic resonance imaging) have rendered inadequate images for management decisions. FFR is a method of evaluating the pressure difference between the distal and the proximal parts of a stenotic lesion during invasive coronary angiography. It is a valuable tool widely used to assess CA lesions and to determine the need for percutaneous coronary intervention.[54] Based on the 2021 American College of Cardiology/AHA/Society for Cardiovascular Angiography & Interventions guidelines, percutaneous coronary intervention is not recommended if FFR is >0.8 in atherosclerotic disease, as this indicates adequate flow in the coronary arteries.[54] The use of FFR in patients with KD remains under investigation.[104,105]

Intravascular ultrasound and optical coherence tomography (OCT) are valuable adjuncts to coronary angiography, offering higher spatial resolution (intravascular ultrasound, 100 to 150 µm; OCT, 10 µm; coronary angiography, 300 µm) and detailed lesion characteristics compared with angiography alone. Intravascular ultrasound has been used for the past 30 years in KD to differentiate among atheroma, thrombus, or myointimal proliferation and in guiding percutaneous coronary intervention in those presenting with acute coronary syndrome or stable angina.[106,107] That said, its effect on long-term outcomes in KD remains to be studied. OCT has been applied in

patients with KD to visualize structural changes in the coronary wall.[56] OCT requires blood clearance from lumen of the vessels for optimal imaging, and its role in patients with KD remains an area of ongoing research.[108] Both intravascular ultrasound and OCT are invasive, and their use is limited as routine surveillance for patients with KD.

Assessment of Inducible Ischemia

Patients with CAA are at risk of CA stenosis and obstruction. Those with CAA Z score ≥10, particularly those with Z score ≥20, and those with complex architecture (eg, multiple branches involved with multiple aneurysms) are at the highest risk. In these patients with CAA Z score ≥10, the cumulative incidence of luminal narrowing >50%, CA thrombosis, and major adverse cardiovascular complications over 10-year follow-up were 20±3%, 18±2%, and 14±2%, respectively.[14] Hence, periodic surveillance for inducible myocardial ischemia is strongly advised in those with CAA Z score ≥10 regardless of the presence or absence of potential symptoms suggestive of ischemia, with frequency of testing calibrated to the severity of maximal and current CAA (Table 2). The selection of imaging modality to assess for inducible myocardial ischemia depends on the patient's age and the center's experience in performing the imaging modality while minimizing the cumulative radiation exposure. Clinical expertise in performing and interpreting the various modalities should also be taken into account when selecting the modality for assessment of inducible myocardial ischemia. Because exercise stress echocardiography does not involve radiation exposure, it is preferable to positron emission tomography and stress nuclear imaging for routine surveillance for inducible myocardial ischemia in asymptomatic children. CMR stress imaging has emerged as a useful imaging modality without radiation when evaluating inducible ischemia in children who are too young to exercise.

Stress Echocardiography

Exercise stress echocardiography testing is more physiologic than pharmacologic stress testing. In a single-center study, exercise stress echocardiography was performed in 53 patients with KD with CAA, and successfully identified myocardial ischemia in a subset of high-risk patients with AHA CA risk level 4 or 5 and had normal results in lower-risk patients.[109] Pharmacologic stress testing with dobutamine can be used in children with KD who are too young to perform the stress exercise protocol. The degree of wall motion abnormalities seen on dobutamine stress echocardiogram in patients with KD and CAA is independently associated with a lower rate of event-free survival to 15 years.[110] Exercise stress echocardiography can be performed in children >7 years of age and is used as a screening tool for assessment of inducible myocardial ischemia.[109]

Health Care Transition

The health care transition for patients with KD is paramount to caring for this growing population of adults. The key element of successful health care transition is a structured intervention that incorporates the components of planning, transfer, and integration into adult care, such as the Six Core Elements approach recommended by multiple academies.[111] Medical teams that care for patients with complex cases of KD with CAA need to establish a formal health care transition program to ensure a smooth transition with uninterrupted medical care as these children become adults. Pediatric clinicians who care for patients with KD must identify an adult cardiologist in their community who is able to care for their patients with KD once the patients reach adulthood. The long-term prognosis and potential interventions in adult patients with KD with CAA that may be related to acute coronary syndrome, heart failure, or arrhythmia remain to be investigated.[87,112] Pregnant women with KD and giant aneurysms taking anticoagulation medication represent a particularly high-risk group of patients who require care from high-risk obstetrics with a knowledge of KD and with cardiology consultation. Further research is needed in this population.

Key Points

1. Long-term surveillance is necessary in patients with CAA, especially in those with large or giant aneurysms 1 year after KD onset. This may be performed with low-radiation CTA, magnetic resonance imaging with ferumoxytol, or invasive angiography depending upon the patient's coronary complexity and clinical circumstances, as well as institutional resources.
2. The advancement of coronary CTA with less radiation when available can be used as a baseline to follow patients with KD with CAA and to identify CA stenoses.
3. Advancement in CMR coronary imaging has helped to evaluate patients with KD with CAA without radiation, although CMR imaging is better for myocardial functional analysis in addition to stress perfusion imaging as a modality for inducible ischemia.
4. Stress echocardiography can be used to evaluate patients with KD with CAA for inducible ischemia.
5. Invasive coronary angiography provides the finest delineation of coronary architecture, and its use must be balanced against risks of an invasive procedure on the basis of patient and institutional factors. Invasive coronary angiography is used for patients with myocardial ischemia and intervention for revascularization.
6. Medical teams that care for patients with KD with CAA need to establish health care transition plans as these children become adults.

FUTURE DIRECTIONS

Over the past 5 decades, tremendous progress has been made in diagnosis, treatment, and long-term management of KD. This update summarizes recent data on several clinically relevant topics. Despite many advances, ongoing knowledge gaps exist on pathogenesis, diagnostic testing, acute adjunctive treatment, and long-term management. Future revision of KD diagnostic criteria will need to be considered on the basis of more published clinical data. Risk scores for both IVIg resistance and development of CAA have been developed in diverse populations and may improve outcomes by allowing targeted adjunctive therapy in higher-risk patients. Iterative improvements in diagnostic testing and algorithms, including potential incorporation of artificial intelligence, as well as risk stratification for both development of CAA and cardiac events in patients with CAA, are needed. Ultrafast ultrasound imaging, a new modality, is able to capture images at frame rates up to 100 times faster compared with conventional echocardiography. One of its emerging clinical applications is CA ultrafast Doppler angiography, a technology that allows anatomic and hemodynamic analysis of coronary flow and seems promising in KD.[113] Surveillance imaging and emerging techniques to evaluate vessel wall inflammation and characteristics (optical tomography) have shown promise in improving understanding of vascular biology and response of vessel wall inflammation to therapy but need further exploration and validation. Larger studies are needed to confirm these findings and study their effects on clinical outcomes and on long-term prognosis. Large, international registries continue to provide fundamental data on outcomes, including compelling recent data showing that small CAAs resolve in the overwhelming majority of cases and these patients are not at risk for later cardiac events, but a burden of CAA and associated long-term cardiac sequelae remains. Randomized trials directly comparing acute intensification with anti-inflammatory agents in high-risk patients could lead to lower CAA incidence and less progression of CAA in patients with CAA at time of diagnosis. Use of statin therapy in patients with acute CAA has shown promise but needs to be further explored over the long term in patients with persistent CAA. Additional data have accumulated showing clear benefit of anticoagulation plus antiplatelet therapy in patients with KD with large CAA, but optimal thromboprophylaxis including newer DOACs and evidence-based criteria for when to initiate anticoagulation remain scarce. Establishing the efficacy of easier-to-use DOACs (in comparison with warfarin or LMWH) holds the potential to improve both cardiac outcomes and lifestyle in patients with large CAA. Evidence of safety and efficacy of DOACs in KD will come from postmarketing surveillance. Establishing further evidence-based criteria for timing and type of coronary interventions in the setting of large CAAs and ischemia is urgently needed. Formal health

care transition programs and care teams are needed for adult patients with KD with CAA to ensure uninterrupted transition of care.

ARTICLE INFORMATION

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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Writing Group Disclosures

Writing group member	Employment	Research grant	Other research support	Speakers' bureau/ honoraria	Expert witness	Ownership interest	Consultant/ advisory board	Other
Pei-Ni Jone	Ann & Robert H. Lurie Children's Hospital of Chicago, Northwestern University Feinberg School of Medicine	None	None	None	None	None	None	None
Kevin G. Friedman	Boston Children's Hospital, Harvard Medical School	None	None	None	None	None	None	Merck (clinical director)†
Nadine Choueiter	Mount Sinai Kravis Children's Hospital, Icahn School of Medicine at Mount Sinai	None	None	None	None	None	None	None
Samuel R. Dominguez	Children's Hospital Colorado and University of Colorado School of Medicine	Pfizer (grant for pneumococcal diagnostics)*; Biofire Diagnostics (grant for BCID in Guatemala)*; DelveBio (grant of NGS in CSF)*	None	None	None	None	Biofire Diagnostics*; Karius*	None
Ashraf S. Harahsheh	The George Washington University School of Medicine & Health Sciences, Children's National Hospital, Washington, DC	None	None	None	None	None	None	None
Ming-Tai Lin	National Taiwan University Hospital Children's Hospital, Taipei	None	None	None	None	None	None	None
Yoshihide Mitani	Mie University Graduate School of Medicine, Japan	None	None	None	None	None	None	None
Adriana Tremoulet	University of California San Diego (UCSD) and Rady Children's Hospital, San Diego	None	None	None	None	None	Janssen Pharmaceutical (unpaid)*	None
Meghan Zimmerman	Dartmouth Hitchcock Medical Center, Geisel School of Medicine at Dartmouth	None	None	None	None	None	None	None

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*Modest.

†Significant.

Reviewer Disclosures

Reviewer	Employment	Research grant	Other research support	Speakers' bureau/ honoraria	Expert witness	Ownership interest	Consultant/ advisory board	Other
Nagib Dahdah	University of Montreal (Canada)	None	None	None	None	None	None	None
Jane C. Burns	University of California	None	None	None	None	None	None	None
Anne H. Rowley	Northwestern University	National Institutes of Health†	None	None	None	None	None	None
Jane W. Newburger	Boston Children's Hospital	Pfizer*; BMS*; NHLBI MUSIC and RECOVER grants on MIS-C*	None	None	None	None	None	None
Dongngan T. Truong	University of Utah	NIH†; Pfizer, Inc†	None	None	None	None	None	None
Mei-Hwan Wu	National Taiwan University Children's Hospital	None	None	None	None	None	None	None

This table represents the relationships of reviewers that may be perceived as actual or reasonably perceived conflicts of interest as reported on the Disclosure Questionnaire, which all reviewers are required to complete and submit. A relationship is considered to be "significant" if (a) the person receives $5000 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 $5000 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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