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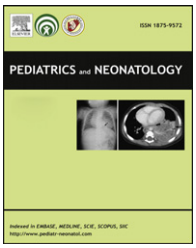

REVIEW ARTICLE

Kawasaki Disease: An Update on Diagnosis and Treatment

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Kawasaki disease (KD) is an acute multi-system vasculitis syndrome of unknown etiology occurring mostly in infants and children younger than 5 years of age. In developed countries, it is the leading cause of acquired heart disease in children. However, KD remains a mysterious disease. Some viruses potentially causing the condition have been isolated, but the results have not been able to be reproduced. This article reviews and summarizes different aspects of KD and provides updated information on diagnosis and treatment. The supplementary criteria for incomplete presentation of KD patients suggested by the American Heart Association, treatment (including tumor necrosis factor-alpha antagonist, methylprednisolone pulse therapy, statins, plasma exchange, and cytotoxic agents) for those with intravenous immunoglobulin treatment failure, and other experiences are also included in this review.
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1. Introduction

Kawasaki disease (KD) is an acute febrile systemic vasculitis that was first described by Kawasaki et al[1] in 1974. In developed countries, it is the leading cause of acquired heart disease in children, however its etiology remains

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unknown.[2–4] KD mainly affects children less than 5 years of age, especially those in Asian countries, but its incidence has increased worldwide. In Japan, Korea, and Taiwan, the incidence ranges from 69 to 218 cases per 100,000 children less than 5 years of age.[5–7] The incidence of KD in Taiwan has increased from 66 to 69 per 100,000 children aged less than 5 years.[5–8] An epidemiologic survey of KD in Taiwan from 2003 to 2006 found that 1.5% of all cases were recurrent.[6] In Taiwan, KD occurs most frequently in the summer (April to June) and least frequently in the winter, but for unknown reasons, its seasonal occurrence varies in other countries. The most serious complication of KD is the involvement of coronary artery lesions (CAL), including myocardial infarction, coronary artery fistula formation,[9] coronary artery dilatation, and coronary artery aneurysm.[10]

The most commonly used definition of CAL (also known as coronary artery abnormality, CAA, or CALs) is based on the Japanese Ministry of Health criteria: maximum absolute internal diameter >3 mm in children younger than 5 years of age or >4 mm in children 5 years and older, or a segmental diameter 1.5 times greater than that of an adjacent segment, or the presence of luminal irregularity.[11–15] Coronary arteries should be corrected relative to body surface area (if available) and expressed as standard deviation units from the mean (Z scores).[16] Several studies have analyzed CAL, including aortic root dimension,[17] and transient CAL (the definition of "transient" varies among studies, from 30 days to 6–8 weeks after diagnosis of disease). As such, KD patients with coronary artery ectasia or dilatation, which disappears within the first 8 weeks after disease onset, are defined as transient ectasia or dilatation (transient CAL). According to our previous report on CAL analysis including 341 KD patients,[18] 35% of KD patients had dilatation during the acute phase of admission, 17.2% had dilatation 1 month after disease onset, 10.2% had dilatation at 2 months, and 4% had persistent CAL for more than 1 year.[19]

Although the clinical features of KD are recognizable, its underlying immunopathogenetic mechanisms are still under investigation, particularly the agent responsible for the development of CAL. KD is regarded as an autoimmune disorder rather than an infectious disease.[17] Kuo et al[20] reported that persistent monocytosis after intravenous immunoglobulin (IVIG) treatment is associated with CAL formation. Eosinophils were also higher in KD patients than in age-matched febrile controls. In addition, IVIG treatment significantly increased eosinophils in KD patients. This increase of eosinophils after IVIG treatment is inversely correlated with IVIG treatment failure in KD.[21] Further studies have shown that changes of eosinophils after IVIG treatment were positively correlated with changes in interleukin (IL)-5 levels. An increase in eosinophils and IL-5 levels after IVIG treatment was inversely correlated with CAL formation.[22]

Immune- and apoptosis-related genes [cytotoxic T lymphocyte-associated antigen 4 (CTLA-4), caspase 3 (CASP3), IL-10, IL-1B, CD40L, programmed death 1 (PD-1), ORAI1, and inositol 1,4,5-trisphosphate 3-kinase C (ITPKC)] have been associated with susceptibility and/or disease outcome,[13,15,18,19,22–30] further highlighting the involvement of immune responses and imbalances between T helper cell 1/2 (Th1/Th2) immune responses in the pathogenesis of KD. A skewed Th2 response (eosinophil and IL-5 levels) may indicate good IVIG treatment response and subsequent disease outcome. Weng et al[26] reported that an IL-10 gene polymorphism is associated with CAL formation and IL-1B is associated with IVIG treatment response.[25] Some studies of genetic variants also found a difference between male and female genders, including CTLA-4 and cytokine genes (IL-1B, IL-4, IL-8, and IL-10).[30,31] Shimizu et al[17] reported that the transforming growth factor-beta (TGF-β) signaling pathway influences KD susceptibility, disease outcome, and the response to IVIG therapy, and also shows immune response dysregulation. The inheritance patterns of these traits have not been described in these studies. It is likely that multiple polymorphic alleles influence KD susceptibility and disease outcome. This suggests that different ethnic populations and different genders may have different susceptibilities to KD.

The diagnosis and treatment of KD has become one of the most controversial issues for pediatricians in Taiwan, based on a nationwide questionnaire conducted by the Taiwan Pediatric Association in 2009. This article reviews updated information on KD and focuses on diagnosis and treatment aspects of the disease.

2. Updates on the Diagnosis of Kawasaki Disease

The clinical characteristics of KD patients include prolonged fever lasting longer than 5 days, diffuse mucosal inflammation, bilateral nonpurulent conjunctivitis, dysmorphic skin rashes, indurative angioedema over the hands and feet, and cervical lymphadenopathy. In addition to the diagnostic criteria, there is a broad range of nonspecific clinical features, including irritability, uveitis, aseptic meningitis, cough, vomiting, diarrhea, abdominal pain, gallbladder hydrops, urethritis, arthralgia, arthritis, hypoalbuminemia,[4] liver function impairment, and heart failure.[3,21,32]

To date, there is no specific diagnostic test for KD. Diagnosis is based on the presence of fever lasting longer than 5 days and four of five specific clinical criteria. In Japan, at least five of six criteria (fever and five other clinical criteria) should be fulfilled for a diagnosis of KD. However, patients with four of the principal clinical features can be diagnosed when coronary aneurysm or dilatation is recognized.[24] From the Japanese Circulation Society Joint Working Groups criteria (JCS 2008, Guidelines for diagnosis and management of cardiovascular sequelae in Kawasaki disease),[33] KD can be diagnosed even when fever lasts less than 5 days. However, according to the American Heart Association (AHA) criteria,[10] fever lasting more than 5 days is essential for KD diagnosis (comparison of diagnosis criteria from JCS and AHA is shown in Table 1).

Some patients who do not fulfill the criteria outlined in Table 1 have been diagnosed with "incomplete" or "atypical" KD, a diagnosis often based on echocardiographic identification of CAL. The term "incomplete" may be preferable to "atypical" because these patients have insufficient criteria instead of atypical presentation.[10]

In countries with a bacillus Calmette-Guérin (BCG) vaccine policy (i.e., Taiwan and Japan), KD with erythematous induration or even ulceration of the BCG scars has

Table 1 Comparison of the diagnostic criteria of Kawasaki disease.

AHA criteria 2004	JCS 2008 Guidelines
Fever ≥5 days and at least 4 of the following 5	At least 5 of the following 6
Bilateral nonsuppurative conjunctivitis	The same
One or more changes to the mucous membranes including pharyngeal injection, dry fissured lips, injected lips, and strawberry tongue	The same
Indurative angioedema of the hands and feet including peripheral erythema, peripheral edema, periungual desquamation, and generalized desquamation	The same
Dysmorphous skin rashes	The same
Acute nonpurulent cervical lymphadenopathy >1.5 cm in diameter	The same
	Fever*

*Fever of more than 5 days is essential for diagnosis in AHA (American Heart Association) 2004 criteria but not in the JCS (Japanese Circulation Society) 2008 criteria.

been observed in one-third to half of KD patients (the incidence of BCG site induration is higher than that of neck lymphadenopathy in these countries).[2] Uehara et al[34] reported that redness or the formation of a crust at the BCG inoculation site is a useful diagnostic sign for KD in children aged 3—20 months. Even if patients have four or fewer signs of the clinical criteria for KD, physicians should consider the redness or crust formation at the BCG inoculation site as a possible indicator of KD.

Atypical cases of KD are not uncommon (up to 15—20%). The incidence of CAL in patients exhibiting four principal symptoms of KD is slightly higher than in patients with five to six principal symptoms.[35] Presentation of a small number (< 4) of principal symptoms does not indicate a milder form of the disease. Patients with at least four principal symptoms require the same treatment as patients with complete (typical) KD, and those with three or fewer principal symptoms should be treated similarly when they meet the supplementary criteria. Herein, common supplementary criteria for the diagnosis of incomplete KD are introduced.

3. American Heart Association (AHA) Criteria 2004

Incomplete KD is more common in young infants than in older children, making accurate diagnosis and timely treatment especially important in these young patients who are at substantial risk of developing coronary abnormalities.[36,37] The incidence of KD is actually higher than previously reported throughout the world, partly because earlier reports did not take incomplete forms into account. The AHA criteria (2004), which incorporate suggestions for laboratory tests and early echocardiography, are helpful for diagnosing incomplete KD.[32,38] Consultation with an expert (cardiologist, immunologist, or rheumatologist) should be sought at any time when assistance in making a diagnosis is needed. Patients with fever for ≥ five days (with 2 or 3 principal clinical features for KD) without other explanation should undergo laboratory testing, and if there is evidence of systemic inflammation, an echocardiogram should be obtained even if the patient does not fully meet the clinical criteria for KD. Infants ≤6 months old with fever for ≥7 days without other explanation should undergo laboratory testing, and if evidence of systemic inflammation is found, an echocardiogram should be obtained even if the infant has no clinical criteria for KD.[10]

The 2004 AHA supplemental laboratory criteria (Table 2) include: (1) albumin ≤3.0 g/dL; (2) anemia for age; (3) elevation of alanine aminotransferase; (4) platelets after 7 days ≥450,000/mm^3; (5) white blood cell count ≥15,000/mm^3; and (6) urine ≥10 white blood cells/high-power field.[10] If a patient has more than three supplementary criteria, incomplete KD is diagnosed and IVIG should be prescribed before performing echocardiography.[10]

4. Updates on the Treatment of Kawasaki Disease

4.1. Aspirin

Aspirin has been used in the treatment of KD for many years, even before the advent of IVIG. Although aspirin has important anti-inflammatory (high-dose) and antiplatelet (low-dose) activity, it does not appear to lower the frequency of CAL formation. During the acute phase of the illness, aspirin is administered at 80 to 100 mg/kg per day (30—50 mg/kg in Japan)[39] in four doses with IVIG. High-dose aspirin and IVIG appear to possess additive anti-inflammatory effects.

Table 2 Supplementary laboratory criteria for incomplete Kawasaki disease.

Fever of >5 d associated with 2 or 3 clinical criteria, C-reactive protein ≥3.0 mg/dL and/or erythrocyte sedimentation rate ≥40 mm/h with the following criteria
(1) albumin ≤ 3.0 g/dL
(2) anemia for age
(3) elevation of alanine aminotransferase
(4) platelets after 7 d ≥ 450,000/mm^3
(5) white blood cell count ≥15,000/mm^3
(6) urine ≥10 white blood cells/high-power field

Modified from Newburger et al.[10]
If ≥3 supplement criteria are met, intravenous immunoglobulin can be prescribed before performing echocardiography.
CRP = C-reactive protein; ESR = erythrocyte sedimentation rate; IVIG = intravenous immunoglobulin.

Practices regarding the duration of high-dose aspirin administration vary across countries and centers, many of which reduce the aspirin dose when the patient is afebrile. When high-dose aspirin is discontinued, low-dose aspirin (3–5 mg/kg/day) is given until there is no evidence of CAL and inflammatory markers [including platelets, C-reactive protein (CRP), and erythrocyte sedimentation rate (ESR)] have returned to normal levels, which usually occurs 6–8 weeks after disease onset. For children who develop CAL, low-dose aspirin (or other antiplatelet agents) is continued indefinitely until the inflammatory markers return to the normal range and the echocardiogram does not show abnormalities. Hsieh et al[39] reported that regardless of timing (before or after Day 5 of the illness), single-infusion, high-dose (2 g/kg) aspirin in the acute stage of KD had no effect on the response rate to IVIG therapy, duration of fever, or the incidence of CAL. This review reiterates the recommendation that exposing children to high-dose aspirin therapy in the acute phase of KD is unnecessary because available data show no appreciable benefit to IVIG therapy response, CAL formation, or fever duration.

Our recent study investigated 609 KD patients from two medical centers in Taiwan.[40] The patients were divided into Group 1, with high-dose aspirin ($n = 274$), and Group 2, without high-dose aspirin ($n = 335$). There were no significant differences between groups 1 and 2 in terms of gender ($p = 0.51$), IVIG resistance rate (34/274 vs. 26/335, $p = 0.06$), CAL formation rate (57/274 vs. 74/335, $p = 0.64$), and total hospital stay (6.3 ± 0.2 vs. 6.7 ± 0.2, $p = 0.13$). There were also no significant differences between total white blood counts, hemoglobin levels, platelet counts, and CRP levels before (within 1 day) and after (within 3 days) IVIG treatment between the two groups ($p > 0.1$). These results provide evidence that high-dose aspirin in the acute phase of KD does not affect the treatment results (CAL and IVIG resistance rate) or inflammatory condition. High-dose aspirin treatment in the acute phase of KD seems to be unnecessary and further randomized controlled trials are needed.

4.2. Intravenous immunoglobulin (IVIG) responsiveness

The efficacy of IVIG administered in the acute phase of KD for reducing the incidence of coronary artery abnormalities is well established.[41] The mechanism of IVIG action is still under investigation. IVIG appears to have a generalized anti-inflammatory effect. Possible mechanisms of action include modulation of cytokine production, neutralization of bacterial super-antigens or other etiologic agents, augmentation of regulatory T cell activity (TGF-β),[17] suppression of antibody synthesis and inflammatory markers (CD40L, nitric oxide, and iNOS expression),[42,43] providing of anti-idiotypic antibodies, and balancing Th1/Th2 responses.[20–22]

KD patients should be treated with a single 12-hour infusion of IVIG, 2 g/kg in a single infusion, together with aspirin in acute phase with fever, or inflammation progression without fever.[2,3,10] This therapy should be performed within 10 days of illness onset, and if this is not possible, within 7 days of illness onset. Treatment of KD before Day 5 of the illness appears no more likely to prevent cardiac sequelae than treatment on Days 5–9. It may, however, be associated with an increased need for IVIG retreatment.[44,45] In the presence of four of five classic criteria for KD, US and Japanese experts agree that only 4 days of fever are necessary before initiating treatment with IVIG.[10,46]

The efficacy of treating patients using IVIG after 10 days of illness is unknown; therefore, early diagnosis and treatment is desired. IVIG should be administered to children presenting after Day 10 of illness (i.e., children with delayed diagnosis or incomplete KD) if they have either persistent fever without explanation or aneurysms and ongoing systemic inflammation, as manifested by elevated ESR or CRP.[3,47–49] Burns et al[3] also suggested that any child with KD who has evidence of persisting inflammation, including fever or high concentrations of inflammatory markers with or without coronary artery abnormalities, should be treated even if the diagnosis is made after 10 days of illness.

4.3. IVIG resistance (initial IVIG treatment failure)

The incidence of IVIG resistance varies between centers, from 9.4% to 23% (but it can be as high as 38%, as reported in one American cohort).[50] Recent studies have identified demographic and laboratory characteristics as predictors of IVIG resistance, including age, illness day, platelet count, ESR, hemoglobin concentration, CRP, eosinophil, lactate dehydrogenase, albumin, and alanine aminotransferase (ALT).[4,21,51–53] Because IVIG-resistant patients are at a higher risk for CAL formation, it is important to identify those who may benefit from a more aggressive therapy. As shown in Figure 1 (modified from Newburger et al[10]), there are no definite treatment principles available for the management of KD patients with initial IVIG resistance or unresponsiveness to other adjuvant therapies. A second dose of IVIG (1 g/kg or 2 g/kg),[10,54] methylprednisolone pulse therapy,[55] tumor necrosis factor-alpha (TNF-α) blockade,[56] cytotoxic agents (cyclophosphoamide, cyclosporine A, or MTX[57]), plasmapheresis,[58] and plasma exchange[59] have been reported to benefit KD patients with initial IVIG treatment failure. These other treatment modalities will be discussed.

4.4. Methylprednisolone (MP) pulse therapy

At present, the usefulness of steroids in the initial treatment of KD is not well established.[10] Newburger et al[16] reported that single-pulsed dose of intravenous methylprednisolone (IVMP) compared to conventional IVIG therapy for routine primary treatment of KD in children does not improve treatment outcome. However, IVMP therapy seems to benefit IVIG-resistant KD patients.[60] Miura et al[61] revealed the effectiveness of IVMP therapy for KD patients that were previously unresponsive to initial IVIG treatment. IVMP suppresses cytokine levels faster, and subsequently, the outcomes are similar to those of IVIG responsive patients who receive a second dose of IVIG. Furukawa et al[62] reported similar findings. IVMP seems to have the same effect on IVIG-resistant KD patients

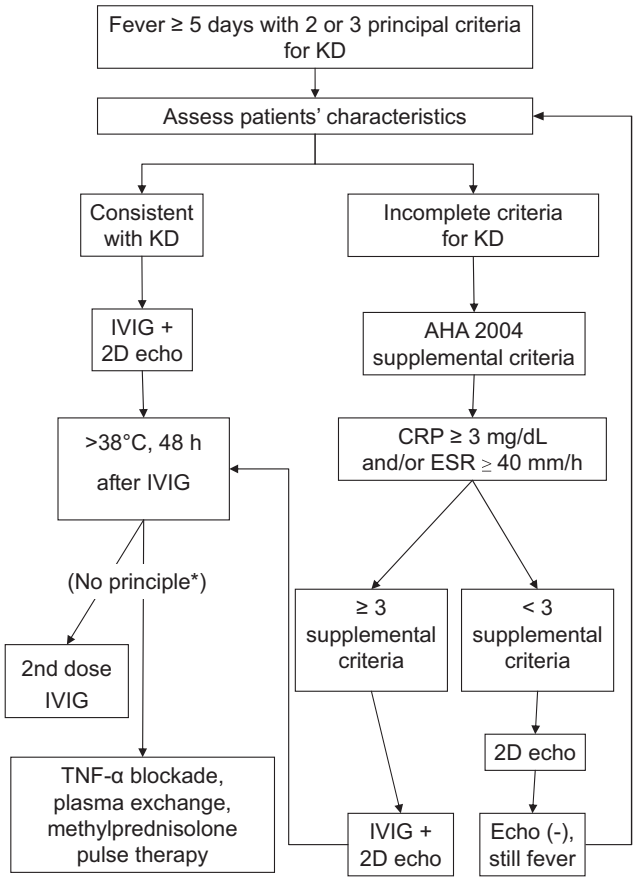

Figure 1 Flow chart reference for the management of refractory and incomplete Kawasaki disease (KD) (modified from Newburger et al[10]). *There were no definite treatment principles available for the management of KD patient with initial IVIG resistance or unresponsiveness to other adjuvant therapies. Second dose of IVIG (1 g/kg or 2 g/kg),[10,54] methylprednisolone pulse therapy,[55] tumor necrosis factor-alpha blockade,[56] cytotoxic agents (cyclophosphoamide, cyclosporine A, or MTX[57]), plasmapheresis,[58] and plasma exchange[59] have been reported to benefit KD patient with initial IVIG treatment failure. Supplemental laboratory criteria for incomplete KD were as shown in Table 2. AHA = American Heart Association; CRP = C-reactive protein; ESR = erythrocyte sedimentation rate; KD = Kawasaki disease; IVIG = intravenous immunoglobulin; 2D echo = two-dimensional echocardiography; TNF-α = tumor necrosis factor-alpha.

compared to an additional IVIG treatment.[33] The cost-benefit differences between IVMP and additional IVIG should be carefully considered, taking into account different medical conditions or health insurance policies among countries. The first dose of IVIG is well established, while IVMP or additional IVIG for IVIG-resistant KD patients requires further investigation. Ogata et al[33] reported that IVMP was useful to reduce fever duration and medical costs for KD patients with initial IVIG resistance. IVMP (n = 13) and additional IVIG treatment (n = 14) were not significantly different in terms of preventing the development of coronary artery aneurysm. IVMP (methylprednisolone 30 mg/kg per day for 3 days) or a second dose of IVIG (2 g/kg) was prescribed to KD patients with fever and marked inflammation (i.e., nonexudative conjunctival injection, strawberry tongue, fissure lips, and erythematous change at the BCG inoculation site) 48 hours after initial IVIG treatment.[16,33,62,63]

The safety of IVMP therapy in patients with KD is uncertain. Miura et al[64] reported that IVMP (n = 11) incurred a higher incidence of sinus bradycardia and hyperglycemia when compared with the additional IVIG group (n = 11). Hypertension did not differ significantly between IVMP and IVIG groups. All of the adverse effects were transient. There were no convulsions, gastrointestinal symptoms, infections, malignant arrhythmias, or sudden deaths in any subjects.[64] Taken together, IVMP is safe for KD patients as additional or adjuvant therapy of initial IVIG treatment.[16,65,66] After additional IVIG therapy, IVMP is considered for KD patients with persistently poor responses to the second IVIG treatment.[54,67]

4.5. Tumor necrosis factor-alpha (TNF-α) blockade

TNF-α levels are elevated in children with KD,[68] and the TNF-α (-308) genetic polymorphism is associated with KD susceptibility, suggesting a role for TNF-α receptor blocking in the treatment of KD, especially for those patients/cases refractory to IVIG. The early administration of TNF-α receptor antagonists in KD may provide effective adjunctive therapy. Infliximab, which binds the proinflammatory cytokine TNF-α, has been evaluated in several studies and shown to have a significant effect in KD patients with IVIG resistance.[69–71] Recently, etanercept, a more suitable TNF-α receptor blocker for children with refractory juvenile idiopathic arthritis,[72,73] was reported to benefit the treatment of IVIG-resistant KD as an adjuvant therapy to initial IVIG.[74,75] TNF-α receptor blocker may be administered after initial IVIG treatment failure or after a second dose of IVIG therapy.

4.6. Statins

Chronic vascular inflammation and endothelial dysfunction persists in KD patients with CAL, even long after the acute stage.[76,77] There is currently no specific treatment for ongoing vascular inflammation and endothelial dysfunction. Low-dose aspirin can be prescribed until CAL normalizes, but it does not have an effect on inflammation or endothelial dysfunction. Lipid abnormalities in the acute phase of KD, with decreased triglycerides and high-density lipoprotein-cholesterol (HDL-C) levels have been reported in previous studies.[78,79]

Statins, hydroxymethylglutaryl coenzyme A reductase inhibitors, have been shown to reduce cholesterol levels as well as improve surrogate markers of atherosclerosis and cardiovascular disease.[80] Huang et al[81] reported that short-term (3 months) statin treatment (simvastatin, 10 mg/day as a single dose at bedtime) in KD patients complicated with CAL (n = 11) can significantly reduce total cholesterol (TC) and low-density lipoprotein-cholesterol (LDL-C) levels, and increase HDL-C level. Chronic vascular inflammation is also significantly improved, as well as endothelial dysfunction, with no adverse effects. However, long-term

and randomized control trials are needed before further conclusions can be made.

Recently, Blankier et al[82] also reported that atorvastatin is able to inhibit critical steps (T cell activation and proliferation, production of the proinflammatory cytokine TNF-α, and up-regulation of matrix metalloproteinase-9 and an elastolytic protease) known to be important in the development of coronary aneurysms in an animal model of KD (murine model with injection of Lactobacillus casei cell wall extract), suggesting that statins may have therapeutic benefits in KD patients. Taken together, statins may be beneficial as an adjuvant therapy in KD patients with CAL. However, the association between dyslipidemia and atherosclerosis in KD patients is not certain.

4.7. Other treatments

Acute KD can lead to the development of large coronary artery aneurysms that may persist for years. Abciximab, a platelet glycoprotein IIb/IIIa receptor inhibitor, is associated with resolution of thrombi and vascular remodeling in adults with acute coronary syndromes. Williams et al[83] reported that KD patients who were treated with abciximab demonstrated greater regression in aneurysm diameter at early follow-up than patients who received standard therapy alone. McCandless et al[84] also reported that abciximab treatment might be associated with vascular remodeling in patients with aneurysms. Abciximab seems to benefit KD patients, especially those who developed aneurysms.

There are still no well-defined treatments for refractory KD. Suzuki et al[85] reported that cyclosporine A (CyA) treatment is considered safe and well-tolerated, and may serve as a promising option for patients with refractory KD. Hyperkalemia developed in 9/28 (32%) patients 3 to 7 days after commencing CyA treatment. Adverse effects such as arrhythmias should be monitored with CyA. Kuijpers et al[86] described a case of mortality, and a review of the literature showed that immunosuppressive medication such as CyA may not influence coronary inflammation and proliferation. Further trials are needed to clarify optimal dose, safety, and timing of CyA treatment.

Specific changes in inflammatory markers [such as white blood cell count, neutrophil count, CRP, IL-6, soluble IL-2 receptor (sIL-2R),[87] T helper type 17/regulatory T cell imbalance,[88] and IL-1 pathway[89]] have been reported to disturb immunological functions and result in KD with IVIG resistance and CAL formation. This indicates the possible treatment role of plasma exchange (PE) for KD with IVIG resistance. Mori et al[59] studied 46 children who had not responded to the second IVIG treatment and subsequently received PE and compared them with 59 children that received a third dose of IVIG therapy. No complications occurred with PE therapy. CAL developed in eight of the 46 children (17.3%) who received PE and in 24 of the 59 (40.7%) who received a third course of IVIG ($p < 0.001$). PE is considered safe and effective in the prevention of CAL in KD that is refractory to IVIG therapy. PE could be performed at an early stage, as soon as fractional increases in inflammatory markers are found after first or second dosage of IVIG therapy.[59]

5. Conclusions

The incidence of KD is increasing globally,[6,8,90–95] especially in Asian countries.[8] Incomplete presentation of clinical symptoms may complicate and delay the diagnosis of KD, or increase the rate of CAL. Supplementary criteria for diagnosing KD should be applied to every pediatric patient who experiences fever for more than 5 days (with two or three principal clinical features of KD) without a known infection source. Due to the rate of resistance to initial IVIG treatment, additional anti-inflammatory agents, a second dose of IVIG, IVMP, or TNF-α receptor blockers should be considered and administered as early as possible to diminish inflammation, endothelial dysfunction, and CAL formation. Because IVIG-resistant patients are at higher risk for CAL formation, it is important to identify those who may benefit from a more aggressive therapy. Early and appropriate treatment of KD may decrease the life-long sequelae of CAL in children.

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