ISSN 2219-2808 (online)

World Journal of *Clinical Pediatrics*

World J Clin Pediatr 2018 February 8; 7(1): 1-66

Published by Baishideng Publishing Group Inc

WJCP

World Journal of Clinical Pediatrics

Contents

Quarterly Volume 7 Number 1 February 8, 2018

Contents

World Journal of Clinical Pediatrics
Volume 7 Number 1 February 8, 2018

ABOUT COVER

Editorial Board Member of *World Journal of Clinical Pediatrics*, Joseph UE Onakewhor, MD, Associate Professor, Department of Obstetrics and Gynecology, University of Benin Teaching Hospital, Benin City 300001, Nigeria

AIM AND SCOPE

World Journal of Clinical Pediatrics (*World J Clin Pediatr*, *WJCP*, online ISSN 2219-2808, DOI: 10.5409) is a peer-reviewed open access academic journal that aims to guide clinical practice and improve diagnostic and therapeutic skills of clinicians.

WJCP covers a variety of clinical medical topics, including fetal diseases, inborn, newborn diseases, infant diseases, genetic diseases, diagnostic imaging, endoscopy, and evidence-based medicine and epidemiology. Priority publication will be given to articles concerning diagnosis and treatment of pediatric diseases. The following aspects are covered: Clinical diagnosis, laboratory diagnosis, differential diagnosis, imaging tests, pathological diagnosis, molecular biological diagnosis, immunological diagnosis, genetic diagnosis, functional diagnostics, and physical diagnosis; and comprehensive therapy, drug therapy, surgical therapy, interventional treatment, minimally invasive therapy, and robot-assisted therapy.

We encourage authors to submit their manuscripts to *WJCP*. We will give priority to manuscripts that are supported by major national and international foundations and those that are of great clinical significance.

INDEXING/ABSTRACTING

World Journal of Clinical Pediatrics is now indexed in PubMed, PubMed Central.

EDITORS FOR THIS ISSUE

Responsible Assistant Editor: *Xiang Li*
Responsible Electronic Editor: *Rui-Fang Li*
Proofing Editor-in-Chief: *Lian-Sheng Ma*
Responsible Science Editor: *Li-Jun Cui*
Proofing Editorial Office Director: *Xiu-Xia Song*

NAME OF JOURNAL
World Journal of Clinical Pediatrics

ISSN
ISSN 2219-2808 (online)

LAUNCH DATE
June 8, 2012

FREQUENCY
Quarterly

EDITORS-IN-CHIEF
Seng H Quak, MD, Professor, Department of Paediatrics, NUS - YLL School of Medicine, NUHS Tower Block, Singapore 119228, Singapore

Consolato M Sergi, FRCP(C), MD, PhD, Professor, Department of Lab Medicine and Pathology, University of Alberta, Alberta T6G 2B7, Canada

Toru Watanabe, MD, PhD, Professor, Department of Pediatrics, Niigata City General Hospital, Niigata 950-1197, Japan

EDITORIAL BOARD MEMBERS
All editorial board members resources online at http://www.wjgnet.com/2219-2808/editorialboard.htm

EDITORIAL OFFICE
Xiu-Xia Song, Director
World Journal of Clinical Pediatrics
Baishideng Publishing Group Inc
7901 Stoneridge Drive, Suite 501, Pleasanton, CA 94588, USA
Telephone: +1-925-2238242
Fax: +1-925-2238243
E-mail: editorialoffice@wjgnet.com
Help Desk: http://www.f6publishing.com/helpdesk
http://www.wjgnet.com

PUBLISHER
Baishideng Publishing Group Inc
7901 Stoneridge Drive,
Suite 501, Pleasanton, CA 94588, USA
Telephone: +1-925-223-8242
Fax: +1-925-223-8243
E-mail: bpgoffice@wjgnet.com
Help Desk: http://www.f6publishing.com/helpdesk
http://www.wjgnet.com

PUBLICATION DATE
February 8, 2018

COPYRIGHT
© 2018 Baishideng Publishing Group Inc. Articles published by this Open-Access journal are distributed under the terms of the Creative Commons Attribution Non-commercial License, which permits use, distribution, and reproduction in any medium, provided the original work is properly cited, the use is non commercial and is otherwise in compliance with the license.

SPECIAL STATEMENT
All articles published in journals owned by the Baishideng Publishing Group (BPG) represent the views and opinions of their authors, and not the views, opinions or policies of the BPG, except where otherwise explicitly indicated.

INSTRUCTIONS TO AUTHORS
http://www.wjgnet.com/bpg/gerinfo/204

ONLINE SUBMISSION
http://www.f6publishing.com

World Journal of Clinical Pediatrics

Submit a Manuscript: http://www.f6publishing.com

World J Clin Pediatr 2018 February 8; 7(1): 27-35

DOI: 10.5409/wjcp.v7.i1.27

ISSN 2219-2808 (online)

REVIEW

Controversies in diagnosis and management of Kawasaki disease

Rakesh Kumar Pilania, Dharmagat Bhattarai, Surjit Singh

Rakesh Kumar Pilania, Dharmagat Bhattarai, Surjit Singh, Department of Pediatrics, Advanced Pediatrics Centre, Post Graduate Institute of Medical Education and Research (PGIMER), Chandigarh 160012, India

ORCID number: Rakesh Kumar Pilania (0000-0002-9015-1704); Dharmagat Bhattarai (0000-0003-4838-5037); Surjit Singh (000-0002-8738-4582).

Author contributions: Pilania RK and Bhattarai D wrote the first draft of the manuscript; Singh S reviewed the draft, made changes and completed the final version; all authors approved the submitted version.

Conflict-of-interest statement: None.

Open-Access: This article is an open-access article which was selected by an in-house editor and fully peer-reviewed by external reviewers. It is distributed in accordance with the Creative Commons Attribution Non Commercial (CC BY-NC 4.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the original work is properly cited and the use is non-commercial. See: http://creativecommons.org/licenses/by-nc/4.0/

Manuscript source: Invited manuscript

Correspondence to: Surjit Singh, FRCP (C), MBBS, MD, FAMS, Professor, Department of Pediatrics, Advanced Pediatrics Centre, Post Graduate Institute of Medical Education and Research (PGIMER), Sector 12, Chandigarh 160012, India. surjitsinghpgi@rediffmail.com
Telephone: +91-987-2283832

Received: October 28, 2017
Peer-review started: October 29, 2017
First decision: December 8, 2017
Revised: December 13, 2017
Accepted: December 28, 2017
Article in press: December 28, 2017
Published online: February 8, 2018

Abstract

Kawasaki disease (KD) is a common medium vessel systemic vasculitis that usually occurs in small children. It has a predilection for the coronary arteries, but other medium sized arteries can also be involved. The etiology of this disorder remains a mystery. Though typical presentation of KD is quite characteristic, it may also present as incomplete or atypical disease in which case the diagnosis can be very challenging. As both incomplete and atypical forms of KD can be associated with serious coronary artery complications, the pediatrician can ill afford to miss these diagnoses. The American Heart Association has enunciated consensus guidelines to facilitate the clinical diagnosis and treatment of this condition. However, there are still several issues that remain controversial. Intravenous immunoglobulin remains the cornerstone of management but several other treatment modalities, especially glucocorticoids, are increasingly finding favour. We review here some of the contemporary issues, and the controversies thereon, pertaining to management of KD.

Key words: Kawasaki disease; Diagnosis; Intravenous immunoglobulin; Treatment; Controversies

© The Author(s) 2018. Published by Baishideng Publishing Group Inc. All rights reserved.

Core tip: The diagnosis of Kawasaki disease poses several challenges for the treating pediatricians as it is based on a set of criteria that are entirely clinical. To further complicate matters, several children present with incomplete and atypical forms of the disease. It is known that children with incomplete and atypical Kawasaki disease do not have milder form of the disease, rather the rate of coronary and non-coronary complications may even be higher in these subgroups as the diagnosis often gets delayed. While intravenous immunoglobulin

remains the cornerstone of management, several children require additional form of therapy thereby further challenging the clinical skills and judgment of the pediatricians.

Pilania RK, Bhattarai D, Singh S. Controversies in diagnosis and management of Kawasaki disease. *World J Clin Pediatr* 2018; 7(1): 27-35 Available from: URL: http://www.wjgnet.com/2219-2808/full/v7/i1/27.htm DOI: http://dx.doi.org/10.5409/wjcp.v7.i1.27

WHAT IS KAWASAKI DISEASE?

Kawasaki disease (KD) is the most common medium vessel vasculitis and usually affects young children. It has a special predilection for coronary arteries[1,2]. KD is now the leading cause of pediatric acquired heart disease in developed countries like Japan, Korea and Taiwan as also in countries in North America and Europe. In several resource poor countries (*e.g.*, India, China) as well, KD is now being increasingly reported[3]. However, anecdotal evidence suggests that many children still remain undiagnosed and untreated in such settings[4]. The etiology of KD remains an enigma[5,6].

This disease was first recognized in 1961 by Dr. Tomisaku Kawasaki based on a constellation of clinical signs and symptoms and he reported it in 1967 as "muco-cutaneous lymph node syndrome"[7]. Since then it has been reported from all continents. Even though the initial description of KD was given more than 50 years ago, the diagnosis still remains clinical and there is no laboratory test that can confirm a clinical diagnosis of KD[8].

DIAGNOSIS OF KD

Diagnosis of KD is essentially based on a constellation of clinical signs and symptoms and supported by laboratory investigations[8-12]. It cannot be overemphasized that there is no pathognomonic laboratory test for diagnosis of KD. A careful and meticulous history from parents, or documented clinical findings by a physician who has seen the child previously, may be useful in facilitating a diagnosis of KD[13].

The diagnostic criteria for KD have been modified from time to time. There are two sets of diagnostic criteria that have been used most frequently for diagnosis of KD. These included the Kawasaki Disease Research Committee guidelines [Japanese Ministry of Health (JMH) guidelines], 2002[14] and the American Heart Association (AHA) guidelines[1,13]. AHA guidelines were published in 2004 and have been widely used since then[1]. Mccrindle *et al*[13] have recently published the AHA 2017 revised guidelines for diagnosis and management of KD. These criteria are based on clinical findings and do not differ significantly from the original descriptions of cases of KD given by Dr. Kawasaki himself in 1967[7].

Complete KD

The AHA 2017 have proposed a set of diagnostic criteria for complete KD (Table 1)[13]. Fever is the most common presenting clinical manifestation and is seen in nearly all patients. While fever is essential for the diagnosis of KD as per AHA criteria but according to the Japanese criteria, fever need not be present in all patients (Table 2)[14]. The duration of fever in KD is variable and is usually less than 2 wk but may persist for much longer periods of time. Clinical manifestations of KD evolve over days and many signs and symptoms may have disappeared by the time the patient seeks medical attention. This issue has been clearly highlighted in the recent AHA 2017 guidelines (Table 3)[13].

Incomplete KD and atypical KD

The diagnosis of KD can test the clinical acumen of even an astute physician. The signs and symptoms of KD are nonspecific and may overlap with those of infectious diseases seen in young children[2]. Adding to this challenge are patients with KD who do not fulfill the diagnostic criteria. A diagnosis of incomplete KD is usually made when there is ongoing fever but less than four clinical features[13]. In such cases the attending pediatrician has to do a thorough clinical assessment and look at supportive laboratory investigations. Incomplete KD is common in infants (especially in babies below 6 mo) and young children. On the other hand, atypical KD is said to be present when there are atypical manifestations, as for instance nephritis[15,16], pneumonia,[17] arthritis[18], myositis[19,20], uveitis[21], retinal vasculitis[22,23] and CNS involvement[24,25]. Incomplete or atypical forms of KD should by no means be considered as mild KD because the risk of coronary abnormalities in these patients is comparable with, if not higher than, classic KD. This fact cannot be overemphasized[26-29].

Important clinical signs not included in the diagnostic criteria

There are several manifestations that are not included in the diagnostic criteria but may provide important clues towards diagnosis of KD. Perineal desquamation is one such clinical sign. It usually appears a few days prior to the appearance of periungual desquamation and may provide the initial clinical clue[30-32]. Similarly, reactivation of the Bacillus Calmette-Guérin (BCG) injection site is a pathognomonic clinical sign of KD and is almost exclusively observed in infants[33-36]. However, this has not been given enough consideration in the diagnostic criteria. Reason for this may be that many developed countries are not using BCG vaccine as a routine. Sterile pyuria[37,38], peripheral arthritis[18] and gall bladder hydrops[39,40] are other important indicators of KD. Extreme irritability, out of proportion to the fever, is often observed in young children with KD and may be a prominent clinical finding-but this too does not find a mention in the diagnostic criteria[41,42].

Table 1 American Heart Association guidelines for diagnosis of Kawasaki disease (2017)[13]

Classic KD is diagnosed with fever persisting for least 5 d
At least four of the five principal clinical features:
Changes in lips and oral cavity: Erythema, lips cracking, strawberry tongue, diffuse injection of oral and pharyngeal mucosae
Changes in extremities
Acute: Erythema of palms, soles; edema of hands, feet
Subacute: Periungual peeling of fingers and toes in weeks 2 and 3
Polymorphous exanthema (diffuse maculopapular, urticarial, erythroderma, erythema-multiforme like, not vesicular or bullous)
Bilateral bulbar conjunctival injection without exudates
Cervical lymphadenopathy (> 1.5 cm diameter), usually unilateral
A careful history may reveal that ⩾ 1 principal clinical features were present during the illness but resolved by the time of presentation
Exclusion of other diseases with similar findings (*e.g.*, scarlet fever, viral infections like measles, adenovirus, enterovirus, Stevens-Johnson syndrome, toxic shock syndrome, drug hypersensitivity reactions, systemic juvenile idiopathic arthritis)

KD: Kawasaki disease.

Table 2 Kawasaki Disease Research Committee guidelines (Japanese Ministry of Health guidelines) for diagnosis of Kawasaki disease (2002)[14]

Five of the following six criteria
Fever persisting ⩾ 5 d
Bilateral conjunctival congestion
Changes of lips and oral cavity
Polymorphous exanthema
Changes of peripheral extremities
Acute non-purulent cervical lymphadenopathy

CONTROVERSIES IN DIAGNOSIS OF KD

Infections and KD

KD should be considered as a diagnostic possibility in all children with fever more than 5 d for which there is no discernable cause[13]. KD is more common in young children and 80% of patients are under 5. This is the age group wherein viral infections are also common. Some of the clinical features of KD (*e.g.*, conjunctival injection, rash and cervical lymphadenopathy) are also a common feature of viral illnesses like measles[43], rubella[32], adenoviral[44,45], and enteroviral infections[13,44]. It is, therefore, not difficult to understand why KD can be confused with a viral illness. There are, however, some clinical features that can help in this differentiation. Children with KD usually do not have rhinorrhea or conjunctival discharge, in contrast to patients with viral infections[46]. They are also often very irritable. Edema over dorsum of hands and feet and the characteristic desquamation (perianal in first few days and periungual after days 10-12) is typical of KD but these findings are not there in all patients and can be easily missed if not looked for carefully[46,47]. However, the picture gets further complicated when KD occurs concomitantly with a viral infection as is sometimes the case[13,44].

One of the closest mimics of KD is scarlet fever. However, involvement of the lips and presence of conjunctival injection are features that are seen in KD but not in scarlet fever. Further, the fever in children with scarlet fever responds briskly to antimicrobials[48].

KD in infants

Diagnosis of KD in infants is a challenging exercise for physicians and delays in diagnosis in this age group are not uncommon. KD in infants often does not fulfil the standard diagnostic criteria. KD may be incomplete in a large proportion of patients in this age group[13]. Morbidity and mortality in this age group is highest compared to any other age group[13,49]. Fever and excessively irritability may be the only clinical manifestations of KD in babies below 6 mo and such presentations can pose several difficult questions for the attending pediatrician. Delays in diagnosis are common in such situations. Young infants are said to be at highest risk of developing coronary artery abnormalities. The presence of fever and pyuria in an infant can be mistakenly attributed to a urinary tract infection. This is not uncommon in our experience. Other clinical features of KD (*e.g.*, rash, red eyes, and red lips) may then be ascribed to an adverse drug reaction to antimicrobials that are often given in such situations. Salgado *et al*[50] have reiterated these facts in their recent publication on KD in infants below 6 mo. Our experience is also similar[51]. It is easy to understand why the diagnosis (and consequently the treatment) of KD gets delayed in these circumstances. Unfortunately, such delays can have disastrous consequences in the baby.

As per the recent AHA 2017 guidelines, the diagnosis of KD in infants may be considered in the following situations[13]: (1) Infants < 6 mo old with prolonged fever and irritability; (2) infants with prolonged fever and unexplained aseptic meningitis; (3) infants or children with prolonged fever and unexplained or culture-negative shock; (4) infants or children with prolonged fever and cervical lymphadenitis unresponsive to antibiotic therapy; (5) infants or children with prolonged fever and retropharyngeal or parapharyngeal phlegmon unresponsive to antibiotic therapy.

KD in older children and adolescents

Diagnosis in older children and adolescents is difficult because KD is rarely kept as differential diagnosis by adult physicians. As the diagnosis usually gets delayed

Table 3 Salient differences between American Heart Association 2004 and 2017 criteria[1,13]

Duration of fever	In the presence of ⩾ 4 principal clinical features, particularly when redness and swelling of the hands and feet are present, KD can be diagnosed even with 4 d of fever
History	Presence of one or more principal clinical manifestations of disease that can be revealed on history but have disappeared by the time of presentation, have been considered important for diagnosis
KD shock syndrome	KDSS has been given special consideration in the 2017 revised guidelines because in the presence of shock the diagnosis of KD is often not considered
KD in infants	Clinicians should have a lower threshold for diagnosis of KD in this age group
Incomplete KD	Algorithm for incomplete KD has been simplified
KD and infections	The issue of infections and KD has been detailed at length. Diagnosis of KD must not be excluded even in the presence of a documented infection when typical clinical features of KD are present
Bacterial lymphadenitis	Ultrasonography and computed tomography findings in differentiating the 2 conditions- bacterial lymphadenitis is often single and has a hypoechoic core on ultrasonography, while lymphadenopathy in KD is usually multiple and is associated with retropharyngeal edema or phlegmon
2D-echocardigraphy	The limitations of echocardiography and other diagnostic modalities have been highlighted. Z-score (by Manlihot *et al*) for severity classification of coronary artery abnormalities has been adapted

KD: Kawasaki disease; KDSS: Kawasaki disease shock syndrome.

in these children, there is higher risk of coronary artery abnormalities[52,54]. Further, echocardiographic coronary artery assessment in this group of patients is difficult because of the thick chest wall[55].

Clinical consequences of missed KD can present as coronary ischemia in early adulthood[56,57]. Due to lack of adequate awareness amongst adult cardiologists, such patients may never get recognized as having had late complications due to missed childhood KD[57].

KD shock syndrome

Myocarditis is nearly universal in acute phase of KD and, at times, it can be severe and symptomatic[58,59]. These patients are usually admitted in intensive care units with cardiovascular collapse and may be mistakenly treated for bacterial sepsis and septic shock[13,60,61]. As a result, the diagnosis of KD gets delayed and this can have serious consequences. Such patients are at high risk of developing coronary artery abnormalities, intravenous immunoglobulin (IVIg) resistance and myocardial dysfunction[62]. It is, therefore, prudent to keep a differential diagnosis of KD in all children presenting with seemingly obscure myocardial dysfunction and shock. A presumptive diagnosis of viral myocarditis / septic shock in the intensive care setting should have a differential diagnosis of KD. It is for these, and many other, reasons that KD shock syndrome (KDSS) has been given special consideration in the AHA 2017 revised guidelines[13].

Laboratory investigations may not always be corroborative

There is no single laboratory test for confirmation of diagnosis of KD. Laboratory markers rarely provide conclusive evidence for diagnosis of KD. Clinical laboratory investigation may be used to support the diagnosis of KD, especially in children with incomplete or atypical KD and to assess the intensity of inflammation. Thrombocytopenia in acute stage of KD can be a marker of macrophage activation syndrome[13,63]. Low platelet count has also been found to correlate with development of coronary aneurysms and such patients often have severe forms of the disease[62].

N terminal pro-B-type natriuretic peptide (NT-pro-BNP) is a cardiac biomarker and has been found to be significantly elevated during acute stage of KD when compared to febrile controls[64]. There are age based Pro-BNP nomograms to help the treating physician in differentiating KD from other febrile illnesses[65]. The values are higher in patients who develop coronary artery abnormalities as compared to those with normal coronaries. Thus it has both diagnostic and prognostic implications. Level of ProBNP is also correlated with myocardial dysfunction in acute stage of KD[66].

CONTROVERSIES IN IMAGING STUDIES IN KD

Role of 2D-echocardiography in KD

2D-echocardiography is an essential component of the diagnostic work-up in children with KD. It is a useful tool to assess the status of coronary arteries and other cardiac structures during acute stage as well as on follow-up[13,55,67]. It is important to bear in mind, however, that a negative echocardiographic examination does not rule out KD. However, from the perspective of a developing country, there are several issues with regard to this investigation. It cannot be overemphasized that the quality of scans obtained on echocardiography is operator dependent. This investigation has significant inter-observer variability and needs expertise and patience, especially in infants and young children[10]. Artifacts pose an important problem and these can make the examination exceptionally difficult, especially when the left circumflex or right coronary artery is being scanned[55]. In developing countries like India there is a dearth of trained pediatric cardiologists. As a result, the investigation may be carried out by an adult cardiologist, who may not have the requisite expertise to assess the coronary arteries especially in young infants. It comes as no surprise that echocardiography reports are often incomplete and inaccurate in clinical practice, especially in developing countries[10].

Table 4 Coronary artery abnormalities severity classification in different guidelines

Criteria	Description
JMH criteria[14]	Aneurysm definition < 5 yr - ID > 3 mm ⩾ 5 yr - ID > 4 mm
Updated JMH (2008)[93]	Small aneurysm (dilatation with ID < 4 mm or if child is ⩾ 5 yr of age, ID ⩽ 1.5 times that of an adjacent segment) Medium aneurysm (dilatation with ID > 4 mm but ⩽ 8 mm or if child is ⩾ 5 yr of age, ID 1.5 to 4 times that of an adjacent segment) Large aneurysm (dilatation with ID > 8 mm or if child is ⩾ 5 yr of age, ID > 4 times that of an adjacent segment)
AHA 2004 criteria[1]	Aneurysm ID z score > 2.5 (as per body surface area adjusted z scores) Small: < 5 mm Medium: 5 to 8 mm Giant aneurysm: > 8 mm based on absolute diameter
AHA 2017 criteria (Manlhiot *et al*)[13,68]	No involvement (Z score < 2) Dilation only (Z score 2 to < 2.5; or if initially < 2, a decrease in Z score during follow-up ⩾ 1 thereby suggesting that coronary artery was dilated during acute stage though diameter was within normal standards and the diameter has regressed on follow-up) Small aneurysm (Z score ⩾ 2.5 to < 5) Medium aneurysm (Z score ⩾ 5 to < 10, and absolute dimension < 8 mm) Large or giant aneurysm (⩾ 10, or absolute dimension ⩾ 8 mm)

ID: Internal diameter; AHA: American Heart Association; JMH: Japanese Ministry of Health.

The Japanese Ministry of Health has enunciated criteria for defining coronary involvement in KD on the basis of absolute dimension of internal diameter of coronary artery[14]. McCrindle *et al*[13] and Manlhiot *et al*[68] have proposed the classification scheme based on z score for severity of coronary artery abnormalities, which has been adapted and recommended by AHA 2017 guidelines (Table 4). It is mandatory that body surface area-adjusted 'Z' scores be used to grade the severity of coronary artery involvement so that objectivity can be maintained and results can be compared with other studies[13]. Echocardiography findings in KD other than coronary artery ectasia, dilatation and aneurysm, include lack of tapering of coronary arteries, myocardial dysfunction, pericardial effusion, aortic root dilatation and valvular regurgitation[13,55,59]. As myocarditis is almost universal, functional abnormalities are likely to be more in acute stage of KD[58]. An echocardiography examination should be done at diagnosis and, if normal, should be repeated on a daily basis for the next few days. Repeat echocardiography should be carried out 1-2 wk later and then at 4-6 wk. A normal echocardiography examination during the first week of illness does not rule out the development of coronary artery aneurysms later. Echocardiography should be repeated more frequently in children who have coronary artery z-scores > 2[13]. Recent literature suggests that follow-up echocardiography examination should include assessment of myocardial functions in addition to assessment of coronary arteries[69].

Computerized tomography coronary angiography in KD

While 2-dimensional echocardiography remains the imaging modality of choice to identify coronary artery abnormalities, it is subject to several fallacies and is operator dependent. Computerized tomography (CT) coronary angiography is rapidly emerging as a useful imaging modality for better characterization of dilatations, ectasia and aneurysms especially in the mid- and distal segments of coronary arteries. It provides precise details in terms of aneurysm size and morphology[70]. The limiting factor in more widespread use of this investigation hitherto was the high radiation exposure and therefore its application in children was rather limited. Over the last 5 years, with the advent of higher detector and dual-source CT scanners (DSCT), it is possible to delineate the coronary artery anatomy with higher temporal resolution and motion-free images at all heart rates with acceptable radiation risk[70]. CT coronary angiography can detect dilatations, ectasia and aneurysms in the mid and distal segments of coronary arteries with precise details in terms of aneurysm size and morphology. In the convalescent phase, it also can be used to delineate complications like segmental stenosis, intra-aneurysmal thrombus and mural calcifications.

Magnetic resonance coronary angiography

Magnetic resonance (MR) is useful in evaluation of coronary artery lesions and myocardial involvement in all stages of KD. The main advantage of MR is that there is no radiation exposure. However, young children would often need to be sedated and the procedure is time consuming. Interpretation of MR images requires a lot of expertise and skill[71,72].

CONTROVERSIES IN MANAGEMENT OF KD

Treatment of KD is yet another challenging and controversial issue. Prompt treatment of KD is absolutely

essential if one is to avoid the chances of development of CAA[11,13]. Intravenous immunoglobulin (IVIG) remains the standard of care based on objective evidence collated from prospective studies and meta-analyses[13]. However, there are still several controversies regarding management of children with KD.

Acute phase management

IVIG: For IVIG to be most effective, it should be given in the first few days of the illness[73]. However, if the child presents after day 10 of fever, IVIG should still be given if the acute inflammatory parameters are high[73]. Though there are recent meta-analyses stating similar outcomes of KD treatment at different doses of IVIg, a dose of 2 gm/kg administered intravenously is the preferred option[13,74]. It has also been suggested that administration of IVIG before day 5 of fever may inadvertently increase the need for further IVIG therapy and also increase the chances of developing a refractory state[75].

Aspirin: Though aspirin is a widely used anti-inflammatory agent in KD and is given along with IVIG, its efficacy remains questionable as there is no proof that addition of aspirin in the acute phase significantly decreases the chances of development of coronary artery abnormalities[76].

Most clinicians prefer to use aspirin in doses of 30-50 mg/kg during the acute phase of KD. Duration of aspirin therapy is another controversial issue[77,78]. Some centres prefer to continue it for 2 wk irrespective of fever status but consensus is rapidly evolving over continuing it only for febrile phase and then to change to a low dose (3 to 5 mg/kg per day) for its anti-platelet effect[79]. This low dose is then continued for 6-8 wk and is stopped if follow-up echocardiographic examination is normal. Aspirin is continued indefinitely if there is persistence of CAA[13].

Corticosteroid therapy in acute phase: Kato *et al*[80] reported that administration of steroids during the acute phase of KD resulted in increased incidence of CAA. But it is now argued that these results were due to the confounding factor of steroids having been given to children who were sicker than the other group[81]. Kobayashi *et al*[82] have recently published their study on use of steroids with IVIG and found that steroids may be useful in acute phase of KD.

Recent AHA guidelines do not support for administration of methylprednisolone pulses simultaneously with IVIG therapy but suggest possible benefit of 2-3 wk tapering steroid therapy along with IVIG and aspirin doses[13]. Upfront steroid therapy may be considered only for patients with KD who are proven to be IVIG resistant or presenting with significant CAA[10,46]. The choice of steroid is usually intravenous methylprednisolone pulse followed by tapering dose of oral prednisolone[13].

Refractory KD

Almost one-tenth patients with KD may be refractory to primary IVIG therapy. In such conditions, fever will continue to appear even after more than 36 to 48 h of IVIG therapy. There is no consensus on management protocols to be followed in such patients. AHA guidelines emphasize use of a repeat dose of IVIG (2 mg/kg) in this subgroup. Alternatively, the guidelines reiterate the role of 3 doses of methylprednisolone with tapering prednisolone[13]. Infliximab, given as a single dose of 5-6 mg/kg intravenously, is also very useful in treatment of refractory KD and appears to decrease the chances of developing CAA[83]. Administration of infliximab often results in prompt reduction of fever[84,85]. Tremoulet *et al*[86] have shown that addition of infliximab in the primary treatment regimen did not reduce the incidence of IVIG resistant KD. However, fever duration, inflammatory markers and reaction rate were less in the infliximab group. There are various ongoing randomized trials to assess the efficacy of anti-TNF drugs. Plasma exchange has also been found to be helpful in patients with intractable KD[87,88]. Other therapeutic options that are being considered includes interleukin-1 antagonist (*e.g.,* anakinara), cyclosporine, and tacrolimus, *etc*[89-91].

For the preventing of thrombosis, low dose aspirin remains the first choice of therapy. If the patients show evidence of rapidly expanding CAA, heparin or warfarin anticoagulation along with aspirin can be given[13]. Aspirin with another antiplatelet agent along with systemic anticoagulant agent like heparin or warfarin may be considered for patients with history of coronary thrombosis or giant aneurysm[79]. Thrombolytic treatment or coronary recanalization procedures may be required for the minority of patients who develop coronary thrombosis in the context of KD. Abciximab is also useful in such patients[13].

Management after acute phase

Risk stratification of coronary artery abnormalities is of primary importance for the long term follow-up and management of patients with KD. It is our practice to keep all children with KD on long term follow-up, because there is some concern regarding development of premature atherosclerosis even in children who do not have overt CAA during the acute phases[92,93]. Healthy lifestyle and an active physical regimen should be emphasized upon.

Patients with coronary dilatation that persists beyond 6 wk need to be kept on low dose aspirin for longer periods of time. For patients with large and giant aneurysms, frequent echocardiographic assessment should be continued. Such patients may also require CT coronary angiography at periodic (say 3-5 yearly) intervals. Statins have also been recommended in these situations. Thromboprophylaxis can be maintained with antiplatelet drugs (*e.g.,* aspirin/dipyrimadole used singly or in combination) and anticoagulants (*e.g.*, heparin/warfarin)[13].

To conclude KD is now one of the most common causes for acquired heart disease in children and all pediatricians need to be familiar with its varied clinical

presentations. With some experience it is not difficult to pick up children with classic KD. However, the diagnosis of children with incomplete and atypical KD can pose significant issues for the attending pediatrician. The recent AHA 2017 guidelines have suggested a simplified management protocol for children with KD. Therapies other than IVIG are now being increasingly used in these patients.

REFERENCES

1 **Newburger JW**, Takahashi M, Gerber MA, Gewitz MH, Tani LY, Burns JC, Shulman ST, Bolger AF, Ferrieri P, Baltimore RS, Wilson WR, Baddour LM, Levison ME, Pallasch TJ, Falace DA, Taubert KA; Committee on Rheumatic Fever, Endocarditis and Kawasaki Disease; Council on Cardiovascular Disease in the Young; American Heart Association; American Academy of Pediatrics. Diagnosis, treatment, and long-term management of Kawasaki disease: a statement for health professionals from the Committee on Rheumatic Fever, Endocarditis and Kawasaki Disease, Council on Cardiovascular Disease in the Young, American Heart Association. *Circulation* 2004; **110**: 2747-2771 [PMID: 15505111 DOI: 10.1161/01.CIR.0000145143.19711.78]

2 **Rowley AH**. The Complexities of the Diagnosis and Management of Kawasaki Disease. *Infect Dis Clin North Am* 2015; **29**: 525-537 [PMID: 26154665 DOI: 10.1016/j.idc.2015.05.006]

3 **Singh S**, Aulakh R, Kawasaki T. Kawasaki disease and the emerging coronary artery disease epidemic in India: is there a correlation? *Indian J Pediatr* 2014; **81**: 328-332 [PMID: 24072580 DOI: 10.1007/s12098-013-1229-y]

4 **Singh S**, Vignesh P, Burgner D. The epidemiology of Kawasaki disease: a global update. *Arch Dis Child* 2015; **100**: 1084-1088 [PMID: 26111818 DOI: 10.1136/archdischild-2014-307536]

5 **Burgner D**, Harnden A. Kawasaki disease: what is the epidemiology telling us about the etiology? *Int J Infect Dis* 2005; **9**: 185-194 [PMID: 15936970 DOI: 10.1016/j.ijid.2005.03.002]

6 **Rowley AH**. Kawasaki disease: novel insights into etiology and genetic susceptibility. *Annu Rev Med* 2011; **62**: 69-77 [PMID: 20690826 DOI: 10.1146/annurev-med-042409-151944]

7 **Kawasaki T**. Acute febrile mucocutaneous syndrome with lymphoid involvement with specific desquamation of the fingers and toes in children. *Arerugi* 1967; **16**: 178-222 [PMID: 6062087]

8 **Singh S**, Kawasaki T. Kawasaki Disease in India, Lessons Learnt Over the Last 20 Years. *Indian Pediatr* 2016; **53**: 119-124 [PMID: 26897142 DOI: 10.1007/s13312-016-0804-5]

9 **Gupta A,** Singh S. Kawasaki disease for dermatologists. *Indian Dermatol Online J* 2016; **7**: 461-470 [PMID: 27990380 DOI: 10.4103/2229-5178.193903]

10 **Singh S**, Sharma A, Jiao F. Kawasaki Disease: Issues in Diagnosis and Treatment--A Developing Country Perspective. *Indian J Pediatr* 2016; **83**: 140-145 [PMID: 26400032 DOI: 10.1007/s12098-015-1890-4]

11 **Newburger JW**, Takahashi M, Burns JC. Kawasaki Disease. *J Am Coll Cardiol* 2016; **67**: 1738-1749 [PMID: 27056781 DOI: 10.1016/j.jacc.2015.12.073]

12 **Scuccimarri R**. Kawasaki disease. *Pediatr Clin North Am* 2012; **59**: 425-445 [PMID: 22560578 DOI: 10.1016/j.pcl.2012.03.009]

13 **McCrindle BW**, Rowley AH, Newburger JW, Burns JC, Bolger AF, Gewitz M, Baker AL, Jackson MA, Takahashi M, Shah PB, Kobayashi T, Wu MH, Saji TT, Pahl E; American Heart Association Rheumatic Fever, Endocarditis, and Kawasaki Disease Committee of the Council on Cardiovascular Disease in the Young; Council on Cardiovascular and Stroke Nursing; Council on Cardiovascular Surgery and Anesthesia; and Council on Epidemiology and Prevention. Diagnosis, Treatment, and Long-Term Management of Kawasaki Disease: A Scientific Statement for Health Professionals From the American Heart Association. *Circulation* 2017; **135**: e927-e999 [PMID: 28356445 DOI: 10.1161/CIR.0000000000000484]

14 **Ayusawa M**, Sonobe T, Uemura S, Ogawa S, Nakamura Y, Kiyosawa N, Ishii M, Harada K; Kawasaki Disease Research Committee. Revision of diagnostic guidelines for Kawasaki disease (the 5th revised edition). *Pediatr Int* 2005; **47**: 232-234 [PMID: 15771703 DOI: 10.1111/j.1442-200x.2005.02033.x]

15 **Veiga PA**, Pieroni D, Baier W, Feld LG. Association of Kawasaki disease and interstitial nephritis. *Pediatr Nephrol* 1992; **6**: 421-423 [PMID: 1457322 DOI: 10.1007/BF00873999]

16 **Chuang GT**, Tsai IJ, Lin MT, Chang LY. Acute kidney injury in patients with Kawasaki disease. *Pediatr Res* 2016; **80**: 224-227 [PMID: 27064240 DOI: 10.1038/pr.2016.81]

17 **Singh S**, Gupta A, Jindal AK, Gupta A, Suri D, Rawat A, Vaidya PC, Singh M. Pulmonary presentation of Kawasaki disease-A diagnostic challenge. *Pediatr Pulmonol* 2018; **53**: 103-107 [PMID: 28950425 DOI: 10.1002/ppul.23885]

18 **Gong GW**, McCrindle BW, Ching JC, Yeung RS. Arthritis presenting during the acute phase of Kawasaki disease. *J Pediatr* 2006; **148**: 800-805 [PMID: 16769390 DOI: 10.1016/j.jpeds.2006.01.039]

19 **Agarwal S**, Gupta A, Suri D, Rawat A, Singh S. Proximal Muscle Weakness in a Child with Kawasaki Disease. *Indian J Pediatr* 2015; **82**: 866 [PMID: 25680785 DOI: 10.1007/s12098-015-1709-3]

20 **Lee EY**, Oh JY, Chong CY, Choo JT, Mahadev A, Tan NW. A Case of Atypical Kawasaki Disease With Myositis. *Glob Pediatr Health* 2015; **2**: 2333794X15599649 [PMID: 27335976 DOI: 10.1177/2333794X15599649]

21 **Madhusudan S**, Singh S, Suri D, Gupta A, Gupta A. Acute anterior uveitis as the presenting feature of Kawasaki disease. *Indian J Pediatr* 2014; **81**: 415 [PMID: 24562721 DOI: 10.1007/s12098-014-1367-x]

22 **Agarwal S**, Mulkutkar S, Suri D, Singh S, Gupta A. Retinal Vasculitis in Kawasaki Disease. *Indian J Pediatr* 2015; **82**: 1183-1184 [PMID: 25990595 DOI: 10.1007/s12098-015-1763-x]

23 **Font RL**, Mehta RS, Streusand SB, O'Boyle TE, Kretzer FL. Bilateral retinal ischemia in Kawasaki disease. Postmortem findings and electron microscopic observations. *Ophthalmology* 1983; **90**: 569-577 [PMID: 6877786 DOI: 10.1016/S0161-6420(83)34522-X]

24 **Wright H**, Waddington C, Geddes J, Newburger JW, Burgner D. Facial nerve palsy complicating Kawasaki disease. *Pediatrics* 2008; **122**: e783-e785 [PMID: 18678602 DOI: 10.1542/peds.2007-3238]

25 **Martínez-Guzmán E**, Gámez-González LB, Rivas-Larrauri F, Sorcia-Ramírez G, Yamazaki-Nakashimada M. Neurological manifestations in atypical Kawasaki disease. *Rev Alerg Mex* 2017; **64**: 376-380 [PMID: 29046034]

26 **Vignesh P**, Bhattad S, Singhal M, Singh S. A 5-year-old boy with only fever and giant coronary aneurysms: the enigma of Kawasaki disease? *Rheumatol Int* 2016; **36**: 1191-1193 [PMID: 27154559 DOI: 10.1007/s00296-016-3490-7]

27 **Maric LS**, Knezovic I, Papic N, Mise B, Roglic S, Markovinovic L, Tesovic G. Risk factors for coronary artery abnormalities in children with Kawasaki disease: a 10-year experience. *Rheumatol Int* 2015; **35**: 1053-1058 [PMID: 25429794 DOI: 10.1007/s00296-014-3186-9]

28 **Perrin L**, Letierce A, Guitton C, Tran TA, Lambert V, Koné-Paut I. Comparative study of complete versus incomplete Kawasaki disease in 59 pediatric patients. *Joint Bone Spine* 2009; **76**: 481-485 [PMID: 19811939 DOI: 10.1016/j.jbspin.2008.11.015]

29 **Sonobe T**, Kiyosawa N, Tsuchiya K, Aso S, Imada Y, Imai Y, Yashiro M, Nakamura Y, Yanagawa H. Prevalence of coronary artery abnormality in incomplete Kawasaki disease. *Pediatr Int* 2007; **49**: 421-426 [PMID: 17587261 DOI: 10.1111/j.1442-200X.2007.02396.x]

30 **Chao SM**, Phua KB. Perineal eruption as an early sign of Kawasaki disease. *Ann Acad Med Singapore* 1991; **20**: 244-247 [PMID: 1883184]

31 **Isidori C**, Sebastiani L, Cardellini MC, Di Cara G, Rigante D,

Esposito S. Early Desquamating Perineal Erythema in a Febrile Infant: A Characteristic Clinical Feature of Kawasaki Disease. *Int J Environ Res Public Health* 2017; **14**: E710 [PMID: 28665334 DOI: 10.3390/ijerph14070710]
32 **Falcini F**, Ozen S, Magni-Manzoni S, Candelli M, Ricci L, Martini G, Cuttica RJ, Oliveira S, Calabri GB, Zulian F, Pistorio A, La Torre F, Rigante D. Discrimination between incomplete and atypical Kawasaki syndrome versus other febrile diseases in childhood: results from an international registry-based study. *Clin Exp Rheumatol* 2012; **30**: 799-804 [PMID: 23020938]
33 **Gamez-Gonzalez LB**, Hamada H, Llamas-Guillen BA, Ruiz-Fernandez M, Yamazaki-Nakashimada M. BCG and Kawasaki disease in Mexico and Japan. *Hum Vaccin Immunother* 2017; **13**: 1091-1093 [PMID: 28281896 DOI: 10.1080/21645515.2016.1267083]
34 **Garrido-García LM**, Castillo-Moguel A, Vázquez-Rivera M, Cravioto P, Fernando G. Reaction of the BCG Scar in the Acute Phase of Kawasaki Disease in Mexican Children. *Pediatr Infect Dis J* 2017; **36**: e237-e241 [PMID: 28498302 DOI: 10.1097/INF.0000000000001633]
35 **Rezai MS**, Shahmohammadi S. Erythema at BCG Inoculation Site in Kawasaki Disease Patients. *Mater Sociomed* 2014; **26**: 256-260 [PMID: 25395889 DOI: 10.5455/msm.2014.26.256-260]
36 **Kumar A**, Singh S. BCG Site Reactivation in Kawasaki Disease. *Arthritis Rheumatol* 2016; **68**: 2026 [PMID: 27059401 DOI: 10.1002/art.39708]
37 **Watanabe T**. Pyuria in patients with Kawasaki disease. *World J Clin Pediatr* 2015; **4**: 25-29 [DOI: 10.5409/wjcp.v4.i2.25]
38 **Choi JY**, Park SY, Choi KH, Park YH, Lee YH. Clinical characteristics of Kawasaki disease with sterile pyuria. *Korean J Pediatr* 2013; **56**: 13-18 [PMID: 23390440 DOI: 10.3345/kjp.2013.56.1.13]
39 **Sun Q**, Zhang J, Yang Y. Gallbladder Hydrops Associated With Kawasaki Disease: A Case Report and Literature Review. *Clin Pediatr* (Phila) 2017: 9922817696468 [PMID: 28952362 DOI: 10.1177/0009922817696468.]
40 **Mathai SS**, Kulkarni VB, Harsh P. Gall bladder hydrops - a rare initial presentation of Kawasaki disease. *Indian J Pediatr* 2013; **80**: 616-617 [PMID: 23180399 DOI: 10.1007/s12098-012-0890-x]
41 **Thapa R**, Chakrabartty S. Atypical Kawasaki disease with remarkable paucity of signs and symptoms. *Rheumatol Int* 2009; **29**: 1095-1096 [PMID: 19381640 DOI: 10.1007/s00296-009-0899-2]
42 **Golshevsky D**, Cheung M, Burgner D. Kawasaki disease--the importance of prompt recognition and early referral. *Aust Fam Physician* 2013; **42**: 473-476 [PMID: 23826599]
43 **Hu P**, Guan Y, Fan XC, Lu FY, Song LM. Incomplete Kawasaki disease induced by measles in a 6-month-old male infant. *Int J Dermatol* 2016; **55**: e34-e36 [PMID: 26518488 DOI: 10.1111/ijd.13122]
44 **Chang LY**, Lu CY, Shao PL, Lee PI, Lin MT, Fan TY, Cheng AL, Lee WL, Hu JJ, Yeh SJ, Chang CC, Chiang BL, Wu MH, Huang LM. Viral infections associated with Kawasaki disease. *J Formos Med Assoc* 2014; **113**: 148-154 [PMID: 24495555 DOI: 10.1016/j.jfma.2013.12.008]
45 **Fukuda S,** Ito S, Fujiwara M, Abe J, Hanaoka N, Fujimoto T, Katsumori H. Simultaneous development of Kawasaki disease following acute human adenovirus infection in monozygotic twins: A case report. *Pediatr Rheumatol Online J* 2017; **15**: 39 [PMID: 28511718 DOI: 10.1186/s12969-017-0169-x]
46 **Singh S**, Newburger JW, Kuijpers T, Burgner D. Management of Kawasaki disease in resource-limited settings. *Pediatr Infect Dis J* 2015; **34**: 94-96 [PMID: 25741801 DOI: 10.1097/INF.0000000000000600]
47 **Jindal AK**, Singh S. Dryness at Fingertips: Is It a Premonitory Sign of Skin Peeling in Kawasaki Disease? *J Clin Rheumatol* 2017; **23**: 286 [PMID: 28661924 DOI: 10.1097/RHU.0000000000000519]
48 **Cox JR**, Sallis RE. Recognition of kawasaki disease. *Perm J* 2009; **13**: 57-61 [PMID: 21373247 DOI: 10.7812/TPP/08-042]
49 **Singh S**, Bhattad S, Gupta A, Suri D, Rawat A, Rohit M. Mortality in children with Kawasaki disease: 20 years of experience from a tertiary care centre in North India. *Clin Exp Rheumatol* 2016; **34**: S129-S133 [PMID: 26633295]
50 **Salgado AP**, Ashouri N, Berry EK, Sun X, Jain S, Burns JC, Tremoulet AH. High Risk of Coronary Artery Aneurysms in Infants Younger than 6 Months of Age with Kawasaki Disease. *J Pediatr* 2017; **185**: 112-116.e1 [PMID: 28408126 DOI: 10.1016/j.jpeds.2017.03.025]
51 **Singh S**, Agarwal S, Bhattad S, Gupta A, Suri D, Rawat A, Singhal M, Rohit M. Kawasaki disease in infants below 6 months: a clinical conundrum? *Int J Rheum Dis* 2016; **19**: 924-928 [PMID: 26990891 DOI: 10.1111/1756-185X.12854]
52 **Kontopoulou T**, Kontopoulos DG, Vaidakis E, Mousoulis GP. Adult Kawasaki disease in a European patient: a case report and review of the literature. *J Med Case Rep* 2015; **9**: 75 [PMID: 25890055 DOI: 10.1186/s13256-015-0516-9]
53 **Gupta K**, Rohit M, Sharma A, Nada R, Jain S, Varma S. An Adolescent with Kawasaki Disease. *Indian Pediatr* 2016; **53**: 51-56 [PMID: 26840674 DOI: 10.1007/s13312-016-0791-6]
54 **Chen J**, Li Y. Acute Complete Adult-onset Kawasaki Disease in a Middle-Aged Woman. *J Coll Physicians Surg Pak* 2017; **27**: 517-519 [PMID: 28903849]
55 **Altman CA**. Clinical assessment of coronary arteries in Kawasaki disease: Focus on echocardiographic assessment. *Congenit Heart Dis* 2017; **12**: 636-640 [PMID: 28921836 DOI: 10.1111/chd.12496]
56 **Vijayvergiya R**, Bhattad S, Varma S, Singhal M, Gordon J, Singh S. Presentation of missed childhood Kawasaki disease in adults: Experience from a tertiary care center in north India. *Int J Rheum Dis* 2017; **20**: 1023-1027 [PMID: 28378434 DOI: 10.1111/1756-185X.13073]
57 **Waterhouse BR**, Tulloh RMR, Kim Y, Creasy W, Adlam D, Johnson TW. Retrospective study of the impact of unrecognised Kawasaki disease, coronary aneurysm and ectasia. *Int J Cardiol* 2017; **248**: 308-313 [PMID: 28818354 DOI: 10.1016/j.ijcard.2017.08.018]
58 **Dahdah N**. Not just coronary arteritis, Kawasaki disease is a myocarditis, too. *J Am Coll Cardiol* 2010; **55**: 1507; author reply 1507-1507; author reply 1508 [PMID: 20359606 DOI: 10.1016/j.jacc.2009.11.067]
59 **Hashimoto I**, Saitou Y, Sakata N, Shibata K. Evaluation of longitudinal and radial left ventricular functions using two- and three-dimensional echocardiography before and after intravenous immunoglobulin administration in patients with acute Kawasaki disease. *Pediatr Int* 2017 [PMID: 28892213 DOI: 10.1111/ped.13423]
60 **Seaton KK**, Kharbanda A. Evidence-based management of Kawasaki disease in the emergency department. *Pediatr Emerg Med Pract* 2015; **12**: 1-20; quiz 21 [PMID: 25693305]
61 **Çakan M**, Gemici H, Aktay-Ayaz N, Keskindemirci G, Bornaun H, İkizoğlu T, Çeliker A. Kawasaki disease shock syndrome: a rare and severe complication of Kawasaki disease. *Turk J Pediatr* 2016; **58**: 415-418 [PMID: 28276216 DOI: 10.24953/turkjped.2016.04.012]
62 **Xie T**, Wang Y, Fu S, Wang W, Xie C, Zhang Y, Gong F. Predictors for intravenous immunoglobulin resistance and coronary artery lesions in Kawasaki disease. *Pediatr Rheumatol Online J* 2017; **15**: 17 [PMID: 28320400 DOI: 10.1186/s12969-017-0149-1]
63 **Dumont B**, Jeannoel P, Trapes L, Rolland E, Gay C, Stephan JL. Macrophage activation syndrome and Kawasaki disease: Four new cases. *Arch Pediatr* 2017; **24**: 640-646 [PMID: 28583781 DOI: 10.1016/j.arcped.2017.04.017]
64 **Rawat A**, Singh S. Biomarkers for Diagnosis of Kawasaki Disease. *Indian Pediatr* 2015; **52**: 473-474 [PMID: 26121719 DOI: 10.1007/s13312-015-0658-2]
65 **Reddy M**, Singh S, Rawat A, Sharma A, Suri D, Rohit MK. Pro-brain natriuretic peptide (ProBNP) levels in North Indian children with Kawasaki disease. *Rheumatol Int* 2016; **36**: 551-559 [PMID: 26849890 DOI: 10.1007/s00296-016-3430-6]
66 **Lin K-H,** Chang S-S, Yu C-W, Lin S-C, Liu S-C, Chao H -y.

Usefulness of natriuretic peptide for the diagnosis of Kawasaki disease: a systematic review and meta-analysis. *BMJ Open* 2015; **5**: e006703-e006703 [PMID: 25872939 DOI: 10.1136/bmjopen-2014-006703]

67 **Kothur K**, Singh S, Sharma Y, Mittal BR. Prospective follow-up cardiac evaluation of children with Kawasaki disease in Northern India using the Japanese echocardiography criteria. *J Cardiol* 2007; **50**: 299-307 [PMID: 18044459]

68 **Manlhiot C**, Millar K, Golding F, McCrindle BW. Improved classification of coronary artery abnormalities based only on coronary artery z-scores after Kawasaki disease. *Pediatr Cardiol* 2010; **31**: 242-249 [PMID: 20024653 DOI: 10.1007/s00246-009-9599-7]

69 **Lee H**, Shin J, Eun L. Myocardial Assessment in School-Aged Children with Past Kawasaki Disease. *J Korean Med Sci* 2017; **32**: 1835-1839 [PMID: 28960037 DOI: 10.3346/jkms.2017.32.11.1835]

70 **Singhal M**, Singh S, Gupta P, Sharma A, Khandelwal N, Burns JC. Computed Tomography Coronary Angiography for Evaluation of Children With Kawasaki Disease. *Curr Probl Diagn Radiol* 2017 [PMID: 29203262 DOI: 10.1067/j.cpradiol.2017.09.013]

71 **Takemura A**, Suzuki A, Inaba R, Sonobe T, Tsuchiya K, Omuro M, Korenaga T. Utility of coronary MR angiography in children with Kawasaki disease. *AJR Am J Roentgenol* 2007; **188**: W534-W539 [PMID: 17515343 DOI: 10.2214/AJR.05.1414]

72 **Tacke CE**, Romeih S, Kuipers IM, Spijkerboer AM, Groenink M, Kuijpers TW. Evaluation of cardiac function by magnetic resonance imaging during the follow-up of patients with Kawasaki disease. *Circ Cardiovasc Imaging* 2013; **6**: 67-73 [PMID: 23197079 DOI: 10.1161/CIRCIMAGING.112.976969]

73 **Rowley AH**, Shulman ST. Pathogenesis and management of Kawasaki disease. *Expert Rev Anti Infect Ther* 2010; **8**: 197-203 [PMID: 20109049 DOI: 10.1586/eri.09.109]

74 **Chen J,** Ma B, Lin L-X, Xue Y-M. Treatment of Kawasaki disease by different doses of immunoglobulin: a meta analysis of efficacy and safety. *Transl Pediatr* 2012; **1**: 99-107 [PMID: 4728885 DOI: 10.3978/j.issn.2224-4336.2012.04.05]

75 **Muta H**, Ishii M, Egami K, Furui J, Sugahara Y, Akagi T, Nakamura Y, Yanagawa H, Matsuishi T. Early intravenous gamma-globulin treatment for Kawasaki disease: the nationwide surveys in Japan. *J Pediatr* 2004; **144**: 496-499 [PMID: 15069399 DOI: 10.1016/j.jpeds.2003.12.033]

76 **Terai M**, Shulman ST. Prevalence of coronary artery abnormalities in Kawasaki disease is highly dependent on gamma globulin dose but independent of salicylate dose. *J Pediatr* 1997; **131**: 888-893 [PMID: 9427895 DOI: 10.1016/S0022-3476(97)70038-6]

77 **Dallaire F**, Fortier-Morissette Z, Blais S, Dhanrajani A, Basodan D, Renaud C, Mathew M, De Souza AM, Dionne A, Blanchard J, Saulnier H, Kaspy K, Rached-d'Astous S, Dahdah N, McCrindle BW, Human DG, Scuccimarri R. Aspirin Dose and Prevention of Coronary Abnormalities in Kawasaki Disease. *Pediatrics* 2017; **139** [PMID: 28562282 DOI: 10.1542/peds.2017-0098]

78 **Ho LGY**, Curtis N. What dose of aspirin should be used in the initial treatment of Kawasaki disease? *Arch Dis Child* 2017; **102**: 1180-1182 [PMID: 29066520 DOI: 10.1136/archdischild-2017-313538]

79 **Zhu FH**, Ang JY. The Clinical Diagnosis and Management of Kawasaki Disease: a Review and Update. *Curr Infect Dis Rep* 2016; **18**: 32 [PMID: 27681743 DOI: 10.1007/s11908-016-0538-5]

80 **Kato H**, Koike S, Yokoyama T. Kawasaki disease: effect of treatment on coronary artery involvement. *Pediatrics* 1979; **63**: 175-179 [PMID: 440805]

81 **Eleftheriou D**, Levin M, Shingadia D, Tulloh R, Klein NJ, Brogan PA. Management of Kawasaki disease. *Arch Dis Child* 2014; **99**: 74-83 [PMID: 24162006 DOI: 10.1136/archdischild-2012-302841]

82 **Kobayashi T**, Saji T, Otani T, Takeuchi K, Nakamura T, Arakawa H, Kato T, Hara T, Hamaoka K, Ogawa S, Miura M, Nomura Y, Fuse S, Ichida F, Seki M, Fukazawa R, Ogawa C, Furuno K, Tokunaga H, Takatsuki S, Hara S, Morikawa A; RAISE study group investigators. Efficacy of immunoglobulin plus prednisolone for prevention of coronary artery abnormalities in severe Kawasaki disease (RAISE study): a randomised, open-label, blinded-endpoints trial. *Lancet* 2012; **379**: 1613-1620 [PMID: 22405251 DOI: 10.1016/S0140-6736(11)61930-2]

83 **Matsubara T**, Furukawa S, Yabuta K. Serum levels of tumor necrosis factor, interleukin 2 receptor, and interferon-gamma in Kawasaki disease involved coronary-artery lesions. *Clin Immunol Immunopathol* 1990; **56**: 29-36 [PMID: 2113446 DOI: 10.1016/0090-1229(90)90166-N]

84 **Singh S**, Sharma D, Suri D, Gupta A, Rawat A, Rohit MK. Infliximab is the new kid on the block in Kawasaki disease: a single-centre study over 8 years from North India. *Clin Exp Rheumatol* 2016; **34**: S134-S138 [PMID: 27086575]

85 **Burns JC**, Mason WH, Hauger SB, Janai H, Bastian JF, Wohrley JD, Balfour I, Shen CA, Michel ED, Shulman ST, Melish ME. Infliximab treatment for refractory Kawasaki syndrome. *J Pediatr* 2005; **146**: 662-667 [PMID: 15870671 DOI: 10.1016/j.jpeds.2004.12.022]

86 **Tremoulet AH**, Jain S, Jaggi P, Jimenez-Fernandez S, Pancheri JM, Sun X, Kanegaye JT, Kovalchin JP, Printz BF, Ramilo O, Burns JC. Infliximab for intensification of primary therapy for Kawasaki disease: a phase 3 randomised, double-blind, placebo-controlled trial. *Lancet* 2014; **383**: 1731-1738 [PMID: 24572997 DOI: 10.1016/S0140-6736(13)62298-9]

87 **Sonoda K**, Mori M, Hokosaki T, Yokota S. Infliximab plus plasma exchange rescue therapy in Kawasaki disease. *J Pediatr* 2014; **164**: 1128-1132.e1 [PMID: 24560183 DOI: 10.1016/j.jpeds.2014.01.020]

88 **Ebato T**, Ogata S, Ogihara Y, Fujimoto M, Kitagawa A, Takanashi M, Ishii M. The Clinical Utility and Safety of a New Strategy for the Treatment of Refractory Kawasaki Disease. *J Pediatr* 2017; **191**: 140-144 [PMID: 29173297 DOI: 10.1016/j.jpeds.2017.08.076]

89 **Shafferman A**, Birmingham JD, Cron RQ. High dose Anakinra for treatment of severe neonatal Kawasaki disease: a case report. *Pediatr Rheumatol Online J* 2014; **12**: 26 [PMID: 25045337 DOI: 10.1186/1546-0096-12-26]

90 **Sánchez-Manubens J**, Gelman A, Franch N, Teodoro S, Palacios JR, Rudi N, Rivera J, Antón J. A child with resistant Kawasaki disease successfully treated with anakinra: a case report. *BMC Pediatr* 2017; **17**: 102 [PMID: 28390409 DOI: 10.1186/s12887-017-0852-6]

91 **Dusser P**, Koné-Paut I. IL-1 Inhibition May Have an Important Role in Treating Refractory Kawasaki Disease. *Front Pharmacol* 2017; **8**: 163 [PMID: 28400731 DOI: 10.3389/fphar.2017.00163]

92 **JCS Joint Working Group.** Guidelines for diagnosis and management of cardiovascular sequelae in Kawasaki disease (JCS 2008)--digest version. *Circ J* 2010; **74**: 1989-2020 [PMID: 20724794 DOI: 10.1253/circj.CJ-10-74-0903]

93 **JCS Joint Working Group**. Guidelines for diagnosis and management of cardiovascular sequelae in Kawasaki disease (JCS 2013). Digest version. *Circ J* 2014; **78**: 2521-2562 [PMID: 25241888 DOI: 10.1253/circj.CJ-66-0096]

P- Reviewer: Al-Haggar L, Gonzalez-Granado L **S- Editor**: Cui LJ
L- Editor: A **E- Editor**: Li RF

Published by **Baishideng Publishing Group Inc**
7901 Stoneridge Drive, Suite 501, Pleasanton, CA 94588, USA
Telephone: +1-925-223-8242
Fax: +1-925-223-8243
E-mail: bpgoffice@wjgnet.com
Help Desk: http://www.f6publishing.com/helpdesk
http://www.wjgnet.com

© 2018 Baishideng Publishing Group Inc. All rights reserved.