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# Kawasaki Disease, Others Heart Injuries, Not Only Coronary Arteritis

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## 1. Introduction

### 1.1 Definition

Kawasaki disease was described in 1967 by Tomisu Kawasaki (Kawasaki, 1967). It is manifested by an acute-course febrile syndrome associated with small-to-medium vessel vasculitis, which can lead to severe cardiovascular complications, including myocarditis, pericardial effusion, valve injuries, coronary aneurisms, and myocardial infarction, eventually involving many organs.

### 1.2 Epidemiology

Kawasaki disease (KD) is not well known worldwide; in Japan, in a recent survey (Nakamura, 2008), an increase was found of (151.0 to 184.0/100,000) in children aged <5 years; in other places, especially in Asiatic countries such as Korea (105/100,000), Taiwan (69.0/100,000), China (55/100,000), and in Hong Kong (39.0/100,000); in New Zealand, 8.1/100,000 were registered; in the U.S. (17.1/100,000), Canada (26.2/100,000); in Europe, (10/100,000) new cases are reported annually, while in Hispanic countries, 11 new cases are registered per year, and in Latin America, no exact figures are available, but it has been estimated that there are 3.0/100,000 cases (Yahi Lin, 2010 ;Martinez,2003 Nakamura, 2008).

In Mexico, the first case of KD was communicated by Rodríguez in 1977 (Rodríguez, 1977); from that date until June 2010, registries of case series published in medical journals in Mexico added up to 155 patients (Sotelo, 2011).

### 1.3 Etiology

The causal agent has not been identified 44 years after the original description; very diverse bacterial viral agents, as well as mites, have been considered, in addition to chemical substances, without fully convincing evidence; it has been suggested that the disease is related with superantigenic toxins due to their having found selective expansion of the cellular families T VB2 and VB8; however, this theory remains controversial. In a multicenter prospective study, no significant difference was shown in the prevalence of the toxin produced in toxin-producing strains in patients with KD and in control patients who

manifested fever due to other causes; with respect to this, on the other hand, an alternative hypothesis has been supported regarding that the immune response in KD is polyclonal, (antigen-driven, i.e., similar to a conventional antigen) rather than polyclonal (as found typically in superantigen-driven responses), and that an immunoglobulin A (IgA) plasma cell possesses a central role (Burns, 2004; Falcini, 2006; Nagata, 2009; Newburger, 2004).

In animal models, the properties of superantigenic proteins obtained from intestinal tract bacteria in 19 children with KD, have been studied it was observed that these had T-cell VB2 expansion properties *in vitro*; these superantigens could be involved in the genesis of this disease. During the past decade, *Staphylococcus aureus*, the *Streptococcus* virus for influenza, and the morbilivirus of the pramyxovirus family, bunyavirus, were investigated as a pathogenic agent for KD (Burns, 2004; Esper 2005; Falcini, 2006; Nagata, 2009; Rochol, 2004). Observations have also acquired importance concerning the participation of adenovirus and a new human coronavirus, denominated "New Haven Coronavirus" (Novel human coronavirus Nco-NH), identified in respiratory pathway secretions from a 6-month-old nursing infant with typical KD; in addition, KD was found positive in 8-11-year-old children utilizing the reverse polymerase transcriptase technique. Also reported has been the mycoplasma infection *pneumoniae*; in a recent publication, the participation is considered of nitric oxide and oxygen reactive species by the neutrophils in acute stages (Bruns, 2004; Esper, 2005; Falcini, 2006; Merlin, 2004; Nagata, 2009; Rochol, 2004; Yoshimura, 2009).

To date, no particular gene has been demonstrated to which the development of KD has been attributed; however, the relationship or association has been suggested of a polymorphic HLA-E histocompatibility antigen that could participate in the pathogenesis of the disease; it also has been considered that an imbalance between the Peroxisome proliferator-activated receptor gamma (PPAR-gamma) and low levels of High-molecular-weight (HMW) adiponectin in the disease can be of clinical importance for future development of premature atherosclerosis (Fukunaga, 2010; Lin, 2009).

## 2. Pathogenesis

Explain the disease's pathogenesis it is complex because of the various interactions among increased immunological components, immune system cells, in addition to vascular components; currently, it is to difficulty to explain the controversy regarding the imbalance the metalloproteins and the tissue inhibitors between KD and other febrile processes ; however, suggested that the complicated pathogenesis of this illness include this imbalance, there have been advances, which we will describe in the following text. (Newburger, 2004, Pinna, 2008, Sakata, 2010)

In the first observations relative to immunological perturbations, we include a marked stimulation in the cytokine cascade and in endothelial cell activation, this being the first step leading to coronary artery injuries, participating in the activation of CD68 endothelial cells, monocytes/macrocyles, and CD8 cytotoxic lymphocytes, and IgA plasma cell appear to be involved. The prominence of IgA plasma cells in the respiratory tract, as also occurs in fatal virus-associated respiratory infections, has suggested that the respiratory tract can be the entrance pathway for causal agents. In the genesis of arterial wall injury, the following intervene: Vascular endothelial growth factor (VEGF); Monocyte activator chemotactic factor (MACF) or Monocyte chemotactic protein-1 (MCP-1); Tumor necrosis factor-alpha

(TNF- $\alpha$ ), and diverse interleukins that lead to the development of vasculitis (Neubauer 2004; Pinna, 2008,)

More recently, one study (Sakata, 2010), showed that the circulating matrix metalloproteins MMPs-9 levels are markedly increased in KD, while MMP-1 and tissue inhibitor metalloproteins (TIMPs), showed no significant changes as compared with control groups, previous reports demonstrate that MMP 1-2 and TIMP -2 were significantly higher in acute stage KD, than controls, those reports showed that the levels of MMPs/TIMPs were increased in other febrile patients, nevertheless there was no significant difference in the ratio of MMP/TIMP between febrile and no febrile patients. This feature could play an important role in the vascular remodeling in this disease. The expression of MMP-9 was detected in entire myocardium of a patient with acute KD, and staining revealed the presence of MMP-9 in Endothelial cells (EC), suggesting that the majority of individual monocytes, neutrophils, or myocardial cells express MMP-9. In the Sakata et al, the authors showed that MMP-9 mRNA expression in Human cells (HUEVECs) treated with plasma MMP-1, -2, and TIMP-2 levels were normal for KD. Plasma MMP-9 increased during the disease's acute phase; MMP-9 stained diffusely in coronary arterial lesions and MMP-9 mRNA levels were higher in HUEVECs treated with plasma in acute and convalescent disease phases. Interleukin (IL)-1B, IL-6, and TNF-alpha stimulated MMP-9 expression. The authors conclude that ECs are a source of MMP-9 in vascular lesions, and that KD is regulated by cytokines IL-1B, IL-6, TNF-alpha, and interferon gamma.

In a recent study conducted to clarify the role of peripheral CD8T cells in KD, researchers investigated these cells' activation, proliferation, and effector function, compared with healthy/febrile controls. Patients with KD showed a striking increase in early activator markers CD69 CD8T cells and in maturation subsets, but HLA-DR CD8T cells, which represent late activation, did not increase. The cell division reflected by Ki67, CD8T increased in KD and in febrile controls; however, the effector cells were lower in acute than in convalescent KD. The CD8T cells denoting cytolytic activity were lower in KD (Ehara, 2010; Sakata, 2010).

### 3. Arterial injury

In the evolution of the arterial injury, there is a series of changes that can involve not only the coronary arteries, but also other arteries, such as those of the muscles, the mesentery arteries, the femoral arteries, the iliac, the renal, the axillary, and the brachial arteries; in the different stages of the disease, in the median layer, edema, muscle cell disassociation, and subendothelial edema are observed, and later, mononuclear infiltration, internal elastic lamina destruction, fibroblastic proliferation, metalloprotein matrix-related remodeling, active inflammation, fibrous scar, and arterial remodeling or revascularization; the progressive stenosis results from the remodeling and the neoangiogenesis; the intimal is markedly thickened and consists of linearly arranged micro vessels, a layer that is rich in smooth muscle cells, and fibrous layers many factors are expressed in aneurysms. (Lau, 2008; Sakata, Newburger, 2004; 2010; Tai-Lin, 2008)

### 4. Myocarditis

From 1978, it was communicated that myocarditis can present during the acute phase of KD and that it can be transitory; 20 years later, it was affirmed that up to 50% of patients with

KD can present myocarditis (Fujiwara, 1978; Rowley, 1998). The mechanism of injury is not yet clear, whether it is considered as secondary to the action of several cytokines, TNF, Interferon, or Interleukins 1 and 6, which can contribute to myocyte contractility dysfunction

On the other hand, there is evidence of myocarditis identified by serialized biopsies of myocardia in patients without coronary aneurysms (Takahashi, 1989; Yutani, 1981; Yonesaka, 1992). Findings from the histological viewpoint have been diverse, and among these are found the following: hypertrophy; myocyte degeneration; fibrosis; infiltration of lymphocytes and plasma cells, and disarray of myocardial fibers and, in adults after KD, we find the description of kariomyocyte dropout and diffuse fibrosis not in the watershed distribution of the epicardial coronary arteries; it has been supposed that the fibrosis is due to ischemic damage because of microinfarcts or kariomyocyte inflammatory damage. Myocarditis in KD is characterized by inflammatory cell infiltration from the coronary arteries to the myocardial interstitium, and necrosis of the myocardium is infrequently observed (Yoshikawa, 2006); on the other hand, diffuse myocarditis followed by myocardial fibrosis can lead to diastolic dysfunction, and in the acute phase of KD, measurement of ventricular flow has revealed an abnormal relaxation and has been associated with increased levels of type B natriuretic peptide.

By other hand Myocarditis is recognized as a component on the half of KD patients, thought the left ventricular dysfunction ; Ajami, et al, evaluated myocardial function in patient during acute phase of illness using the myocardial performance index also known as a Tei index, and they assessed the Tei index, the ejection fraction, shortening fraction and valvular regurgitation, pericardial effusion or coronary arterial involvement, they compared the changes in acute phase compared with post-treatment data, confirming left ventricular dysfunction these index measures combined systolic and diastolic function is a simple sensitive and accurate tool for estimating myocardial function (Ajami 2010;Kurotobi, 2005). The pathogenesis of these myocardial injuries and their consequences in the long term with respect to the heart are little understood to date and should not be underestimated; thus, it is necessary to establish methodological follow-up patterns in these patients. The possibility has also been set forth of reclassifying the clinical signs and other findings regarding left ventricle dysfunction in KD (Gordon, 2009; Dahdah, 2009).

## 5. Valvulitis

During the acute phase of KD, approximately 2% of children develop valvulitis followed by scarring of the valves leaflets, most commonly in the mitral valve, leading to valvular incompetence and the need for valve replacement in a subset of patients (Gordon, 2009; Pinna,2008; Sotelo, 2011).

## 6. Myocardial infarct

This is the main cause of death and occurs in 1.4 to 2.8% of patients; this can be caused by thrombosis or rupture of aneurysms, which lead to acute infarct; histopathologically, changes are observed in the cytoplasm, loss of transversal striae and of the nuclear membrane, neutrophil, lymphocyte, and macrophage infiltrate in the dead cell zone, with a formation of collagen that will confer later scarring (Schoen and Mitchell, 2008; Newbauer, 2004; Shimizu, 2009 )

## 7. Other manifestations

In the heart, the development of progressive dilation of the aortic root with aortic valvular regurgitation has been observed. Pericardial effusion with ventricular dysfunction has also been observed (MacMorrow, 2001).

## 8. Ages at presentation

KD is more frequent in children <5 years of age in 76% of the cases, observing a maximum peak at between 2 and 5 years; in infants <1 year of age, special characteristics are present, with a higher number of atypical cases and also more complications. In adolescents, it presents with a lesser frequency; recently, a series of cases has been described in adult patients that, until now, has been limited to one hundred cases, in the majority of which the disease appears, to a greater degree, follow an atypical course, such as has been described in children, the existence of Incomplete KD in adults, suggest that the study algorithm proposed by multidisciplinary committee on experts to diagnose of this disease in children could be useful in adults. On the other hand, in patients with HIV, it is more feasible to find patients affected with KD in adults (Gommar-Menesson, 2010; Seve, 2011).

The children at greatest risk of complications and of having a deficient treatment response are those aged <1 year. With respect to gender, masculine predominates at a ratio of 1.7:1 (Cimaz, 2009; Newburger, 2004).

### 8.1 Season of the year

KD can present in isolated fashion, but in areas of greatest prevalence, epidemic outbreaks are registered, and it is the months of spring and fall that have the greatest number of cases, coinciding with the times of greatest incidence of viral diseases (Lin, 2010; Newburger, 2004).

## 9. Clinical manifestations

Currently, the most important elements for diagnosis are based on the clinical findings; included among these are fever >4 day, at the age < 5 years, associated with skin rash, oropharyngeal and lip erythema conjunctival injection, edema of the hands and feet, erythema of palms and soles, and, in the convalescent phase, these signs comprise the principal criteria for being able to make a diagnosis of KD of day 4 of the illness (Newburger, 2004). Periungual desquamation is a sign that presents at between 10 and 21 days of disease evolution, although additional clinical signs can also be observed, such as hepatomegaly, ictericia, abdominal pain, vesicular colic pain (gall bladder), vomiting, diarrhea, dysuria, the arthralgias, and interphalangeal articular pain; other less frequent clinical data have been described, but it is urgent to have among these the deep, transverse grooves across the nail (Beau's lines). These changes appear 1 or 2 months after disease initiation; striated leukonychia, which consists generally of two smooth bands that are parallel to the lunula of the nails, apparently are associated with Periungual edema and can be observed ca. day 9 of disease evolution (Berard, 2008; Imaz, 2009; Yeo, 2009).

Another sign observed in children <1 years of age is reddening of the Bacillus Calmette-Guérin (BCG) scar, which is considered to be related with a cross-reaction (Shina, 2005) of the thermal shock protein HPS 65 and its human homologue, HPS; on the other hand, the

hydrotropic biliary vesicle, colonic edema, and pulmonary nodules are rare manifestations, but should be considered when there is abdominal pain in acute state and persistent respiratory manifestations (Freeman, 2003; Kim, 2008; Newbauer, 2004; Rigante, 2010) (Table 1).

In cases of suspicion of KD that are catalogued as atypical, we should bear in mind the following data that are useful in the diagnosis: fever for >9 days; skin exanthema for some time, and the three basic disease signs, including leukocytosis with neutrophilia, elevation of transaminases, and albumin <3.5 g/dl, and thrombocytosis. There is also a scoring system, designed by Harada, for predicting coronary aneurisms, comprising the following parameters: masculine gender; age <1 year; leukocytes >12,000 × mm<sup>3</sup>; reactive C protein >3 mg/dl; hematocrit >35; platelets >350, 000 mm<sup>3</sup>, and albumin >3.5 g; a patient is considered to be at risk if he/she scores 4 or more points between day 1 and day 9.

There are serious difficulties involved in establishing the diagnosis in breast-feeding infants and in children aged <1 year, because the patients do not express the characteristic pain; it is, therefore, important to possess laboratory support in determining creatine kinase with the MB fraction, in addition to the Electrocardiogram (EKG) to observe test segment, V<sub>f</sub>, Q, and T waves, echocardiogram, and myocardial perfusion and magnetic resonance gammagrams (Bao-thing, 2010; Javadzagean, 2009; Newburger, 2004; Shulman, 2003).

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#### Basic signs

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Persistent fever for >5 days

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The presence of four or more signs of the disease

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Conjunctival bulbar injection without exudates

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Changes in lips and oral cavity

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Erythema, cracking of lips, strawberry tongue, diffuse oral injection, and pharyngeal mucosa

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Erythema of palms, soles, edema of hands, feet, leukonychia striata in nails at day 9

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Polymorphous exanthema

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Cervical lymphadenopathy (>1.5 cm in diameter), unilateral or bilateral

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Periungual peeling of fingers, toes, in weeks 2 and 3, transversal grooves in fingernails (Beau's lines) in week 4.

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#### Other Clinical Features

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**Cardiovascular System:** Precordial murmur, congestive heart failure, **myocarditis**, pericarditis, pericardial effusion, valvular regurgitation, coronary artery abnormalities.

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Aneurysms of medium-size non coronary arteries.

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**Skin:** Raynaud's phenomenon, peripheral gangrene, desquamating rash in groin, erythema, induration at Bacillus Calmette-Guérin (BCG) inoculation site.

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**Musculoskeletal System:** Arthralgias, arthritis.

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**Gastrointestinal Tract:** Diarrhea, vomiting, abdominal pain, hepatic dysfunction, hydops of gallbladder, colonic edema.

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**Central Nervous System:** Irritability, sensorineural hearing loss, aseptic meningitis.

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**Genitourinary system:** Meatitis, urethritis.

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(Berard, 2008; Kim, 2008; Newburger, 2004; Shina, 2005; Sotelo, 2011).

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Table 1. Basic signs and other findings that can present in Kawasaki disease.

## 10. Laboratory tests and others

There are no specific laboratory studies, although leukocytosis, an increase in globular sedimentation speed, and a discrete elevation of bilirubins in 10% of patients tend to be observed during the first 2 weeks, as well as a moderate increase of transaminases in 40% of cases; in the general urine test, elevated leukocytes can be observed in 4 to 6 of every 10 patients, and thrombosis with a 3- to 6-week duration. In addition, with positive C-reactive protein in concentrations  $>6$  mg/l, other studies have been recommended that suggest vasculitis, such as the following: Antinuclear antibodies (ANA); Anti-neutrophil cytoplasmic antibodies (ANCA), and endothelial anti-cellular antibodies, which have not demonstrated full usefulness and that can lead to confusion; in determination of Creatinine phospho kinase (CPK), MB fractions are useful for patients with very severe clinical pictures and with risk points that suggest greater susceptibility for presenting myocardial infarct. Methods have also been developed, such as determination of tryptophase and kynurenine in plasma by the liquid chromatography method, finding higher levels in patients with KD; this is a method that, once validated, could have an application as a useful laboratory diagnostic index; also, in patients with atypical clinical situations, it has been suggested that determination of natriuretic peptides is a good marker of evolution to myocardial infarct, and it has been recommended that this could be added to the diagnostic tests (Card, 2009; Dahdah, 2009; Kurotobi, 2005; Javadzagean, 2009; Newburger, 2004; Shulman, 2003; Zhan, 2009).

It has been found recently that early neutropenia indicates that circulating neutrophils on day 10 of illness evolution can play an important role in following the sequence of the formation of coronary artery injuries (Onouchi, 2009).

More recently, the measurement has been proposed of CD69 CD8T in peripheral blood as a marker to determine disease progression, treatment response, and convalescence in KD (Ehara, 2010).

On the other hand, studies have been conducted in order to identify whether there are genetic markers related with risks of complications in children with KD, and polymorphisms found in the *HLA-E* gene have been associated with the possibility of the development of coronary aneurysms; on the other hand, alterations in the extracellular matrix associated with Pro-collagen type III (PIIINP) and metalloproteins identified with biomarkers in 35 adolescents and young adults who had KD have shown an association between high levels of PIIINP and the severity of the coronary injuries; nonetheless, more confirmatory studies are required in this respect (Lin MT, 2008; Lin YJ, 2009). Unfortunately, many of these procedures are not within the reach of the poorest countries (Sotelo, 2007, 2011).

### 10.1 Thoracic x-rays

These can show pneumonic infiltrate in 15% of cases, especially in patients who present cough and respiratory difficulty, although there are radiologic changes that can be caused by pneumonitis, hemorrhages, and vasculitis-related pulmonary nodules (Freeman, 2003).

### 10.2 Electrocardiogram (EKG)

EKG can be normal in the first disease phases, or can show changes such as tachycardia, PR-QT prolongation, and abnormal Q waves (data of the infarct).



### 10.3 Echocardiography

This is a study conducted in the physician's office that is perhaps the most important in the diagnosis and it is necessary in the acute phase and within the first 15 days, independently of adequate treatment, and is especially required in children with an atypical or incomplete clinical situation who manifest fever and at least four basic disease signs. This procedure is also necessary to demonstrate left ventricular function in patients with myocarditis and shortening of the fraction of the left ventricle with ( $<0.28$ )-decreased values; however, fraction shortening increased significantly after treatment; also is utilized Tei index for measures combined systolic and diastolic function and estimating myocardial dysfunction as an evidence of myocarditis, these has been demonstrated by means of other methods, for example, utilizing Galio citrate and scanner (planar or single-photon-emission [SPE]-CT) and Tc labeled with blood cell scans. By these methods and by echocardiography, it has been observed that there is improvement in the myocarditis after treatment. This situation probably is related with the fact that myocarditis has been considered as a transitory event, without its being studied more profoundly (MacMorrow, 2001; Newburger, 2004; Yoshikawa, 2006).

### 10.4 Perfusion gammagrams

To demonstrate coronary injuries, there are procedures that are also utilized that permit greater precision in the identification of these coronary lesions; among these procedures are found myocardial perfusion gammagrams and coronariographies; it is also possible to request coronary Angiography by magnetic resonance (MRA), which provides images equivalent to those of coronary angiography. In addition, there as also been information on flow in dilated arteries. Another procedure such as Electron beam computed tomography (EBT) is employed to estimate the characteristics of the myocardium and is useful for detecting progressive myocardial ischemia. Spiral CT (Multislice Spiral Computed Tomography) EBT is a non-invasive resource that is comparable with coronary angiography for visualizing arterial stenosis in children with KD; lately, there has been a recommendation for the use of Dual CT (DSCT) as a resource of greater usefulness than the color Doppler echocardiogram for the detection of coronary abnormalities. Notwithstanding this, of recent date technological innovations in echocardiography have also been described that allow to evaluate treatment response to GGIV, assessing the cardiac walls. Some of these procedures could in the future constitute the diagnostic and follow-up standards in KD (Abe, 2010; Bao-Ting, 2010; Endoh, 2004; Magroverni, 2004).

## 11. Treatment

Early identification of this disease and initiating treatment with gammaglobulin and aspirin during the course of week 1 has demonstrated that this avoids the development of coronary injuries and diverse cardiovascular injuries that, in the acute as well as in later disease stages, place the patient's life at risk (Mueller, 2009; Newbauer, 2004).

The most utilized treatment is the application of Intravenous gammaglobulin (GGIV) at a dose of 2 per kg in a sole dose for a 12- infusion; this is the most accepted treatment and has allowed to the reduction of prevalence of aneurysms to  $<5\%$  and a mortality of 2% to 0.3%, although the GGIV scheme is at a dosage of 400 mg  $\times$  kg  $\times$  day for 5 days, plus aspirin at 80 to 100 mg  $\times$  kg  $\times$  day. According to response, the GGIV dose can be repeated, or corticoids can be added, especially in refractory cases (Cha, 2008; Chung, 2009; Falcini, 2006; Hung, 2009; Miura, 2008; Newbauer, 2004; Ogata, 2009; Okada, 2009; Sano, 2010; Tremoulet, 2008).

Other therapeutic agents have been recommended, such as cyclophosphamide, cyclosporine, and Ulinastatin in a limited number of cases (Newbauer, 2004).

Infliximab is a product based on monoclonal antibodies against Tumor necrosis factor-alpha (TNF- $\alpha$ ), and it has been employed successfully in cases of resistance to gammaglobulin. (Burns,2008)

Abciximab is another monoclonal antibody that inhibits the platelet glycoprotein receptor IIb/IIIa, favoring the more rapid resolution of the aneurysms; however, these drugs require greater clinical experience (Burns, 2008; Williams, 2002; Tremoulet, 2008).

Concerning recommendation for treatment of KD during the past 3 years, it as been mentioned that the greatest effectiveness in cases of relapse or resistance is obtained on utilizing pulses of methylprednisolone in addition to GG.

In cases of recurrence of fever or resistance to GGIV, this combination has even been recommended as initial therapy (Cha, 2008; Chung, 2009; Miura, 2008; Ogata, 2009; Okada, 2009; Sha, 2008).

Cardiovascular sequelae of KD in the adult in Japan. A systematical follow-up all the patients who were diagnosed with this disease with observation periods of >15 years; The Committee of Experts of the American Heart Association has designed a follow-up model that includes stratification in five levels (I toV),Table 2 (Newburger,2004), the latter including coronary changes, size of the aneurysms, and the obstruction, and they also provided pharmacological recommendations and the procedures and diagnostic studies, both invasive and non-invasive, that should be performed, in addition to the surgical options (Gordon, 2009; Newburger, 2004). Included an indication that there should be long-term follow-up for patients who had echocardiogram-indicated coronary ectasias in an acute episode and who presented for development of aneurysms, independently of the internal diameters of these, but with special emphasis on patients who presented giant aneurysms of >8 mm, and also subjects who additionally had other cardiovascular risk factors, such as obesity and hypertriglyceridemia.

The complications most frequently observed in adults as sequelae of KD are the following: angor pectoris; ventricular tachycardia ventricular with left cardiac failure, secondary to calcified aneurysms, myocardial infarct, arrhythmias, and sudden death (Gordon JB, 2009).

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***Risk Level I – Patients with no coronary artery changes on echocardiography at any stage of the illness***

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No antiplatelet therapy is needed beyond the initial 6 to 8 weeks after the onset of illness.

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No restriction of physical activity is necessary after 6 to 8 weeks.

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Because the degree of future risk for ischemic heart disease in this category of patients is still undetermined, periodic assessment and counseling about known cardiovascular risk factors every 5 years is suggested.

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Coronary angiography is not recommended.

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***Risk Level II – Patients with transient coronary artery ectasia or dilatation (disappearing within the initial 6 to 8 weeks after the onset of illness)***

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No antiplatelet therapy is needed beyond the initial 6 to 8 weeks after the onset of illness.

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No restriction of physical activity is necessary after 6 to 8 weeks.

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Risk assessment and counseling is recommended at 3- to 5-year intervals.

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Coronary angiography is not recommended.

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**Risk Level III** – Patients with isolated (solitary) small to medium (>3 mm but <6 mm, orzscore between 3 and 7) coronary artery aneurysm in  $\geq 1$  coronary arteries on echocardiography or angiography

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Long-term antiplatelet therapy with aspirin should be administered, at least until the aneurysms regress.

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Physical activity without restriction in infants and children in the first decade of life is permitted after the initial 6 to 8 weeks. Stress tests with myocardial perfusion evaluation may be useful in the second decade to guide recommendations for physical activity. Participation in competitive collision or high-impact sports is discouraged in children receiving antiplatelet therapy.

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Annual follow-up by a pediatric cardiologist with echocardiogram and ECG is recommended. Stress tests with myocardial perfusion imaging is recommended every 2 years in patients >10 years old.

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Coronary angiography is indicated if myocardial ischemia is demonstrated by stress tests with imaging.

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**Risk Level IV** – Patients with  $\geq 1$  large coronary artery aneurysm ( $\geq 6$  mm), including giant aneurysms, and patients in whom a coronary artery contains multiple (segmented) or complex aneurysms without obstruction

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Long-term antiplatelet therapy is recommended. Adjunctive therapy with warfarin with a target INR of 2.0:2.5 is recommended for patients with giant aneurysms. Daily subcutaneous injections of low-molecular-weight heparin merits consideration as an alternative to warfarin for infants and toddlers, in whom blood drawing for INR testing is difficult. Low-molecular-weight heparin also may be used as a bridge during the initial phase of warfarin therapy or during the reintroduction of warfarin after the interruption of therapy for the purpose of elective surgery; therapeutic levels are assessed by measuring antifactor Xa levels. Some experts recommend a combination of aspirin and clopidogrel for patients with multiple or complex aneurysms.

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Recommendations about physical activity should be guided by annual stress tests with myocardial perfusion evaluation. Collision or high-impact sports should be discouraged because of the risk of bleeding. Participation in noncontact dynamic or recreational sports is encouraged if no evidence exists of stress-induced myocardial ischemia.

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Cardiology evaluation with echocardiogram and ECG should be done at 6-month intervals. Stress tests with myocardial perfusion evaluation should be performed annually. The patient should be monitored for known risk factors of atherosclerosis and his or her family should be counseled accordingly.

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Cardiac catheterization with selective coronary angiography should be performed 6 to 12 months after recovery from the acute illness, or sooner if clinically indicated, to delineate the complex coronary artery anatomy. Follow-up angiography may be indicated if noninvasive studies suggest myocardial ischemia. In addition, elective cardiac catheterization in the absence of noninvasive evidence of myocardial ischemia may be useful to rule out subclinical major coronary artery obstructions in some situations, such as when the patient experiences atypical chest pain, the ability to perform dynamic stress testing is limited by age, unique activity restrictions or insurability recommendations are needed, or the anatomy or size of the aneurysm cannot be clearly defined by echocardiography for decisions regarding anticoagulation.

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For females of childbearing age, reproductive counseling is strongly recommended.

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***Risk Level V – Patients with coronary artery obstruction confirmed by angiography***

Long-term antiplatelet therapy with or without adjunctive therapy with warfarin anticoagulation is recommended (see Risk Level IV)

β-Adrenergic-blocking drugs should be considered to reduce myocardial oxygen consumption.

Recommendations about dynamic physical activities should be based on the patient's response to stress testing. Collision or high-impact sports should be discouraged because of the risk of bleeding. Patients should avoid a sedentary lifestyle.

Cardiology evaluation with an echocardiogram and ECG should be obtained at 6-month intervals. Stress tests with myocardial perfusion evaluation should be performed annually. The patient should be monitored for known risk factors of atherosclerosis and his or her family should be counseled accordingly.

Cardiac catheterization with selective coronary angiography is recommended to address the therapeutic options of bypass grafting or catheter intervention and to identify the extent of collateral perfusion. Repeat cardiac catheterization may be indicated when new onset or worsening myocardial ischemia is suggested by noninvasive diagnostic testing or clinical presentation. If the patient has undergone surgical revascularization or a catheter intervention, then repeat cardiac catheterization may be indicated to evaluate the efficacy of the treatment.

For females of childbearing age, reproductive counseling is strongly recommended.

Table 2. Risk Stratification according American Heart association (Newburger, 2004).

## 12. Conclusion

In view of the growing number of patients with KD who have been identified in different parts of the world, it is necessary for Pediatricians, Pediatric Cardiologists, Pediatric Cardiologist Internists, and Cardiologists for adults to carry out correct follow-ups, taking into consideration that patients can develop vascular injuries with different types of atherosclerosis, coronary aneurysms, with valve incompetence due to scarring of the leaflets or progressive aortic root dilation, and it is important not to underestimate the myocardial lesions, and the biochemical markers of this inflammatory process during acute phase, including moreover, diffuse fibrosis or local scarring in regions of myocardial, ischemia or infarct (Takahasi, 1989; Dahdah, 2009).

KD-associated inflammatory damage can potentially affect all of the components of the cardiovascular system and even other bodily areas as a consequence of vasculitis; thus, systematic follow-up is necessary until adult age in all children who have had this disease, even when his/her manifestations have not been severe, and especially in these children who manifested myocarditis without coronary artery injuries, because to date we do not know the characteristics and long-term consequences of this particular problem. On the other hand, some reports note an up to 12% frequency for myocarditis. The treatment for sequelae in coronary arteries is infrequent in pediatric ages and in the adult, and will depend on the damage established and the patient's evolution at the long term; the decision for the choice of the most adequate procedure (intervention with percutaneous catheter or surgery for bypass placement or specific procedures for valvular problems) will be determined by Cardiologists and Cardiovascular Surgeons (Careaga-Reyna, 2008; Crystal, 2009; Fukazawa, 2010; Gil-Veloz, 2009; Huerta-García, 2009; Kato, 1996; Mueller, 2009; Simizu, 2010; Sudo, 2010; Sotelo, 2011, Vizcaino, 1991).

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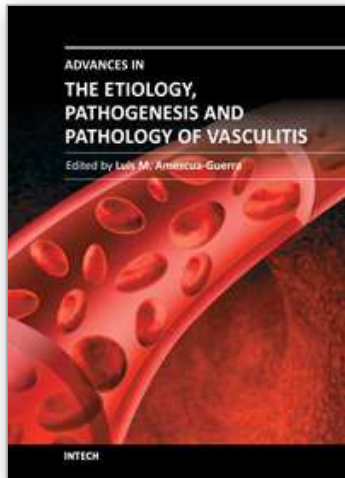


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This book represents the culmination of the efforts of a group of outstanding experts in vasculitis from all over the world, who have endeavored to devote their work to this book by keeping both the text and the accompanying figures and tables lucid and memorable. Here, you will find an amalgam between evidence-based medicine to one based on eminence, through an exciting combination of original contributions, structured reviews, overviews, state-of-the-art articles, and even the proposal of novel pathogenetic models of disease. The book contains contributions on the etiology and pathology of vasculitis, the potential role of endothelial cells and cytokines in vascular damage and repair as well as summaries of the latest information on several primary and secondary vasculitis syndromes. It also covers selected topics such as organ-specific vasculitic involvement and quality of life issues in vasculitis. The editor and each of the authors invite you to share this journey through one of the most exciting fields of the medicine, the world of Vasculitis.

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