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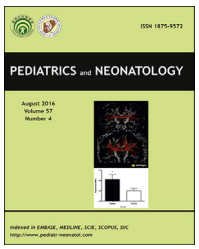

Review Article

State-of-the-art acute phase management of Kawasaki disease after 2017 scientific statement from the American Heart Association☆

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Abstract Kawasaki disease (KD) has become the most common form of pediatric systemic vasculitis. Although patients with KD received intravenous immunoglobulin (IVIG) therapy, coronary arterial lesions (CALs) still occurred in 5%–10% of these patients during the acute stage. CALs may persist and even progress to stenosis or obstruction. Therefore, CALs following KD are currently the leading cause of acquired heart diseases in children. The etiology of CALs remains unknown despite more than four decades of research. Two unsolved problems are IVIG unresponsiveness and the diagnosis of incomplete KD. The two subgroups of KD patients with these problems have a high risk of CAL. In April 2017, the American Heart Association (AHA) updated the guidelines for the diagnosis, treatment, and long-term management of KD. Compared with the previous KD guidelines published in 2004, the new guidelines provide solutions to the aforementioned two problems and emphasize risk stratification by using coronary artery Z score systems, as well as coronary severity–based management and long-term follow-up. Therefore, in this study, we merged the AHA Scientific Statement in 2017 with recent findings for Taiwanese KD patients to provide potential future care directions for Taiwanese patients with KD.

☆ The current manuscript represents the authors' point of view rather than the journals'.

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1. Introduction

Kawasaki disease (KD) is an acute febrile systemic vasculitis and first reported by Tomisaku Kawasaki in 1967.[1] The connection between KD and cardiac complications was initially unknown. In the 1970s, the first nationwide survey of KD in Japan uncovered the potential link between KD and coronary vasculitis.[2,3] KD is currently the leading cause of acquired heart diseases in children in developed countries.

Most patients with KD respond favorably to single high-dose intravenous immunoglobulin (IVIG) plus aspirin. Nevertheless, approximately 10%—20% of patients with KD do not achieve defervescence after the first dose of IVIG treatment.[4,5] The optimal treatment for these patients remains in doubt. The American Heart Association (AHA) published a scientific statement for the diagnosis, treatment, and long-term management of KD in April 2017.[6] The new guidelines emphasize the early recognition of incomplete KD in infants, greater use of the Z score for coronary arteries, and thrombosis prevention in long-term care. In the new guidelines, the follow-up strategy was also revised. The purpose of this paper is to describe the major changes in the 2017 AHA KD statement compared with the 2004 KD guidelines[7] and to update the acute management of KD on the basis of domestic findings and literature review.

1.1. Epidemiology

KD has been reported in more than 60 countries worldwide (Supporting file 1). Previous studies have comprehensively described the epidemiologic features of KD, including incidence, age of onset, seasonal trends, and rates of cardiac lesions. Approximately 90% of patients with KD are less than 5 years. KD is more prevalent in Asian children.[6,8]

In Taiwan, the cumulative incidence of KD among children aged less than 5 years is 2.78 per thousand children, and the time trend with the birth year has increased from 2.28 per thousand children in 2000 to 3.67 per thousand children in 2009.[9] Each year, we estimate that approximately 700 patients are newly diagnosed with KD in Taiwan. A program from a cross-section point of view in Taiwan can also provide an estimate of patients with KD-associated complications such as coronary artery sequelae.[10] Among the 23,349 patients with KD (aged $<$ 40 years) identified from 2000 to 2010, 1254 (5.37%) (861 men and 393 women) had various forms of coronary complications. The recurrence rate is approximately 2% in Taiwan and 3.5% in Japan. The case fatality rate is $<$0.1% in both Japan and Taiwan.[6,9] The peak seasons of KD are late spring and summer in Taiwan.[11]

1.2. Etiology

The exact etiology of KD remains unclear and is beyond the scope of the current review. KD is a disease with acute systemic inflammatory process. Inflammatory cell infiltration has been observed in the affected tissues.[12] A study in Taiwan determined that 61% of household members of patients with KD had an acute illness during the acute stage of patients with KD.[13] According to the aforementioned studies, infectious triggers for KD are reasonable. Some studies have supported this viewpoint.[12,14] Furthermore, the risk of KD in siblings of affected children is 10 times the risk in the general population, and the risk of KD is twice as high in children born to parents with a history of KD compared with the general population.[15,16] In agreement with these epidemiological data, several genome-wide association studies (GWAS) have determined that the genetic variants of ITPKC,[17] FCGR 2A,[18] BLK, and CD40 genes[19,20] are involved in genetic susceptibility to KD. Other factors, such as the climate, environment, and rug and carpet cleaning, are reportedly associated with KD.[6] However, these studies have provided inconsistent results. The cause of KD remains unknown in the 2017 AHA guidelines for KD.

2. Diagnosis of classic KD

The clinical diagnostic criteria for KD have been used for more than 40 years.[3] No major revision of the diagnostic criteria occurred in the 2017 AHA guidelines compared with 2004 AHA guidelines for KD. Classic KD is diagnosed based on at least 5 days of fever plus at least four of the five following clinical features: (1) bilateral bulbar conjunctival injection without exudates, (2) erythema and cracking of lips, strawberry tongue, or erythema of the oral and pharyngeal mucosa, (3) cervical lymphadenopathy ($\geq$1.5 cm in diameter), usually unilateral, (4) rash: maculopapular, diffuse erythroderma or erythema multiform-like, and (5) erythema and edema of the hands and feet in the acute phase and/or periungual desquamation in the subacute phase.[6] If patients already have at least four clinical features, including redness and swelling of the hands and feet, KD can be diagnosed if they exhibit 4 days of fever. These clinical features may not present at the same times.

2.1. Common pitfalls in diagnosis

No specific symptoms or laboratory tests can serve as the golden standard diagnostic tools for KD. Therefore, a high index of suspicion for diagnosis is the only means of avoiding the delayed diagnosis of KD, particularly in certain clinical situations. In infants aged $<$6 months, prolonged fever and irritability may be the only clinical manifestations of KD.[6] Chang et al. reported that in Taiwan, only 45% of patients with KD younger than 6 months met the diagnostic criteria within 10 days of disease onset. These children are also at a high risk of coronary artery abnormalities.[21] In children, particularly those aged less than 6 months, with prolonged fever plus any one of the following clinical manifestations: (1) irritability, (2) unexplained aseptic meningitis, (3) unexplained or culture-negative results, (4) cervical lymphadenitis unresponsive to antibiotic therapy, or (5) retropharyngeal or parapharyngeal phlegmon unresponsive to antibiotic therapy, KD should be considered one of the differential diagnoses.[6] Patients who present with shock may be misdiagnosed as having bacterial sepsis or staphylococcal or streptococcal toxic shock syndrome. Physicians usually consider the diagnosis of KD shock syndrome (KDSS) substantially later.[6] The differential diagnosis between toxic shock syndrome and KDSS is described in

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another section. Another finding is erythema and induration at the inoculation site of Bacille Calmette–Guérin (BCG) vaccination. In Taiwan, 30.4% of patients with KD exhibited BCG scar reactivation during the acute phase of KD.[22] This finding is common in countries where BCG vaccination is widely applied, such as Japan, Korea, and Taiwan.

Some laboratory tests can help physicians diagnose KD. Please refer to the study of Tremoulet et al.[23] for details. Briefly, leukocytosis with neutrophil predominant, normocytic anemia and thrombocytosis are common in the acute phase and resolve spontaneously. The platelet count usually peaks during the third week (mean: 700,000/mm^3) and normalizes by 4–6 weeks after disease onset.[23] Thrombocytopenia is rare but can occur in the first to second week. A low platelet count is associated with the development of coronary artery abnormalities and indicates consumption due to intravascular clot formation.[24] Hypoalbuminemia is common in patients with KD and is associated with greater severity of the illness and the occurrence of progressive coronary dilatation.[25] Sterile pyuria (defined as $\geq$12 white blood cell [WBC]/mL for men and $\geq$20 WBC/mL for women) has been reported in up to 80% of patients with KD[26] Therefore, some patients with KD may be treated as urinary tract infection if other clinical manifestations are unapparent.

3. Incomplete (atypical) KD

Although the diagnostic criteria of KD have been adequately established, 20%–30% of all patients with KD don't fulfill the diagnostic criteria. For patients with prolonged unexplained fever and any principal clinical feature, KD should be considered in the differential diagnosis. KD can be further confirmed by laboratory examinations or by detecting coronary abnormalities through echocardiography. However, coronary artery dilatation or aneurysm rarely occurs during the first week of the illness. In addition, normal coronary artery findings during the first week do not exclude the possibility of KD. The 2004 AHA guidelines for KD first proposed the diagnostic algorithm for incomplete KD. Incomplete KD should be suspected in patients with fever for more than 5 days and two or three principal clinical features. Some useful laboratory findings including leukocytosis, anemia, elevation of erythrocyte sedimentation rate (ESR) or C reactive protein (CRP), elevated alanine aminotransferase (ALT), and sterile pyuria can help physicians diagnose incomplete KD. Positive echocardiographic findings including coronary artery dilatation or aneurysm, mitral regurgitation (MR), and pericardial effusion are key clues for the diagnosis of incomplete KD.[6]

Incomplete KD is more common in infants than in children. The incidence of strawberry tongue and erythematous swelling of the palms and soles is lower among infants younger than 6 months.[21] Some diagnostic pitfalls are mentioned earlier.

4. Cardiovascular manifestations and complications

Cardiovascular complications are major concerns in patients with KD. Before the introduction of IVIG, the incidence of coronary artery abnormalities was approximately 20%. The incidence of coronary dilatation or aneurysms peaks within 4 weeks after disease onset.[27,28] In a trial of IVIG infusion in patients with KD, the incidence of coronary artery abnormalities in patients treated with a 4-day course low-dose infusion and a single high-dose infusion was 7.9% and 3.2%, respectively.[29] Coronary artery aneurysms occur more prevalently at the proximal left anterior descending (pLAD) and the proximal right coronary artery (pRCA), followed by the left main coronary artery (LMCA) and the left circumflex (LCX).

Myocarditis occurs in the acute phase of KD and can cause left ventricular dysfunction. It is related to the inflammatory response of KD. Myocarditis in KD usually resolves completely after the acute phase and recovers more rapidly than the other causes of myocarditis.[30] Hemodynamic instability, including hypotension or clinical signs of inadequate perfusion, rarely occurs and comprises an unique condition called KDSS. Compared with toxic shock syndrome, KDSS occurs at a younger age, and patients with KDSS are prone to have lymphadenopathy, coronary involvement, and less identifiable foci. Using the national health insurance database of Taiwan between 2000 and 2009, Lin et al. demonstrated that the incidence of KDSS was 1.45 per 100 KD cases (the annual incidence ranged from 0.9% to 1.98%).[31] Patients with KDSS require close monitoring and might require hemodynamic support in intensive care units. Fluid resuscitation and inodilator therapy (e.g., milrinone) should be administered on the basis of cautious monitoring of cardiac output, central venous pressure, and systemic vascular resistance.

Valvular abnormalities have been observed in some patients. A multicenter US study demonstrated that up to 27% of patients had MR in the acute stage of KD. MR in most of these patients resolved gradually during follow-up.[30] Aortic dilatation has been noted in only 1% of patients and is usually associated with aortic root dilatation. Aortic root dilatation (Z score $>$2) was demonstrated in 10% of patients and had a positive correlation with coronary dilatation.[30]

In addition to the coronary arteries, KD involves other medium-sized arteries. Common sites include the axillary, subclavian, brachial, femoral, iliac, renal, and lateral thoracic arteries.[32] Dilatation and aneurysms usually occur near or at the branching points of the arteries. They can manifest as bruits or pulsatile masses. Thrombosis of the involved arteries causes ischemic changes in target organs or tissues. Rarely, peripheral gangrene or autoamputation develops in these patients with medium-sized artery abnormalities.

4.1. Evaluation of coronary arteries

Evaluation of coronary arteries is crucial for the diagnosis and management of patients with KD. The initial echocardiogram should be performed as soon as KD is suspected, but treatment initiation should not be delayed by the timing of the study. To obtain high-quality echocardiographic images, sedation is recommended in irritable young children. Additionally, the initial echocardiogram in the first week of the illness is typically normal and does not rule out KD diagnosis.[6]

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The Child Coronary Arterial Diameter Reference Study Group of the Japan Kawasaki Disease Society recommends ultrasound imaging as the standard method for measuring the diameters of coronary arteries in children with KD. The diameters should be measured from the inner to inner edge. Focal dilatation may be observed at the points of branching. If the sharp angle of the branching points becomes blunt, dilatation or aneurysms should be considered. The standard procedure, setting, echo beam directions, and focused segment for coronary artery echocardiography are described previously.[33] Furthermore, the currently available nomograms and Z score calculators for coronary artery diameters are only for the LMCA, pRCA, and pLAD. Therefore, we briefly reviewed the standardized echocardiographic observation and diameter measurement of the aforementioned three segments of coronary arteries. The LMCA and pRCA are observed at the level of the aortic valve in the precordial short-axis view (Fig. 1). We usually define the diameter measured at the middle point of the LMCA (from orifice to bifurcation) as the LMCA diameter (Fig. 2A and B). The pRCA is defined as the segment between the RCA orifice and the origin of the right ventricular branch of the RCA (Fig. 3A). The pRCA and mid-RCA in the right atrioventricular groove are easily detected when one notices the anterior ring of the tricuspid valve (Supporting file 2). We define the diameter measured at the middle point of the pRCA as the RCA diameter (Fig. 3B).

To detect the LAD, we usually modify the parasternal short-axis view clockwise slightly and cranially turn the probe (Supporting file 3). Thus, the pLAD and mid-LAD can be delineated clearly (Fig. 4A and B). The pLAD ranges between its origin (from the LMCA) and the septal branch of the LAD. Similar to the measurement of the LMCA and pRCA, we define the diameter measured at the middle point of the pLAD as the LAD diameter (Supporting file 4).

In addition to coronary artery diameters, evaluation of echogenicity at the bilateral coronary fossa and the possible loss of LAD tapering can further provide clues for the coronary involvement of KD, although the exact prognostic roles of the two echocardiographic characteristics remain unclear.[6]

Based on their morphology, aneurysms can be classified into saccular and fusiform. Saccular aneurysms have nearly equal axial and lateral diameters. Fusiform aneurysms have symmetrical dilation with gradual tapering at the proximal and distal ends. Saccular aneurysms have a lower incidence of regression.

Initially, the abnormality of coronary arteries is defined by the absolute diameter.[34] The 2004 AHA guidelines defined abnormality of the coronary artery lesions by using a Z score $\geq +2.5$ and classified the severity of coronary aneurysms by using the absolute diameter.[7] In the past 1–2 decades, several formulas for Z score calculation of coronaries have been derived.[35–38] The 2017 AHA guidelines emphasized the application of Z scores for coronary artery evaluation and classified the severity of coronary abnormalities by using Z scores (Table 1). Coronary Z scores of $+2.5$, $+5.0$, and $+10.0$ were recommended as the cut-off points for small, medium-sized, and giant coronary aneurysms, respectively (Table 1). These Z scoring systems are usually applied for the pRCA, LMCA, and pLAD. Other coronary segments can be evaluated by comparing them to adjacent segments. Dilatation or small aneurysms are defined as a segment with a diameter 1.5 times that of the adjacent segment. If the diameter is between 1.5 and 4 times that of the adjacent segment, it is defined as a medium aneurysm. If the diameter is more than four times that of the adjacent segment, it is defined as a large aneurysm. The frequency of echocardiography follow-up should be based on the initial echocardiography result (Table 1).

As shown in Table 1, the absolute diameter of 8 mm is used as a criterion for giant aneurysms. This cut-off point is effective because many studies on long-term coronary and cardiac outcomes of KD patients with giant aneurysms have been based on the 8-mm criteria.[39–41] Furthermore, based on the Taiwanese coronary Z score calculator,[35] an 8-mm LMCA corresponds to a coronary Z score of $+8.5$ in children with a body surface area (BSA) of 0.5 m^2 and of $+5.7$ in children with a BSA of 1.0 m^2. Therefore, this troublesome aspect should be considered when the AHA guidelines are applied to Taiwanese patients with KD (see Table 1).

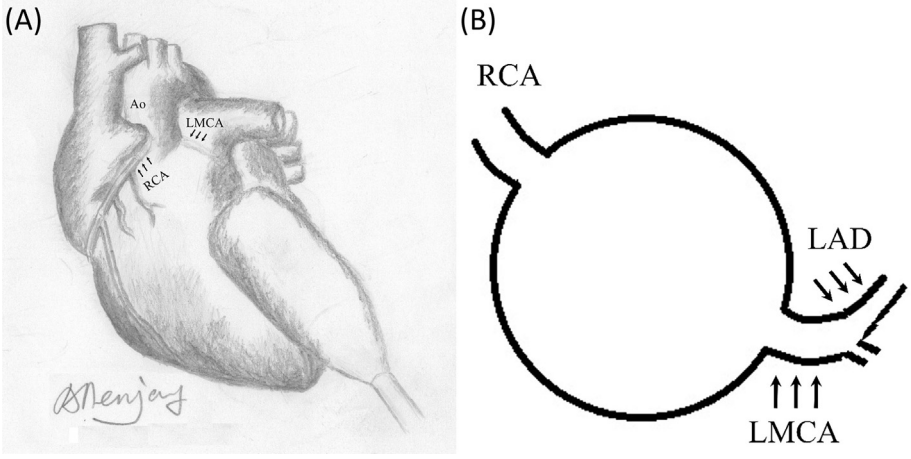

Figure 1 Precordial short-axis view at the base of the heart. Right coronary artery (RCA), left main coronary artery (LMCA), and left anterior descending (LAD) coronary artery observed in the precordial short-axis view. (A) Probe position showing parasternal short-axis view. (B) Diagram showing the LMCA, LAD, and RCA.

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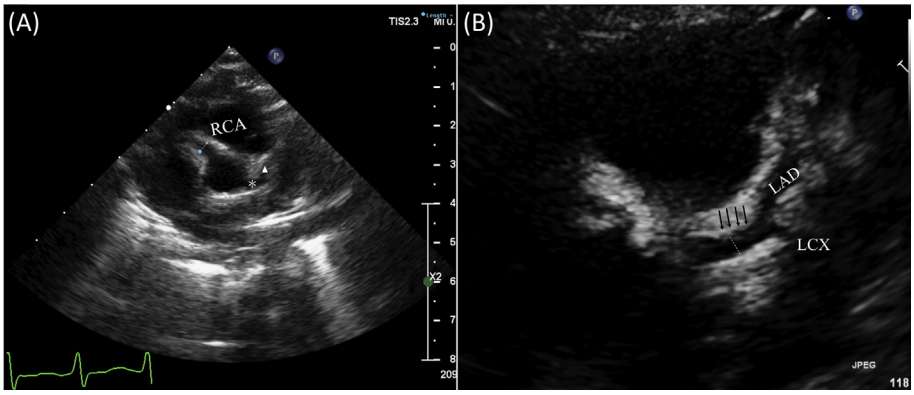

Figure 2 Precordial short-axis view (A) Echocardiographic image showing the LMCA (❊), LAD (▲), and RCA. (B) Echocardiographic image showing the LMCA, LAD, and LCX. The LMCA diameter is measured at the middle of LMCA (dotted line).

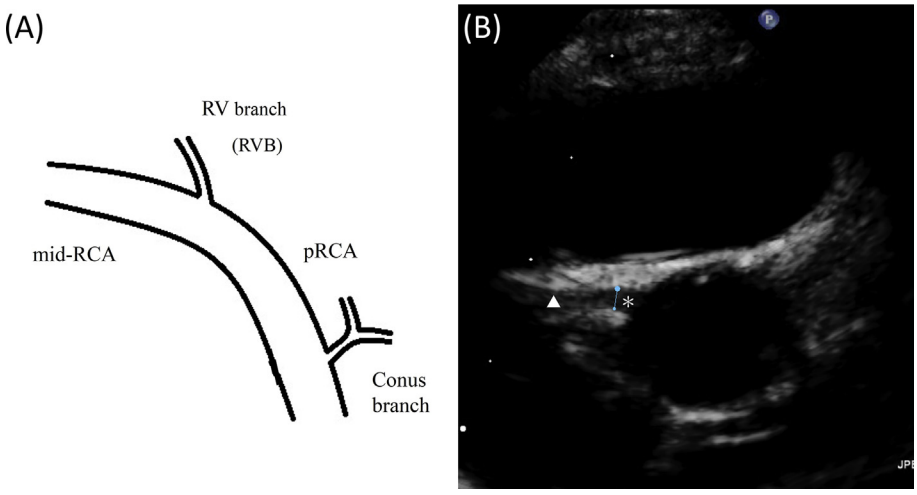

Figure 3 Proximal RCA (pRCA) and middle RCA (mid-RCA) are observed in the right atrioventricular groove. The right ventricular branch (RVB) arises at the border of the pRCA and mid-RCA. (A) Diagram showing the pRCA, mid-RCA, and RVB; (B) Echocardiographic image showing the pRCA (❊), mid-RCA (▲), and RVB (black arrow).

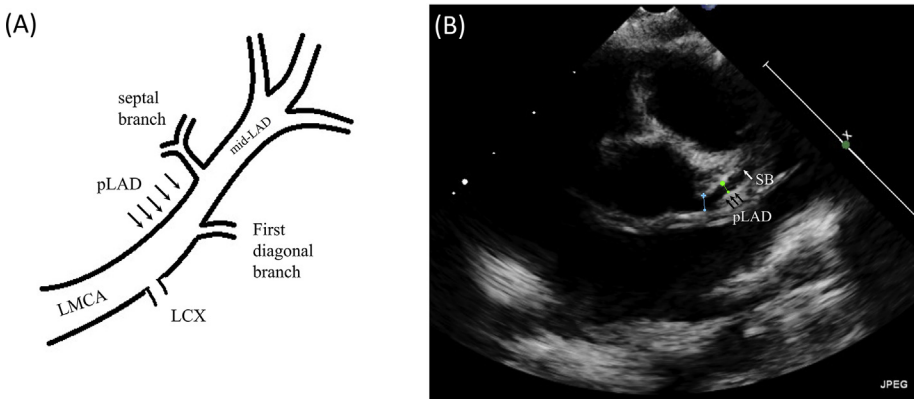

Figure 4 LAD. (A) Diagram showing the LMCA, left circumflex coronary artery (LCX), proximal LAD (pLAD), middle LAD (mid-LAD), septal branch (SB), and first diagonal branch (D1). (B) Echocardiographic image showing the LMCA, pLAD (black arrow), and SB (white arrow).

This classification method has substantial implications for echocardiographic follow-up schedules. The initial coronary severity is associated with the risk of developing coronary aneurysms at 1 month after KD onset.[25] Furthermore, coronary severity at 1 month after KD onset is associated with long-term cardiovascular outcomes.[40]

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Table 1 Coronary Z score classification and timing of echocardiography.

Severity of coronary artery abnormality	Z score or diameter	Timing of echocardiography
No involvement	Z score $< +2$	1- 2 weeks and 4–6 weeks after treatment
Dilatation only	Z score $\geqq +2$ to $< +2.5$, or Initial Z score $< +2$, decrement of Z score $\geqq +1$ during follow-up	1- 2 weeks and 4–6 weeks after treatment
Small aneurysm	Z score $\geqq +2.5$ to $< +5$	Twice per week till no progression
Medium aneurysm	Z score $\geqq +5$ to $< +10$ and absolute diameter < 8 mm	Twice per week till no progression
Large/Giant aneurysm	Z score $\geqq +10$ or absolute diameter $\geqq 8$ mm	Twice per week, at least once weekly in first 1.5 month, then monthly until the 3rd month

Table 2 Treatment regimens for refractory KD.

Treatment agent	Administration
IVIG	2 g/kg intravenous infusion for 10–12 h
IVIG plus prednisolone	2 g/kg IVIG plus intravenous prednisolone 2 mg/kg/d in 3 divided doses until defervescence and CRP normalization, followed by the oral form with tapering over 15 days.
Infliximab	Single dose: 5 mg/kg infusion for 2 h
Cyclosporine	Intravenous: 3 mg/kg/day every 12 h Oral: 4–8 mg/kg/day every 12 h Dose adjusted according to the blood drug level. Trough: 50–150 ng/mL 2-h peak: 300–600 ng/mL
Aakinra	2–6 mg/kg/day by subcutaneous injection
Cyclophosphamide	2 mg/kg/day intravenous infusion
Plasma exchange	Plasma replaced with albumin

The first three regimens were administered more frequently.

Therefore, the 2017 AHA guidelines recommended the following echocardiographic check-up schedules in the acute and subacute phases of KD: (1) For patients with uncomplicated KD (coronary Z score $<+2.5$), echocardiography should be repeated both within 1–2 weeks and 4–6 weeks after treatment; (2) for patients with coronary artery abnormalities (Z score $\geq+2.5$) detected during the acute stage, more frequent check-ups through echocardiography (at least twice per week) should be performed until the luminal dimensions have ceased progression to determine the presence and risk of thrombosis (Class I; Level of Evidence B); (3) for patients with expanding giant aneurysms ($\geq$8 mm), to detect potential coronary arterial thrombosis, performing echocardiography is reasonable twice per week while the dimensions are expanding rapidly, at least once weekly during the first 45 days of the illness, and subsequently monthly until the third month after illness onset because the failure to escalate thromboprophylaxis in time with the rapid expansion of aneurysms is a primary cause of morbidity and mortality (Class IIa; Level of Evidence C).

Visualization of the distal segments of coronary arteries through echocardiography is usually insufficient. With the growth and increments of body size, effective visualization of the coronary arteries becomes difficult. Echocardiographic detection of the intracoronary thrombi is not sensitive. Consequently, using advanced imaging techniques, such as computed tomographic angiography (CTA), cardiac magnetic resonance imaging (CMRI), and invasive angiography is reasonable in KD patients with severe coronary artery abnormalities.

5. Treatment in the acute phase

5.1. IVIG

Reducing the inflammatory response and preventing coronary artery abnormalities are the goals of initial therapies in the acute phase. The efficacy of IVIG administered in the acute phase of KD has been well established to reduce the prevalence of coronary artery abnormalities.[28] The standard initial treatment is single high-dose IVIG (2 g/kg) administered over 10–12 h plus aspirin.[29] IVIG should be administered as early as possible within 10 days of fever onset. For children with a diagnosis of KD after 10 days of fever and symptoms of an ongoing inflammatory process, IVIG should nevertheless be administered as soon as possible. IVIG is not required for patients with defervescence, normalization of laboratory tests, and normal echocardiographic results.[6]

IVIG exerts anti-inflammatory effects. Possible mechanisms of IVIG include the modulation of cytokine production, neutralization of toxins, pathogenic agents or Fc

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receptors, augmentation of regulatory T cell activity, and suppression of antibody synthesis. For patients who have received high-dose IVIG, immunization with measles, mumps, rubella, and varicella vaccines should be delayed for 11 months after IVIG infusion.[6]

Even with IVIG infusion, approximately 20% of patients develop transient coronary dilatation. At 1 month after KD onset, 5% of patients develop coronary aneurysms, and 1% of patients develop giant aneurysms.[6]

5.2. Aspirin

Although aspirin exerts anti-inflammatory effects and has long been used to treat KD, it does not particularly reduce the incidence of coronary artery abnormalities.[42,43] In the United States, high-dose aspirin (80—100 mg/kg/day) is administered in the acute stage and divided to every 6 h. The dose is only 30—50 mg/kg/day in Japan and Europe.[6] In Taiwan, some reports have suggested applying IVIG therapies without aspirin.[44] The aspirin dose can be reduced to 3—5 mg/kg/day if patients become afebrile for 48—72 h. Low-dose aspirin exerts antiplatelet effects and can prevent intracoronary thrombosis.

For patients with varicella or influenza infection, high-dose aspirin administration can induce Reye syndrome.[45] High-dose aspirin should be substituted with an alternative antiplatelet agent, such as clopidogrel or dipyridamole, if patients with KD have concomitant varicella or influenza infection. Patients with low-dose aspirin use should receive an annual inactivated influenza vaccine. Aspirin should be avoided until 6 weeks after vaccination with varicella. For patients with a high risk of thrombosis formation, aspirin can be substituted with clopidogrel or dipyridamole.

5.3. Adjuvant therapies

In addition to IVIG, several adjunctive therapies, such as corticosteroid, infliximab, and etanercept, can be applied in the acute phase of KD. Corticosteroid was used for the initial treatment before IVIG therapy became widespread. Some Japanese studies have revealed that both pulsed intravenous methylprednisolone (30 mg/kg/day) and low-dose prednisolone (2 mg/kg/day) reduce the prevalence of coronary aneurysms.[45,46] However, another multicenter, randomized, double-blind, placebo-controlled trial in North America revealed no benefit of adding single pulsed dose of methylprednisolone to IVIG in the initial treatment for KD.[47] Some scoring systems have been created for the risk stratification of IVIG unresponsiveness in Japan. For example, for KD patients with Kobayashi scores of >4, IVIG plus titrated-dose prednisolone (2 mg/kg/day) effectively reduced the incidence of coronary artery abnormalities from 23% to 3% ($P < 0.0001$).[48] Nevertheless, physicians should be careful when applying the Kobayashi scoring system to patients with KD because of its low sensitivity in patients from North America, Taiwan, or mainland China.[6,49,50] The scoring system should be adjusted for different ethnic groups. The 2017 AHA guidelines recommended that IVIG plus aspirin should be the first-line therapy for patients with KD. Additionally, low-dose corticosteroid together with IVIG and aspirin may be administered as the initial treatment in patients with KD at a high risk of IVIG unresponsiveness or coronary involvement, and single pulsed dose of methylprednisolone should not be used for the initial treatment.[6]

Infliximab is a chimeric monoclonal antibody that binds with high affinity to TNF-α. One randomized, double-blinded, placebo-controlled study[51] revealed that IVIG plus infliximab shortened fever duration and normalized inflammatory parameters more rapidly compared with IVIG alone. However, the incidence of coronary aneurysms was similar between these two groups. Etanercept is a soluble TNF-α receptor that can bind to circulatory TNF-α. The efficacy of etanercept as an adjunctive treatment for KD is under investigation.[6]

KD patients with coronary artery abnormalities must be administered medications for thrombosis prevention. Low-dose aspirin is sufficient for prophylaxis of thrombosis in KD patients with coronary artery dilation only or small coronary artery aneurysms ($+2.5 \leq Z < +5.0$). For KD patients with medium-sized coronary artery aneurysms ($+5.0 \leq Z < +10$ and diameter <8 mm), dual antiplatelet agents use may be considered. For KD patients with a giant aneurysm (Z score $\geq +10$ or diameter ≥ 8 mm), administering one anticoagulant, such as low-molecular-weight heparin (LMWH) or warfarin, is reasonable. The recommended therapeutic target in the United States is 0.5—1.0 of activated factor Xa level for LMWH or the international normalized ratio (INR) of 2—3 for warfarin. However, the main problem with warfarin use is the risk of intracranial hemorrhage (ICH). It has been shown that with a similar level of time in the therapeutic range, Asians have a four-fold higher risk of ICH than white people.[52] Additionally, the ICH mortality rate is higher in Asians than in white people.[53] On the basis of this difference in the warfarin-associated ICH risk between Western and Asian adults with atrial fibrillation, we recommend that the INR should be kept between 1.5 and 2.0 for Taiwanese children with KD taking warfarin.

6. Treatment for (IVIG-)refractory KD

Refractory KD is defined as persistence of fever for >36 h or recurrence of fever <7 days after completion of the first IVIG infusion. IVIG unresponsiveness occurs in most populations worldwide.[6] As shown in supporting file 1, between 6.7% and 26.8% of patients with KD from various cohorts were reportedly IVIG resistant and were at an increased risk of coronary complications.[8] Notably, the incidence of IVIG resistance is not proportional to the incidence of KD. For example, the incidence of KD in children younger than 5 years was 264.8/100,000 and 55.9/100,000 in Japan and Taiwan, respectively.[9,54] However, the incidence of IVIG resistance was 17.0% and 12.5% in Japan and Taiwan, respectively.[25,54] In Germany, the incidence of KD was 7.2/100,000 in children aged less than 5 years, and the incidence of IVIG resistance was 26.8%.[55] The reasons for these discrepancies remain unclear. Delayed treatment initiation, younger age, and IVIG brand may influence IVIG resistance.[56] IVIG resistance is associated with a higher risk of coronary artery abnormalities. Patients with a high risk

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of IVIG resistance can be identified using scoring systems, such as the Kobayashi or Formosa scoring system.[49,57] Some treatment regimens have been developed for IVIG resistance, but no absolute consensus regarding the standard regimen exists (Table 2). Most experts have proposed retreatment with a second dose of IVIG (2 g/kg). Although retrospective studies have supported the efficacy of retreatment with IVIG, compelling randomized controlled trials are still lack.

Corticosteroid is an alternative agent for refractory KD treatment. Some Japanese studies have compared the efficacy of pulsed intravenous methylprednisolone with that of IVIG to treat refractory KD, and the results were controversial. Another large retrospective study assessed the efficacy of intravenous low-dose prednisolone. The dose regimen was 2 mg/kg/day in 3 divided doses initially until defervescence and CRP normalization (<0.5 mg/dL), followed by the oral form with a three-step tapering regimen over 15 days. Patients treated with IVIG plus prednisolone had a lower rate of treatment failure and CALs than patients treated with IVIG only or prednisolone only.[58] At present, a Randomized controlled trial to Assess add-on Steroid efficacy for Taiwanese refractory KD (RAST trial) is being conducted to evaluate whether IVIG plus low-dose prednisolone is more effective for treating patients with refractory KD than IVIG alone. The results of this RAST study will be published in the near future.

Other treatments including infliximab, cyclosporine (an inhibitor of the calcineurin–NFAT pathway), cyclophosphamide (an alkylating agent for the DNA replication block), anakinra (a recombinant human IL-1β receptor antagonist), and plasma exchange require additional studies to evaluate their efficacy.

6.1. Follow-up

The follow-up schedules vary and mainly depend on the initial 1 month after KD onset and the current severity of the coronary artery abnormalities classified using coronary Z scores and diameters. Regression to the normal luminal diameter is common and generally occurs within the 2 years following the illness in patients with small coronary aneurysms. Most small aneurysms regress within 1 year after KD onset.[40] However, thickening intima and vascular reactivity impairment of the coronary arteries are often observed in these patients.[59] Half of the medium-sized aneurysms regress to normal, and few aneurysms lead to coronary events in patients with KD.[44] However, patients with giant aneurysms have a high risk of coronary artery events during long-term follow-up. One study at a tertiary medical center in Taiwan reported that one-quarter of KD patients with giant aneurysms had major cardiac events within 10 years after KD onset, and half of these patients had ischemic events within 20 years after KD onset.[40]

Low-dose aspirin should be administered for 6–8 weeks after the illness in patients with normal or transient coronary dilatation. In KD patients with small aneurysms, low-dose aspirin should be administered until the Z score is less than +2.5. Low-dose aspirin should be prescribed for lifelong in patients with persistent medium or large/giant aneurysms. Dual antiplatelet agents may be administered in patients with medium or large/giant aneurysms. For Taiwanese patients with large/giant aneurysms, the administration of LMWH or warfarin with a target INR of 1.5–2.0 (2.0–3.0 for white people) is reasonable. If large/giant aneurysms regress in size to medium aneurysms, discontinuation of the anticoagulant may be considered.[6]

To prevent potential cardiovascular events, the 2017 AHA guidelines proposed an algorithm for the long-term assessment of the subacute and convalescent phases of KD, including images, laboratory tests, physical activity counseling, and pregnancy counseling depending on the severity, and risk stratification of coronary artery abnormalities. These topics are beyond the scope of this review. Interested readers should refer to the following link for further details: https://doi.org/10.1161/CIR.0000000000000484.

7. Conclusion

KD is the leading cause of acquired heart diseases in children in developed countries. The diagnostic criteria and initial treatment regimen are well established, but the timely diagnosis of KD is difficult in patients aged less than 6 months because of atypical presentations. KD should always be considered in children with prolonged unexplained fever. The role of the coronary Z scores has become increasingly crucial for managing and following up patients with KD. IVIG only and IVIG plus low-dose prednisolone are both reasonable choices of treatments for patients with refractory KD, and a prospective randomized control trial is underway. Future studies that facilitate the earlier diagnosis of atypical KD and personalized treatment for refractory KD are warranted. Timely diagnosis, timely treatment, and an effective risk-stratified treatment regimen can reduce the incidence of coronary artery abnormalities in the acute and chronic phases of KD.

Conflicts of interest

The authors have no conflicts of interest to this article.

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