Review Article

Kawasaki disease in 2019—past controversies, present insights and future directions: a narrative review

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Background and Objective: Kawasaki disease (KD) is a condition that is of interest to many pediatricians. Notwithstanding possible complications to coronary arteries, there is much that is yet unknown, including the controversies which surround this vasculitis. This article discusses evolution of our knowledge in KD over 5 decades, and reviews the advances which have been made.

Methods: We searched relevant articles in PubMed and also using Google Scholar search engine on 1 October 2018 without any date restrictions. The main search term included Kawasaki disease combined with paediatric using AND operator, and further combining these terms with phrases like diagnosis, management, echocardiography, risk factors, IVIG resistance, treatment, post-KD vascular health. Being a narrative review, we did not have any specific exclusion criteria and included all types of study designs published in English language, as long as they provided information to meet the scope of the current narrative review.

Key Content and Findings: Making a timely and accurate diagnosis is essential for appropriate treatment, and incomplete KD adds a dimension to this complexity. While there are guidelines available for diagnosis, including clinical and echocardiographic findings, there is no definitive laboratory test, given the still unclear etiology. The best treatment option for recalcitrant disease is also debatable, as are the factors for those at high risk for coronary dilation. Although scoring systems are now available to risk stratify, these have variable success.

Conclusions: From the first description of KD in 1967, we now know better how to detect, treat and follow up its complications. It is envisaged that with rapid advances in research and collaborative work among physicians in this field, that we will be even better equipped with knowledge to risk-stratify, diagnose and manage KD, especially the incomplete and complex variants, in achieving better outcomes

Keywords: Kawasaki disease (KD); echocardiography; coronary dilation; intravenous immunoglobulins (IVIG); risk scoring

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Kawasaki disease (KD) is an acute medium vessel vasculitis of still unclear aetiology which typically afflicts children under 5 years (1). The peak onset is between 18 and 24 months, with an ethnic predilection for Asian populations. It is associated with long-term coronary artery abnormalities, such as coronary artery aneurysm (CAA) and ectasia in up

Table 1 AHA versus JMH clinical diagnostic guidelines

AHA 2017 (McCrindle *et al.* 2017)
Fever for at least 5 days
And at least 4 out of 5 of the following:
Bilateral bulbar conjunctival injection without exudates
Erythema and cracking of the lips, strawberry tongue, or erythema of the oral and pharyngeal mucosa
Cervical lymphadenopathy (>1.5 cm diameter), usually unilateral
Rash: maculopapular, diffuse erythroderma or erythema multiform like
Changes in extremities with erythema of palms and/or soles; edema of hands and/or feet in the acute phase and periungual peeling of fingers and toes in weeks 2 and 3
JMH 2013 (JCS Joint Working Group 2014)
5 of 6 of the following:
Fever for at least 5 days
Bilateral conjunctival congestion
Changes of lips and oral cavity
Acute non-purulent cervical lymphadenopathy
Polymorphous exanthema
Changes of peripheral extremities

AHA, American Heart Association; JMH, Japanese Ministry for Health.

to 15–25% of untreated children (1), and has surpassed rheumatic heart disease as the leading cause of pediatric acquired cardiac disease in the developed world (2). It has even been postulated that there is immune disequilibrium with abnormal and increased inflammatory and allergic manifestations (3,4).

Description of method

We searched relevant articles in PubMed and also using Google Scholar search engine on 1 October 2018 without any date restrictions. The main search term included Kawasaki disease combined with Paediatrics using AND operator, and further combining these terms with phrases like diagnosis, management, echocardiography, risk factors, IVIG resistance, treatment, post-KD vascular health. The relevant articles were also identified and included from the personal folders. Being a narrative review, we did not have any specific exclusion criteria and included all types of study designs published in English language as long as they provided information related to the presented narrative review. Both the authors reviewed all the studies in order to prepare the current narrative review. Any discrepancies were resolved with mutual consensus.

History of KD

In recent times, the management and prognosis for KD has been extensively studied with a few controversies. What remains unquestioned is that as an entity, KD was first described by Dr. Kawasaki in his seminal Japanese series of 50 cases published in the "*Japanese Journal of Allergy*" (5), and subsequently in English in 1974 (6). Dr. Kawasaki himself saw his first case in 1961 (7), although KD as an unnamed disease has surely been around before that not known by an eponymous name. Reports of fatal coronary arteritis have been described in the literature in at least 46 cases in the Western literature and 11 cases in Japan prior to 1967 (8). Nevertheless, the likely earliest case reported was by Dr. Samuel Gee of St. Bartholomew's, London, in 1870 (8) reporting on the autopsy of a 7-year-old boy. Dr Gee described "*…consequence of scarlatinal dropsy … The heart natural in size, and the valves healthy. The coronary arteries were dilated into aneurysms at three places*".

Diagnosing KD

Diagnostic criteria for KD have been relatively unchanged in the last 50 years. Currently, two guidelines are utilized (*Table 1*) (9,10) in different parts of the world. They however both share the same 6 variables of fever for at least 5 days, conjunctivitis, oral mucosal changes, polymorphous rash, peripheral extremity swelling or peeling and cervical lymphadenopathy.

Using these criteria, some important caveats need to be considered. Firstly, more than one clinical feature may have resolved by the time of presentation. Secondly the presence of a concomitant infection in KD should not rule out KD. In general, concomitant infections have been identified in up to 33% of patients with KD (11-13). In a Korean population of 54 KD patients, Cho and colleagues (12) reported a positive multiplex real-time PCR rate of 22%, and Jordan-Villegas and colleagues (13) reported a positive direct fluorescent antibody assay in 8.8% of patients to a variety of virus in 251 KD patients in Dallas. The situation

becomes especially challenging when one considers that common differentials of KD have been found as concomitant infections, including measles (14-16), scarlet fever (11,12,17-19), infectious mononucleosis (20) and adenovirus (12,13,21).

The major limitation of both guidelines is that they are based entirely on clinical criteria, with no pathognomonic laboratory test for diagnosis. Clinical acuity and acumen are key to recognising these patients. Therefore, there is a major challenge in diagnosing atypical presentation that constitutes 20–30% of cases (22). As a consequence, there are 3 major pitfalls: (I) risk of under-diagnosis, with resultant higher risk of coronary and non-coronary complication; (II) risk of over-diagnosis with side effects of medication and healthcare burden; (III) recognising incomplete or atypical forms of the condition.

Incomplete KD

Clinical judgment becomes more tedious in atypical ages such as infants, especially in those <6 months, where fever and irritability may be the only clinical manifestation. In this group, <50% of patients meet the traditional criteria (23). As a consequence, the burden of coronary artery disease is significantly higher in infants. Salgado and colleagues (24) reported >2× rate of any CAA in 43.4% in patients with KD <6 months old compared to 19.5% in those >6 months old. Furthermore, 18.6% of infants<6 months with normal echocardiogram at diagnosis, developed CAA on follow-up within 8 weeks.

It is therefore prudent to be vigilant and maintain a high index of suspicion for KD in infants <6 months with prolonged fever and any of the following: (I) irritability; (II) aseptic meningitis; (III) unexplained or culture-negative shock; (IV) cervical lymphadenitis unresponsive to antibiotic therapy; (V) retropharyngeal or parapharyngeal phlegmon unresponsive to antibiotic therapy (9).

A similar diagnostic challenge occurs in the older patient beyond 5 years. Not only is echocardiography of the coronary vessels challenging in this group but the clinical picture is skewed, with a higher incidence in those with human immunodeficiency virus infection (25), increased rates of lymphadenopathy (93% of adult *vs.* 15% of paediatric cases) and joint involvement in (61% of adults *vs.* 24% to 38% of children) (26). To date more than 100 cases of adult onset KD have been reported in the literature (25,27-36) with the oldest diagnosed at 48 years old (36). This group, similarly to those <6 months is associated with higher risk of CAA (25,37).

There is another high-risk group in up to 5% of patients who present with the KD shock syndrome. These cases are usually diagnosed late, after they are initially treated for bacterial sepsis and septic shock (9,38,39). As a consequence, higher rates of coronary artery abnormalities, Intravenous Immunoglobulin (IVIG) resistance and myocardial dysfunction arise in this subset (40,41).

To aid in the issue of incomplete KD, current guidelines have attempted to propose pathways to tackle the issue of atypical presentation (9). Index of suspicion is raised with these pathways when 2 or 3 criteria are met with fever of at least 5 days, or in the higher risk group of infants less than 6 months with unexplained fever for 7 days. In these patients, any elevated inflammatory markers [C-reactive protein (CRP) ≥3.0 mg/dL and/or erythrocyte sedimentation rate (ESR) ≥40 mm/h] warrants further workup. A positive diagnosis is presumed if 3 or more laboratory findings are positive (anemia for age, platelet count ≥450,000 after 7th day of illness, Albumin ≤3.0 g/dL, elevated AST, WBC count ≥15,000/mm^3, urine ≥10 WBC/hpf) or if the echocardiogram is positive.

Despite these, clinical acumen is still required to recognise the potential of KD in the first place. To help identify these patients, it is prudent to evaluate supporting clinical features that are not part of the formal guidelines. Of these, reactivation of the Bacillus Calmette-Guérin injection site appears to be specific, present in up to 30.4% (42-45) of cases. Other features include extreme irritability, out of proportion to the fever (46,47), peripheral arthritis (48), perineal desquamation (49-51), aseptic meningitis (52), transient peripheral facial nerve palsy (53,54) and even sensorineural hearing loss (55). Additionally, supporting biochemical data can be useful. This includes elevated acute phase reactants and total white cell count with neutrophil predominance, low serum sodium and albumin levels (9), mild to moderate transaminases or gamma-glutamyl transferase (GGT) in 40% to 60%, mild hyperbilirubinemia in ≈10% (56,57), sterile pyuria in up to 9% (58-60) and gallbladder hydrops (61,62).

Newer markers such as N terminal pro-B-type natriuretic peptide (63,64), IL-6 and inflammatory cytokines (65) have been promising. Beyond biochemical markers, the role of molecular modalities is gaining interest. Jaggi and colleagues (66) analysed blood transcriptional profiles and identified a classic KD bio-signature that was validated in three additional KD cohorts. They observed overexpression of inflammation, platelets, apoptosis and neutrophil

Table 2 AHA versus JMH guidelines for coronary aneurysm

Definition	AHA 2017 (McCrindle *et al.* 2017)	JMH 2013 (JCS Joint Working Group 2014)
No involvement	z-score <2.0	–
Dilatation only	2.0< z-score <2.5	–
Small aneurysm	2.5≤ z-score <5	ID <4 mm, or if child ≥5 years ID ≤1.5 times adjacent segment
Medium aneurysm	5≤ z-score <10 and absolute <8 mm	ID >4 to ≤8 mm, or if child ≥5 years ID 1.5 to 4 times adjacent segment
Large aneurysm	z-score >10 or absolute ≥8 mm	ID >8 mm, or if child ≥5 years ID >4 times adjacent segment

AHA, American Heart Association; JMH, Japanese Ministry for Health; ID, internal diameter.

genes, and under expression of T and NK cell genes. In addition, serum exosomal miR-328, miR-575, miR-134 and miR-671-5p have also been described as potential biomarkers for the diagnosis of KD (67) furthering the scope of diagnostic markers in the future.

The role of genetics in KD is another advancing area which has attracted keen recent interest, with a slew of genetics polymorphisms identified to detect those at risk. To-date, more than 62 genes have been described, associated with susceptibility and 47 associated with CAA (40,68-75). A systematic review and meta-analysis of genetic associations with KD susceptibility narrowed down the list and identified gene polymorphisms to *ACE*, *BLK*, *CASP3*, *CD40*, *FCGR2A*, *FGB*, *HLA-E*, *IL1A*, *IL6*, *ITPKC*, *LTA*, *MPO*, *PD1*, *SMAD3*, *CCL17* and *TNF* (40).

Echocardiography

The utility of echocardiography in KD is one of the few modalities that is not controversial. The diagnosis of KD remains a clinical one, and it is important to note that initial echocardiogram is usually normal in the first week of illness, and this does not rule out KD (9). Nevertheless, echocardiography should be performed at diagnosis as a baseline to evaluate early coronary status and associated cardiac involvement such as valvar regurgitation present in up to 25% of individuals (9,76-78), aortic root dilatation in up to 10% (78), myocardial dysfunction and pericardial effusions, and dilatation of the aortic root with mild aortic regurgitation (AR) which can be present in up to 4% of individuals within 1 year of follow-up (79,80).

In addition, echocardiography can help support the diagnosis of incomplete KD by identifying CAA including dilatation and aneurysm (normalized to z-score), the presence or lack of tapering of the coronary arteries and echogenicity of coronary vessels (perivascular brightness) (9,81). This brings about another long-drawn controversy, what is the definition of a CAA. Both the AHA 2017 criteria's (9) and JMH 201 (10) define aneurysm differently, either by z-score or absolute internal diameter (ID) of the coronary artery at a given age respectively (*Table 2*) (9,10).

The mode of normalization of coronary dimensions for body surface area (BSA) with the use of a z-score calculator brings up another quandary. Which formula for calculating z-score should be used? Many formulae for deriving the z-score have been described (81-89) and each uses their own methods of regression and within unique populations with regards to age, race and gender. Currently the more widely used models based on more rigorous systems are the z-score calculators by Dallaire and colleagues (86) in a Canadian population and the calculator based on a Japanese population by Kobayashi and colleagues (84). Both show good and comparable outcomes. Ogata and colleagues (90) applied the Kobayashi (84) and Dallaire (86) scoring systems on 1,082 KD patients from 2 centers in the US and 3 centers in Japan with no significant differences in outcomes for either.

Risk factors for coronary dilatation

Abnormal early echocardiogram findings, with coronary dilatation in particular, are an independent risk factor of progressive coronary dilatation (91-95). Biochemical markers such as hypoalbuminemia have also independently been associated with the occurrence of progressive coronary dilatation (91). The key may lie in molecular and genetic baselines to risk stratify our patients. Optimal therapy should be based on being able to accurately identify and manage patients according to their risk stratification, allowing for individualised tailored therapy. Kwon and colleagues identified *TIFAB* gene as a susceptibility locus

for CAAs of more than 5 mm (68). Variations in *BTNL2*, *CASP3*, *FCGR2A*, *FGF23*, *FGβ*, *GRIN3A*, *HLA-E*, *IL10*, *ITPKC* and *TGFBR2* have also been identified as markers of coronary artery involvement (40).

Management

Reducing inflammation or "putting out the fire" is key in the management of KD. This is achieved with the use of pharmacological "fire extinguishers", for which the efficacy of IVIG has been well described by Newburger and colleagues in 1986 (96). There is a strong inverse relationship between the IVIG dose and prevalence of CAA (97,98) with described improved coronary outcomes from 15–25% to 3–5% (99-101).

Current standard first-line management of KD include the use of IVIG (2 g/kg) as a single infusion plus oral Aspirin (80 to 100 mg/kg/day or 30 to 50 mg/kg/day in 4 divided doses) until 48 hours afebrile or day 14 of illness. This is followed by oral aspirin (3 to 5 mg/kg/day) for 6 to 8 weeks which can then be discontinued if no further CAA are present on follow-up.

The role and use of IVIG is not in doubt, with an optimum dosing of IVIG validated at 2 g/kg as a single infusion (97,102), preferred over the previous regime of smaller doses given over 5 days. The timing of IVIG therapy is however important, with commencement of treatment after 10 days associated with poorer outcomes with a published odds ratio (OR) 2.9 (103) and higher incidence of CAA (16% *vs.* 5%) (104). Despite this, many would consider IVIG if the patient is still febrile after 10 days, has coronary involvement or any signs of persistent inflammation (9).

Even the preparation of the IVIG is important. Being a pooled product with various manufacturing techniques, the choice of IVIG preparation may have a bearing on patient outcome with results to safety, side-effect profile and efficacy (105-109). The ideal preparation has been reported to have no B-propiolactonation, no acidification and be deplete in IVIG (106).

IVIG infusion is generally safe, although one has to be mindful of possible and potential unknown side effects. These include a Coombs-positive hemolytic anemia, especially with AB blood type (110), aseptic meningitis in 0.6–1% (111) and rare, but potentially serious transfusion-related, acute lung injury (112). In addition, the attending physician has to be aware that measles, mumps, and varicella immunisations should be deferred for 11 months after receiving high-dose IVIG (9,113).

The role and dosing of oral aspirin in the acute management remains controversial (97,114-121), with regards to IVIG resistance rates and CAA abnormalities. Although a reduction in fever duration has been reported with the use of high-dose aspirin (115,117,121), the role of CAA outcomes is not so straightforward. A limitation of most studies is the definition of CAA at 6–8 weeks with no long-term outcomes. Furthermore, clinical bias with higher rates of high-dose aspirin prescription to those with early CAA would confound the results.

Kim and colleagues (115) reported a large retrospective study including 8,456 children managed in Korea comparing IVIG with medium to high-dose aspirin versus IVIG with low-dose aspirin. They observed higher rates of IVIG resistance 10.5% *vs.* 16.9% (P<0.001) in those managed with low-dose aspirin. Higher rates of overall CAA were observed in those managed with IVIG and medium-high-dose Aspirin, with no differences in giant aneurysm rates. Currently, Kuo and colleagues (122) are carrying out a multi-center randomized double control trial to evaluate the efficacy of IVIG alone or IVIG with high-dose aspirin (80–100 mg/kg/day). A limitation however is that their primary endpoint is CAA at 6–8 weeks, and its value in long-term CAA sequalae will need follow-up. We nevertheless await the outcome of this trial on this controversial topic.

Regardless, the risks of aspirin include raised liver enzymes, gastrointestinal bleeding, and sensorineural hearing loss with high-dose aspirin albeit reversible (118). The risk of Reye syndrome is rare with prolonged use of high-dose aspirin only (123,124), and no association reported with low-dose aspirin. Whichever dose used, it is important for the prescribing physician to be aware of the antagonistic effect with Ibuprofen and the effect on the antiplatelet activity of aspirin (125). Furthermore, should patients require chronic aspirin therapy, annual inactivated influenza vaccine is recommended (113).

Alternatives include oral clopidogrel (0.1–1.0 mg/kg/day) for Aspirin resistance or allergy or oral dipyridamole (1–5 mg/kg/day) for patients who require ibuprofen for alternative diagnosis, aspirin resistance and allergy or at risk of Reye syndrome (9).

IVIG resistance

Despite adequate and timely therapy, the risk of IVIG resistance is documented in 9.7% to 32.2% (93,126-132) of KD children, with an up to nine-fold increased risk of CAA (133). Response to IVIG is defined as resolution of fever (T <37.5 ℃) and

mucocutaneous features, and may take up to 36 hours from end of IVIG infusion. (9,100). The conundrum of what next when patients don't respond to first-line standard therapy will be discussed later.

Multiple risk factors have been identified for IVIG resistance. Two meta-analysis (134,135) identified multiple risk factors including higher total bilirubin, polymorphonuclear leukocytes (PMN), pro-brain natriuretic peptide (pro-BNP), aspartate aminotransferase (AST), alanine aminotransferase (ALT), ESR and CRP levels, with lower sodium levels, albumin level, haemoglobin, and platelet count. Even clinical variables have been associated with IVIG resistance including fever duration (136), perianal changes (137), cervical lymphadenopathy (138), changes in oral mucosa, cervical lymphadenopathy, swelling of extremities, and polymorphous rash (135).

To expand on these variables, multiple scoring systems have been proposed (126,129-132,137,139-142). These included various variables and different scoring algorithms. Cross translation of these data to different populations has however been variable in populations of different ethnic backgrounds (92,93,126,128,129,142,143,), with generally poor sensitivities. The use of four of the more commonly cited scoring methods including the Egami (131), Kobayashi (132), Sano (130) and Fukunishi (139) in our local Singaporean Chinese population had poor sensitivities resulting in 42–85% of patients with IVIG resistance missed (144). It is possible that the baseline genetic profile of the different populations would result in different risks. The different ethnic incidences of KD are already well established, being highest in Japan ~250/100,000 (145,146) followed by other Asian nations including Korea 134/100,000 (147) and Taiwan 69/100,000 (148), and lowest in Western countries including the US Mainland 17.5 to 20.8/100,000 (149,150), UK 8.4 to 9/100,000 (151,152) and Australia 8/100,000 (153). Furthermore, biochemical marker variations are observed with variable contributions of ESR, hemoglobin and platelet count in Asian and non-Asian populations (135). These differences occur even within different Asian populations with subgroup analysis of ESR in these patients showing different outcomes (135).

Moving forward into an era of personalised medicine, a genetic risk profile could help tailor targeted therapy. Jaggi and colleagues (66) generated a genomic score that was higher at baseline in IVIG resistance (median 12,290 *vs.* 5,572 in responders, P=0.009) and independently predicted IVIG response. In addition, Kuo and colleagues (154) calculated a weighted genetic risk from 11 single nucleotide polymorphisms (SNPs) identified by genome-wide association study recognizing a significant association between weighted genetic risk score ($P=4.518\times10^{-3}$) and the response to IVIG ($P=8.224\times10^{-10}$).

With further work, new algorithms combining clinical, biochemical and genetic data would facilitate more accurate and population-specific risk estimations, allowing for more appropriate targeted therapy.

Alternative treatment options

Steroids were the first-line management of KD prior to the emergence of IVIG-directed therapy (155). Data on its role as first line has been controversial (156-165). As an adjuvant therapy though, this appears more promising. A meta-analysis of corticosteroid with IVIG as an initial treatment in high-risk patients demonstrated reduced coronary involvement, fever duration and inflammation in this group (166). This is supported by a recent Cochrane review (167) which included 922 participants. The studies predominantly used steroid therapy as an adjuvant to IVIG with similar outcomes of reduced CAA, shorter duration of fever and improved inflammatory markers. The limitation of the report was the short duration of follow-up with no study details beyond 24 weeks. In view of the promising early results, low-dose corticosteroids as an adjuvant to IVIG and Aspirin has been proposed in the most recent guidelines (9,157) in the management of higher risk groups. The role of monotherapy with steroids is however not indicated.

Other alternative therapies, which were evaluated, have not demonstrated conclusive evidence as yet. The use of infliximab, a TNF-alpha inhibitor, with IVIG does not decrease overall risk of CAA (168). However, its use in patients with IVIG resistance fared better, with reduced CAA in 6.3% of patients managed with IVIG and adjuvant Infliximab, compared to 20% in patients managed with IVIG alone (169). Burns and colleagues (170) similarly achieved greater defervescence rates within 48 hours in IVIG resistant patients managed with infliximab.

Methotrexate has also been tried as salvage therapy in IVIG resistance, and it has demonstrated defervescence and clinical improvement with normalization of acute phase reactants (171). There is only limited published data, and more work needs to be done. The same goes for the use of calcineurin inhibitor cyclosporine, with no significant data sets available (172). There is currently a phase III trial going on in Japan (KAICA Trial) evaluating the outcomes of cyclosporine A with IVIG versus IVIG alone (173)

and we await the outcomes of this in evaluating its role in management of KD. It is likely that these additional agents may have a role as adjuvant therapy in second- or third-line treatment for IVIG resistance.

Vascular health post-KD. Risks to the post-paediatric heart

As more children with a history of KD reach adulthood, the adult cardiologists looking after these patients must therefore be mindful of the coronary sequelae of KD. They must be prepared in the distinct treatment challenges that they will face in managing this group of patients. Unfortunately, the data on this group is limited, exemplified by the fact that KD as a disease as it is known is only slightly more than half a decade old. The management of adult patients with a history of KD draws suggestions from the paediatric guidelines (9). Unfortunately, the transition from paediatric to adult cardiologists is fraught with lost follow-ups (10). It is useful to have a more seamless transition, with joint reviews by both the paediatric and adult cardiologists, especially for the complex KD to allow for a smooth transition and reduce dropout rates. It is during these visits that individual risk status should be addressed and assessed.

We know from available literature that KD has an effect on the coronary arteries, and this manifests not just only as macro changes but also micro changes. Regardless, the long-term outcomes for KD are generally good with high rates for normalisation of coronary dimensions in small to medium vessels in 45% to 91% of cases (10,174,175). In contrast, giant aneurysms, which accounts for 1–2% of CAA rarely regress (9,174-176). In our own local data 97.5% of small and moderate aneurysms regressed with regression in 25.0% of giant aneurysms (unpublished). In general, in the presence of any CAA the 10-year ischaemia event-free probability is 87.5%, for which the only independent risk factor is aneurysm severity at 1 month after onset of KD (174).

Any coronary artery damage during acute KD can also lead to calcification and stenotic lesions associated with myointimal proliferation later in life (177,178). As such, coronary sequelae of KD are present in 5% to 9.2% of young adults evaluated by angiography for myocardial ischemia or presenting with sudden death (179,180). Tsuda and colleagues (181) in a review of 562 KD with known early coronary involvement identified 17 new or expanding aneurysms in 15 patients, all associated with localised stenosis 2 to 19 years post-KD onset. Tsuda and colleagues (182) subsequently reviewed 50 cases of acute coronary syndrome presenting as ST-segment elevation myocardial infarction (MI) in patients with a history of probably KD. The age of presentation ranged from 18 to 69 years. Of these patients, 43 had thrombotic occlusion of aneurysm with 40 patients having giant aneurysms. Of particular interest is that no aneurysms were visualised in 3 patients despite previous giant aneurysms in childhood. Notwithstanding regression of the giant aneurysms, they still had acute coronary syndrome in adulthood. Iemura and colleagues (183) reported an 86% thrombotic occlusion rate and 80% had giant aneurysms in patients with early MI at a median age of 28 years.

Patients with giant aneurysms are an important high-risk group and possess challenges. Suda and colleagues (184) reviewed 76 patients with giant aneurysm followed up for a median period of 19 years. Overall survival rates were 95%, 88%, and 88% at 10, 20, and 30 years post-KD respectively. However, high cumulative coronary intervention rates were observed with a rate of 28%, 43%, and 59% at 5, 15, and 25 years after onset respectively. Overall the reported risks associated with giant aneurysms includes a 41.6% to 64.5% risk of thrombosis or stenosis (184-186), 2.6% to 46% MI risk (175,184-187), mortality risk of 6.0% to 15.6% (184,186,187) and 30- to 35-year survival of 88% to 90% (184,187).

Despite these changes, the long-term outcome of KD remains generally favorable for patients with no coronary sequelae. Nakamura and colleagues (188) even demonstrated a lower mortality relative to the general population [standardized mortality ratios (SMR), 0.65; 95% confidence interval, 0.41–0.96].

The management and follow-up plans for patients with coronary involvement should be guided by principles established for atherosclerotic disease. Biochemical changes have been described in KD patients, with significantly elevated total cholesterol and apolipoprotein B (189). Zhang and colleagues (190) in a meta-analysis reported risk factors for atherosclerosis in 421 patients with KD and 449 controls. They identified that total cholesterol level [mean difference (MD) 3.99 mg/dL, 95% CI, 0.66–7.33, P=0.02] and low-density lipoprotein level (MD 3.42 mg/dL, CI 0.50 to 6.33, P=0.02) were significantly higher in KD patients. As such the role of statins has been proposed as a potential management strategy, in addition to aspirin, even in the paediatric guidelines (9). A phase I/IIa trial is currently underway to evaluate the use of Atorvastatin in patients with KD (191). In addition, combination use of antiplatelet and systemic anticoagulation will be required for large

aneurysms long term (10,184,192,193).

Routine standard cardiovascular fitness parameters including lipid profile every 1 to 2 years are prudent, as is the evaluation and management of risk factors including diabetes, hypertensions, obesity, smoking and alcohol. Additional specific non-invasive evaluation such as transthoracic echocardiogram should be done to assess cardiac function with regional wall motion abnormalities using automated functional imaging with tissue Doppler imaging and strain assessment to evaluate for early changes. Furthermore, it is reasonable to assess for inducible myocardial ischemia [stress echocardiography, stress magnetic resonance (MR), stress nuclear medicine] every 2 to 3 years with angiographic [computed tomography (CT) and/or MR imaging (MRI)] performed every 3 to 5 years similar to the pediatric surveillance recommendations (9). Invasive angiographic catheterization should be limited to those requiring interventional procedures.

The use of MRI is a useful modality, with the benefits of no radiation exposure and possibility of repeat imaging. With the use of late gadolinium enhancement myocardial fibrosis and scarring can be detected myocardial inflammation seen on T2-weighted images (194-196). The role of CT coronary artery calcium (CAC) scoring in screening patients with previous KD and persistent coronary abnormalities has demonstrated excellent results with a sensitivity of 95% and a specificity of 100% for detecting coronary artery abnormalities (defined as CAA and/or stenosis) (197,198).

Adult patients with KD presenting with MI frequently exhibit significant thrombus, and as such the true ID may also be undersized. The role of intravascular ultrasound has been proposed to circumvent this issue (180,199). In the interventional management, high balloon filling pressures may be required during percutaneous transluminal angioplasty, although this carries a risk of neoaneurysm formation (200).

Regular routine monitoring should not be limited to those with CAA; however, one has to rationalise the timing of further investigations including MR and CT. In patients with a history of KD and normal coronary arteries, the modality and frequency of investigations must be safe, induce minimal psychological harm and be cost effective. The Japanese Circulation Society 2013 (10) suggested non-invasive testing every 4 years with electrocardiogram (ECG) and echocardiogram, and this is a fair option. Furthermore, given the increased risk of atherosclerosis, a diagnosis of previous KD could count as a modified variable and be added into traditional risk scoring.

Being a systemic vasculitis, KD is likely to affect the systemic arterial structure with even microvascular changes of the retina observed (37). Therefore, normal macroscopic evaluation with echocardiogram or angiography (CT, MRI, invasive) does not equate to normal vascular function. Endothelial dysfunction as reflected by abnormal brachial artery reactivity and flow-mediated dilation was first reported by Dhillon and colleagues (201). Since then a variety of studies have been undertaken to evaluate the effect of KD on endothelial dysfunction including flow mediated dilation, nitroglycerin-mediated dilation and peripheral arterial tonometry; vascular thickness including stiffness index, pulse wave velocity (PWV) in both patients with and without CAA (202). In addition, the evaluation of carotid intima-media thickness (cIMT), a well-established surrogate marker of atherosclerosis (203,204) has been undertaken.

Dietz and colleagues (202) reported a systematic review and meta-analysis of 30 studies which showed important heterogeneity between studies. Most striking was the evidence for systemic arterial endothelial dysfunction in patients with CAA compared to KD in general. However, in studies of patients with no coronary involvement these were less conclusive. The data supports long-term subclinical vascular changes which affect patients with KD, afflicting primarily those with coronary artery involvement. It is interesting to note that these changes occur early with most studies performed in patients with a mean of <10 years since KD (20 of 30 studies). Only 4 studies evaluated, the vascular changes occurred with a mean time of >15 years (189,205-207).

The use of novel modalities to measure arterial stiffness such as the cardio-ankle vascular index (CAVI) could be useful to help answer these questions in a clinical setting. Developed in Japan by Fukuda Denshi, CAVI is a blood pressure-independent index of arterial stiffness (208) which correlates with the stiffness parameter β in the thoracic aorta and has a reported better reproducibility than brachial-ankle PWV (baPWV) (209,210). CAVI is increased in the presence of cerebrovascular disease (211), dementia (212), cardiovascular disease (213-215), nephrosclerosis (188), vasculitis (216,217), hypertension (218), hyperlipidemia (188), and lifestyle-related diseases including diabetes mellitus (219), smoking (220), and obesity (221), all risk factors for atherosclerosis. It also correlates with other cardiovascular risk markers, such as intimal-medial thickening and

coronary atherosclerosis (222). In other forms of vasculitis, CAVI as a marker of arterial stiffness was 17% higher in the systemic lupus erythematosus (SLE) patients than in controls (7.5±0.8 *vs.* 6.4±0.7) (216). The use of CAVI in patients with KD has been reported in one recent study by Nakagawa and colleagues (223) in 201 patients with KD versus 129 healthy controls, with significantly higher aPWV in KD group. Looking into the future, CAVI potentially arms the managing cardiologist with a bedside functional vascular analysis, making it an attractive option in risk stratification.

Conclusions

KD though uncommon is a fascinating condition. Our understanding of this has come such a long way since its first description in 1967. We now know better how to detect, treat and follow up its complications. It is envisaged that with rapid advances in research and collaborative work among physicians in this field, that we will be even better equipped with knowledge to risk-stratify, diagnose and manage KD, especially the incomplete and complex variants, in achieving better outcomes.

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Footnote

Conflicts of Interest: Both authors have completed the ICMJE uniform disclosure form (available at https://pm.amegroups.com/article/view/10.21037/pm.2019.03.03/coif). SCQ severs an unpaid editorial board member of *Pediatric Medicine* from Aug 2018 to Jul 2020. The other author has no conflicts of interest to declare.

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