Iranian Journal of Pediatrics Society
Volume 1, Number 1, 2007: 9-23

Review Article

Kawasaki Disease

Ahmad Siadati MD, Farah Sabouni MD, Parisa Saleh Anaraki MD
Department of Pediatrics, Tehran University of Medical Sciences and Health Services, TEHRAN-IRAN.

ABSTRACT

Kawasaki disease is an acute vasculitis of childhood that predominantly affects the coronary arteries. The etiology of Kawasaki disease remains unknown, although an infectious agent is strongly suspected based on clinical and epidemiologic features. A genetic predisposition is also likely, based on varying incidences among ethnic groups, with higher rates in Asians. Symptoms include fever, conjunctival injection, erythema of the lips and oral mucosa, rash, and cervical lymphadenopathy. Some children with Kawasaki disease develop coronary artery aneurysms or ectasia, ischemic heart disease, or sudden death. Kawasaki disease is the leading cause of acquired heart disease among children in developed countries. This article provides a summary of the history, etiology, clinical diagnosis, treatment guidelines and lifelong follow up of KD.

Key words: *Kawasaki disease, Syndrome, Fever and rash, Cardiac disease, Coronary artery aneurysm.*

Corresponding author: Siadati A, M.D.
Address: *Department of Pediatrics, Tehran University of Medical Sciences and Health Services,*
Email: *info@irisp.org*

Kawasaki disease is a rash/fever illness of early childhood in which coronary artery aneurysms (CAA), sometimes fatal, may develop in up to 25 percent of untreated children. The incidence is highest in Japan, with an annual rate of 130–140 per 100,000 in children under five years of age (1). In comparison, incidence for under-fives in the continental United States varies between 9 and 20/100,000, and, among Japanese Americans living in Hawaii, between 120 and 130/100,000 (2). Since the etiologic agent(s) and pathophysiological mechanisms of Kawasaki disease remain unknown, and also because there is no diagnostic laboratory test, diagnosis relies on the observation and recognition of clinical signs that comprise the Kawasaki disease case definition (3-4).

The illness is named after the Japanese pediatrician Tomisaku Kawasaki, who in 1967 described fifty cases of infants with persistent fever accompanied by rash, lymphadenopathy, edema, conjunctival injection, redness and cracking of the lips, “strawberry tongue,” and convalescent desquamation (5).

Kawasaki's Sign Complex (1967)

1. Even with the use of various antibiotics, fever higher than 38°C persists longer than 6 days. 50 cases (100%)
2. Bilateral bulbar conjunctiva presents injection. 49 cases (98%)
3. Erythematous rash seen particularly on bilateral palms and/or bilateral soles, but never forms vesicles. 43 cases (86%)
4. Redness, dryness, erosion, cracking, sometimes bleeding and hemorrhagic scab on lips and sometimes diffuse injection of oral mucosa and strawberry tongue are recognized. 48 cases (96%)

a. No formation of vesicles, ulcers, pseudomembrane or aphtha.

5. Acute swelling of cervical lymph node(s) (equal or bigger than the thumb head) 33 cases (66%).

a. Never develops pyesis.

6. Both hands and feet present vaso-neurogenic edema. 22 cases (44%)
7. Desquamation starts from nail-skin junction of fingers and toes, mostly in the second week of the disease. 49 cases (98%)
8. More than half of the cases are under the age of 2 years. 27 cases (54%)
9. No recurrence.
10. Resolves without intervention; no sequelae.

No contagion between siblings was observed. Adapted from Tomisaku Kawasaki, "Acute Febrile Muco-Cutaneous Lymph Node Syndrome in Young Children with Unique Digital Desquamation: Clinical Observation of 50 Cases" [in Japanese], *Arerugi* [*Jpn. J. Allergology*], 1967, *16* (3): 178–222.

The typical history of Kawasaki disease provides a narrative that emphasizes Kawasaki's careful clinical observations and his subsequent classification of clinical signs into a distinct syndrome. It relates the story of how he identified what he and his supervisor and colleagues at the Red Cross Hospital considered to be a novel childhood illness. Kawasaki labeled the illness "mucocutaneous lymph node syndrome" (MLNS or MCLS). Initially, he assumed that the syndrome was self-limiting and benign, requiring no special intervention; however, the death of a number of patients reported in early surveys persuaded him to acknowledge a connection between the illness and coronary artery abnormalities. Simultaneously with Kawasaki's discovery, a team of American pathologists identified a fatal cluster of childhood CAA as a distinct syndrome that they labeled "infantile polyarteritis nodosa" (IPN). Within a decade, pathologists determined that IPN and fatal cases of MCLS were identical; soon after, MCLS and IPN were renamed Kawasaki disease, in honor of its discoverer (6).

EPIDEMIOLOGY AND ETIOLOGY

Kawasaki disease is the most common cause of acquired heart disease in children in the developed world. The exact cause has not yet been identified but there is considerable evidence supporting the fact that it is due to an infectious agent causing disease among genetically vulnerable individuals (7-13).

Children under the age of 5 years are predominantly affected, (14) with a peak incidence at 9-11 months (15). There is a peak occurrence in winter (16).

Elucidation of the etiology of disease would direct treatment and provide a more rational basis for its management. Towards this aim there has been considerable focus on a bacterial superantigen toxin being the cause of Kawasaki disease over the past decade; this superantigen is believed to act in a similar fashion to the superantigen toxins of staphylococcal and streptococcal toxic shock syndromes (17-19).

There are laboratory based studies that lend support to this hypothesis. One study found that the peripheral blood macrophages/ monocytes (which function as antigen presenting cells (APC)) of patients with Kawasaki disease are decreased following the administration of immunoglobulin (IVIG). The APC and T cells are implicated in

superantigen disease, as the superantigen binds across the APC to the variable region of the T cell non-specifically at the V ß2 region and hence causing a massive upregulation of T cell activation. As IVIG has considerable benefit in treating Kawasaki disease, this would lend support to the idea of superantigen involvement in its etiology (20).

In Kawasaki disease there is a large increase in circulating B cells and fewer T cells; the effect of IVIG in vitro on peripheral lymphocytes is to decrease the percentage of B cells, and increase T cells, as well as CD4, CD8 T and CD5+ cells in acute Kawasaki disease (there is a much less effect with aspirin alone) (21).

Causes: The etiology of Kawasaki disease remains unknown (8). At present, most of the epidemiologic and immunologic evidence indicates that the causative agent is probably infectious. The search for an etiologic agent could cover an infectious disease textbook (8). This idea of an infectious etiology is supported by the age of the patients affected, the periodic epidemics, the wavelike and geographic spread of illness during the epidemic, and the self-limiting nature of the illness. Furthermore, 1.4% of cases in Japan involve siblings. The overall clinical presentation of patients with Kawasaki disease is similar to that of patients with a viral or superantigenic disease (Table 1).

Table 1. Clinical findings of Kawasaki disease and coincidental infections in studies by Siadati and Sabouni (I)-Benseler (II)

Clinical feature	I(%)	II(%)	Infection	I (%)	II (%)
Conjunctival injection	54	95	Up.resp.Inf	24	23.5
Oral changes	70	91	Low.resp. inf	4	4
Rash	56	91	UTI	8	3
Peripheral changes	49	71	Sepsis	2	1
Lymphadenopathy	43	52	Gastroint.	6	2.5

The failure to isolate one pathogen highlights the likelihood that the cause of Kawasaki disease is multifactorial and that genetic and immunologic factors, and possibly a vector, influence the disease. Superantigens and cytotoxic T cells appear to be involved. Passive maternal immunity might account for the failure of most cases to develop before the age of 4 months.

Kawasaki disease has been linked to a variety of infections, including the followings:

- Parvovirus B19
- Meningococcal septicemia
- *Coxiella burnetii*
- Bacterial toxin–mediated superantigens
- HIV
- *Mycoplasma pneumoniae*
- Adenovirus
- *Klebsiella pneumoniae* bacteremia
- Parainfluenza type 3 virus
- Rotavirus infection
- Measles
- Human lymphotropic virus infection

A case of Kawasaki disease with CAAs and *Yersinia pseudotuberculosis* infection has been reported. Kawasaki disease does not appear to be linked to *Rickettsia conorii, Rickettsia typhi, C burnetii,* or *Ehrlichia phagocytophila* group allergens, such as anionic detergents and house dust mites, and some chemicals (including heavy metals). No association exists between KD and infection with human herpesvirus 8, transfusion transmitted virus (TTV), GB virus C/ hepatitis G virus, or *Chlamydia pneumoniae.*

The search for the etiologic agent of Kawasaki disease:

Recent findings in 2007:

Two recently proposed theories regarding Kawasaki disease etiology, the toxic shock syndrome toxin-1 hypothesis and the coronavirus NL-63 hypothesis, have been studied extensively and have been disproved. Surprisingly, IgA plasma cells infiltrate inflamed tissues in acute Kawasaki disease,

including the coronary artery, and are oligoclonal, or antigen-driven. Synthetic versions of predominant IgA antibodies in acute Kawasaki disease (arterial tissue) bind to an antigen present in acute Kawasaki disease (ciliated bronchial epithelium) and in a subset of macrophages in acute inflamed Kawasaki disease tissues. Light and electron microscopic studies of the antigen in acute Kawasaki disease (ciliated bronchial epithelium) indicate that the Kawasaki disease-associated antigen localizes to cytoplasmic inclusion bodies that are consistent with aggregates of viral protein and associated nucleic acid. Because most ubiquitous microbes enter the host via the respiratory or gastrointestinal tracts, one or both of these portals of entry would be likely for the putative agent(s)(8). Hypercoagulability does not occur during the acute stage of Kawasaki disease.

KD AROUND THE WORLD

The reason for the simultaneous recognition of this disease around the world in the 1960_s and 1970_s remains unknown. There are several possible explanations. KD may have been a new disease that emerged in Japan and emanated to the Western world through Hawaii , where the disease became prevalent among Asian children . Alternatively, KD and IPN may be part of the spectrum of the same disease and clinically mild KD masqueraded as other diseases, such as scarlet fever in the preantibiotic era. Case reports of IPN from Western Europe extend back to at least the 19^{th} century , but , thus far , cases of IPN have not been discovered from Japan before World War II (18). Perhaps the factors responsible for KD were introduced into Japan after the war and then reemerged in a more virulent form that subsequently spread through the industrialized Western world . It is also possible that improvements in health care and , in particular , the use of antibiotics to treat infections caused by organisms including toxin – producing bacteria reduced the burden of rash/fever illness and allowed KD to be recognized as a distinct clinical entity .

In Iran, the first KD patient was diagnosed by Ahmad Siadati in 1986, in Children Medical Center. Previously, All similar cases had been diagnosed and admitted as IPN in that center. Since 2004, Iranian Kawasaki disease Research Center has recorded medical files of all KD patients reported by Iranian physicians. We have registered more than 500 KD patients in our center till now.

DIAGNOSIS

Kawasaki disease has two phases: an acute phase lasting 1 to 2 weeks, followed by a chronic (“convalescent”) phase (17). Untreated disease usually resolves spontaneously after several weeks.

Classic (Typical) Clinical Criteria

There is no specific diagnostic assay for Kawasaki disease; therefore, diagnosis is based on clinical criteria, which include fever for at least five days and four or more of the five major clinical features (i.e., conjunctival injection, cervical lymphadenopathy, oral mucosal changes, polymorphous rash, and swelling or redness of the extremities),(Figure 1,2) and exclusion of alternative diagnoses. Clinical features may not be present simultaneously, and taking a careful history is necessary in children who lack a clear explanation for fever. If the typical clinical findings are present in a child with fever for less than five days, the diagnosis still can be made by experienced physicians and treatment can be initiated. In addition, classic Kawasaki disease can be diagnosed with three clinical features if coronary artery abnormalities are observed on echocardiography (2). Because many of the clinical features of Kawasaki disease may be present in other illnesses, exclusion of other illnesses in the differential diagnosis is often necessary.

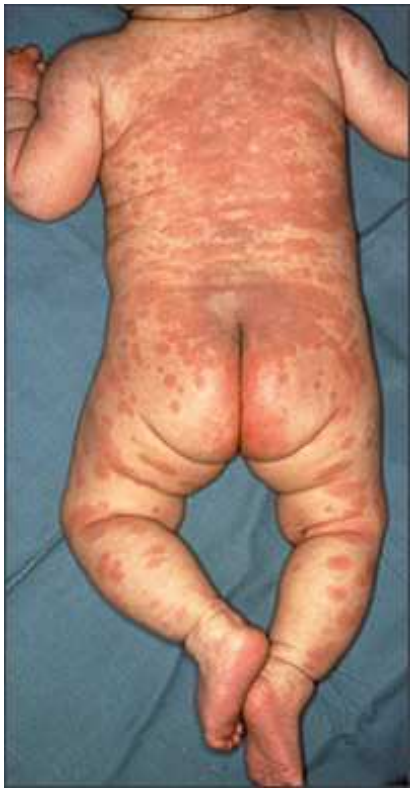


Figure 1. Infant with Kawasaki disease with an erythematous, predominantly truncal rash.

The fever in Kawasaki disease is usually higher than 102.2°F (39°C) and often above 104.0°F (40°C); if untreated, it lasts for an average of 11 days, although fever lasting for several weeks has also been reported. Conjunctival injection is typically bilateral and nonpurulent, and photophobia and eye pain are not often present. The injection is primarily of the bulbar conjunctiva with sparing of the limbus (the area immediately adjacent to the cornea). Swelling or erythema of the hands and feet is characterized by a sharp demarcation at the ankles and wrists; the swelling may be painful. Classic peeling of the fingers and toes (starting in the periungual region) usually does not occur until two to three weeks after onset of symptoms, when fever has typically resolved. Oral mucosal changes can manifest as red and cracked lips, strawberry tongue, or diffuse erythema with no focal lesions, ulcerations, or exudates.

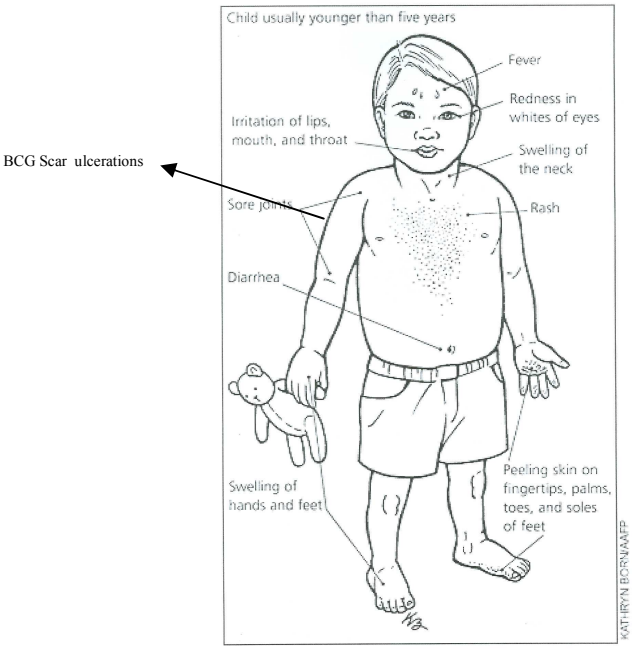


Figure 2 . Clinical Guideline for families .

Rash tends to appear within the first five days of illness and is truncal, often with accentuation in the groin region *(Figure 1)*. Most commonly, the rash is erythematous and maculopapular, although it may appear urticarial, scarlatiniform, erythema multiforme-like, or as erythroderma. Bullous and vesicular lesions are not present. Cervical lymphadenopathy of at least 1.5 cm in diameter is the least common clinical feature but may be the presenting and most prominent sign (especially in older children), leading to a misdiagnosis of bacterial lymphadenitis.[4] There are other clinical features often shared by children with Kawasaki disease that are not incorporated into the diagnostic criteria (Table 2) (2).

Laboratory and other ancillary studies, although nonspecific, may support the diagnosis of Kawasaki disease. With more severe and prolonged illness,

some laboratory abnormalities (including anemia and hypoalbuminemia) may become quite pronounced. Acute phase reactants, including the erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) level, are particularly helpful because they are usually elevated to a degree not typically found in common viral infections. The ESR is often above 40 mm per hour and, not uncommonly, is elevated to levels of at least 100 mm per hour; CRP typically reaches levels of 3 mg per dL (30.0 mg per L) or more. Of note, intravenous immunoglobulin (IVIG) elevates the ESR; therefore, the CRP test is more accurate after IVIG therapy.

Table 2. Clinical and laboratory findings that should prompt consideration of incomplete (atypical) KD.

Clinical findings
Daily high spiking fevers especially if for>5 days and particularly in infants, without evidence of a bacterial infection
With or without
1. One or more other diagnostic criteria for KD, especially conjunctival injection, oral mucosal changes and/ or rash
2. Anterior uveitis on slit-lamp examination
and
Laboratory findings
1. markedly elevated ESR and/or C-reactive protein
2. elevated peripheral white blood cell count or normal white blood cell count with neutrophil predominance and immature forms on differential
3. thrombocytosis after 7th day of fever
with or without
1. sterile pyuria
2. elevated alanine aminotransferase
3. aseptic meningitis
4. anemia
5. hypoalbuminemia
6. echocardiogram showing pericardial effusion

With the exception of echocardiography, imaging studies are not performed routinely in patients with suspected Kawasaki disease. However, abnormalities on chest radiography are observed in about 15 percent of patients (5) usually revealing peribronchial cuffing or increased interstitial markings, with occasional pulmonary nodules (6). Abdominal ultrasonography may reveal gallbladder hydrops (7).

Echocardiography. Although aneurysms generally are not present during the first 10 days of illness, any patient in whom Kawasaki disease is strongly suspected should receive echocardiography because abnormalities that aid in diagnosis may appear within the first 10 days of fever. In the acute phase of illness, coronary artery abnormalities include lack of tapering, perivascular brightness, and ectasia (2). Echocardiography also may reveal decreased ventricular function, mild valvular regurgitation, and pericardial effusion.

Incomplete (Atypical) Kawasaki Disease

Incomplete Kawasaki disease refers to patients who do not fulfill the classic criteria of at least four of the five findings. Incomplete Kawasaki disease is more common in children younger than one year, in whom the rate of coronary artery aneurysms is paradoxically higher if not treated (8); therefore, establishing the diagnosis and initiating treatment are essential.

The diagnosis of Kawasaki disease can be difficult because many features mimic common childhood illnesses (e.g., adenovirus, scarlet fever) and drug reactions. Therefore, physicians need to keep Kawasaki disease in their differential diagnoses for children who have prolonged fever without clear etiology, because the consequences of missed diagnoses can be serious morbidity or, in rare cases, death.

An algorithm to evaluate febrile patients who do not fit the classic criteria for Kawasaki disease is provided in table *2.* Children with at least five days of fever and at least two of the Kawasaki disease criteria should be assessed for other clinical features

associated with the disease . In children who have received BCG vaccine, reactions of erythema, induration and ulcerations may occur at the site of inoculation with the development of Kawasaki disease. Reactions can also occur at the site of *M. tuberculosis* antigen skin tests (2). If the clinical characteristics are compatible with Kawasaki disease, laboratory tests including CRP and ESR should be obtained. If characteristic results are not found, the child should be reassessed only if fever persists. Clinical characteristics that would help exclude the diagnosis include exudative conjunctivitis or pharyngitis, discrete intraoral lesions, bullous or vesicular rash, and generalized lymphadenopathy.

Evaluating Febrile Patients Without Classic Kawasaki Disease Criteria

In patients with compatible features and elevated CRP levels or ESR, supplemental laboratory tests including measures of serum albumin and transaminase levels, complete blood cell count, and urinalysis should be performed (2). If these results are consistent with Kawasaki disease (2), patients should have echocardiography and be treated for Kawasaki disease. If these laboratory abnormalities are not present, echocardiography should be performed and the child should be treated if abnormalities are noted on the echocardiogram. Patients whose clinical assessment indicates that treatment is unnecessary, should be followed closely, with serial laboratory testing, if needed. Because young infants often have fewer clinical findings and are at increased risk of cardiac sequelae, those who are six months or younger and have fever for at least seven days with no clear etiology should undergo laboratory assessments even if no features of Kawasaki disease are present; echocardiography should be performed if evidence of inflammation is found.

Evaluation of Suspected Incomplete Kawasaki Disease (Algorithm: see Figure 3 in original guideline document)

1. In the absence of gold standard for diagnosis, this algorithm cannot be evidence based but rather represents the informed opinion of the expert committee. Consultation with an expert should be sought anytime assistance is needed.
2. Infants $\leq$6 months old on day $\geq$7 of fever without other explanation should undergo laboratory testing and, if evidence of systemic inflammation is found, an echocardiogram, even if the infants have no clinical criteria.
3. Patient characteristics suggesting Kawasaki disease are listed in the table above entitled "Clinical and Laboratory Features of Kawasaki Disease." Characteristics suggesting disease other than Kawasaki disease include exudative conjunctivitis, exudative pharyngitis, discrete intraoral lesions, bullous or vesicular rash, or generalized adenopathy. Consider alternative diagnoses (see Table 2 in the original guideline document).
4. Supplemental laboratory criteria include albumin $\leq$3.0 g/dL, anemia for age, elevation of alanine aminotransferase, platelets after 7 days $\geq$450,000/mm^3, white blood cell count $\geq$15,000/mm^3, and urine $\geq$10 white blood cells/high-power field.
5. Can be treated before performing echocardiogram.
6. Echocardiogram is considered positive for purposes of this algorithm if any of 3 conditions are met: *z* score of LAD or RCA $\geq$2.5, coronary arteries meet Japanese Ministry of Health criteria for aneurysms, or $\geq$3 other suggestive features exist, including perivascular brightness, lack of tapering, decreased LV function, mitral regurgitation, pericardial effusion, or *z* scores in LAD or RCA of 2 to 2.5.

7. If the echocardiogram is positive, treatment should be given to children within 10 days of fever onset and those beyond day 10 with clinical and laboratory signs (CRP, erythrocyte sedimentation rate [ESR]) of ongoing inflammation.
8. Typical peeling begins under nail bed of fingers and then toes.

Figure 3 showed the algorithm to evaluate febrile patients who do not fit the classic criteria for Kawasaki disease.

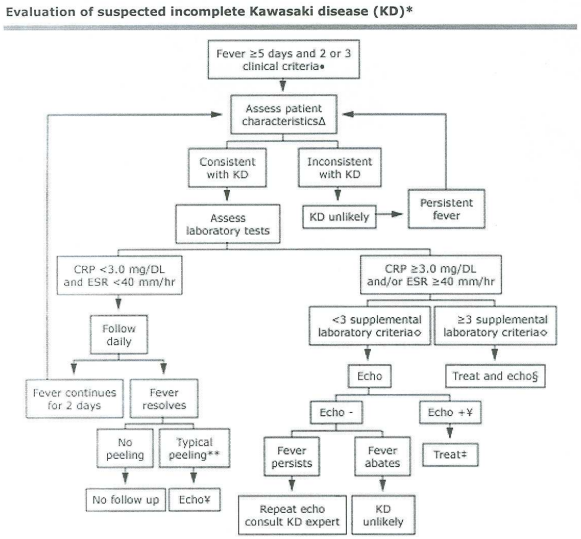
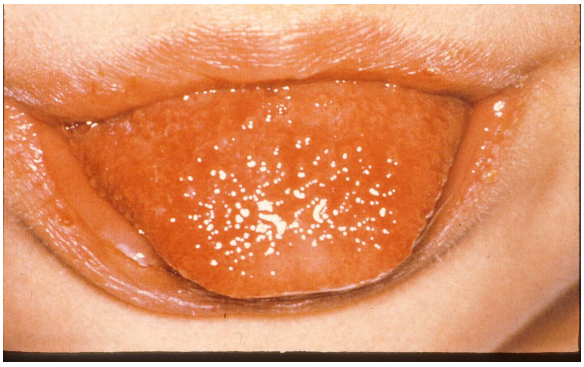


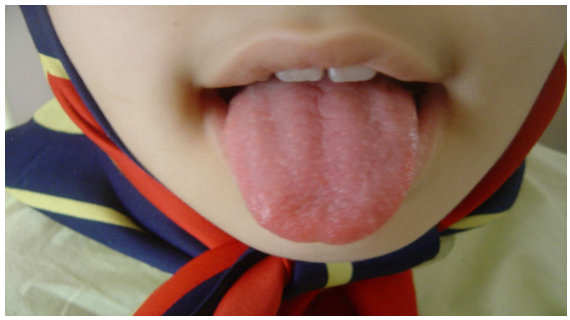
Figure 3 . Evaluation of Suspected Incomplete Kawasaki Disease (KD)

Multiorgan Involvement of Vascular and Nonvascular tissues (figure 4).

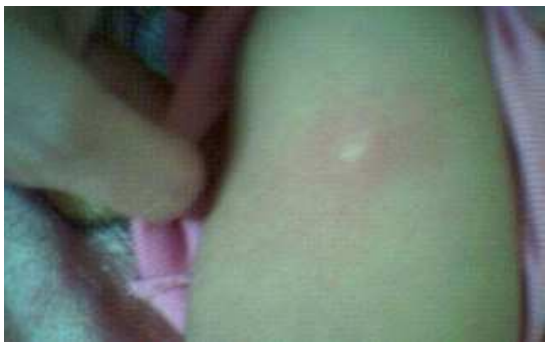
Cardiovascular (myocarditis, pericarditis, endocarditis).



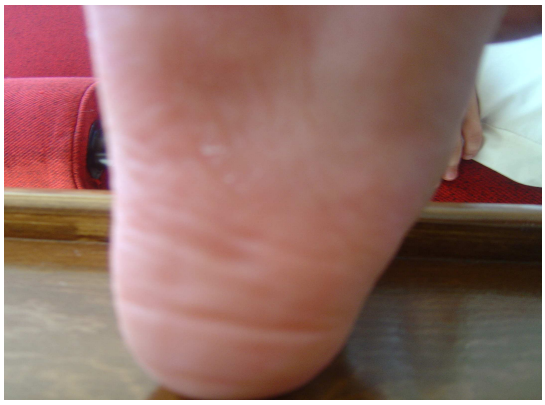
A) Strawberry tongue



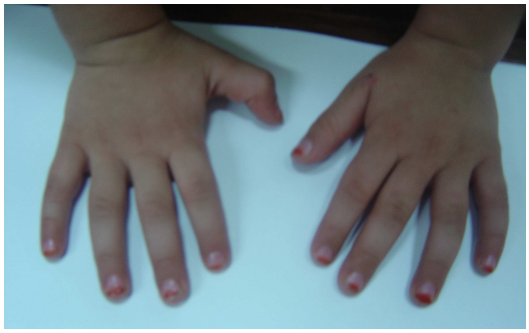
B) Strawberry tongue



C) BCG Scar Ulceration

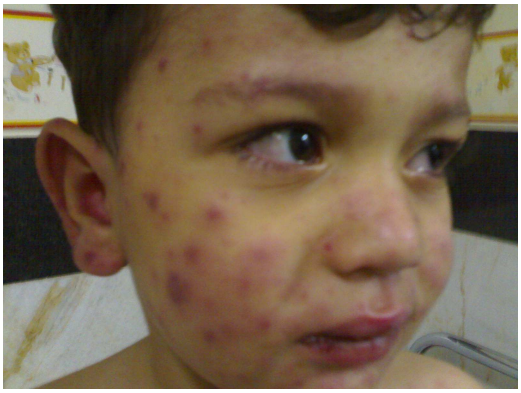


D) Peeling of extremities

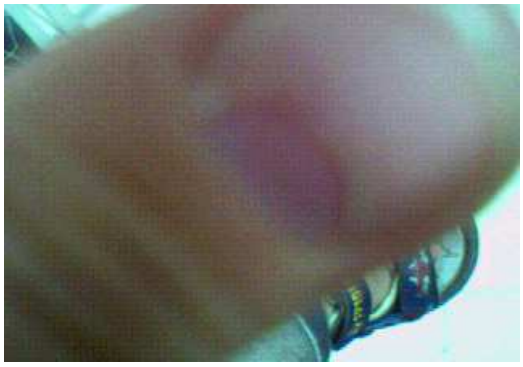


E) Peeling of extremities

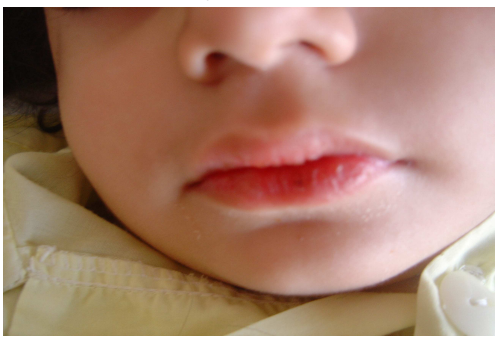
F) Conjunctival Infection



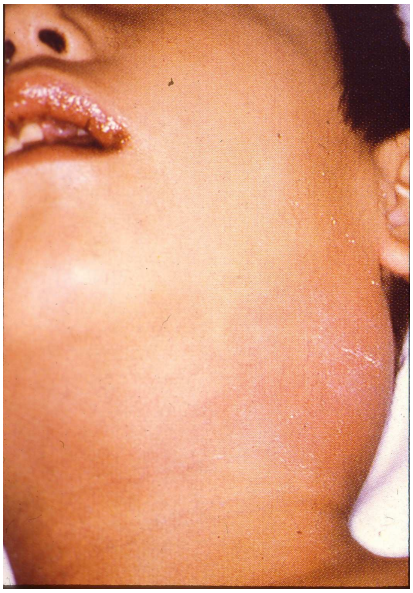
G) Conjunctival Infection



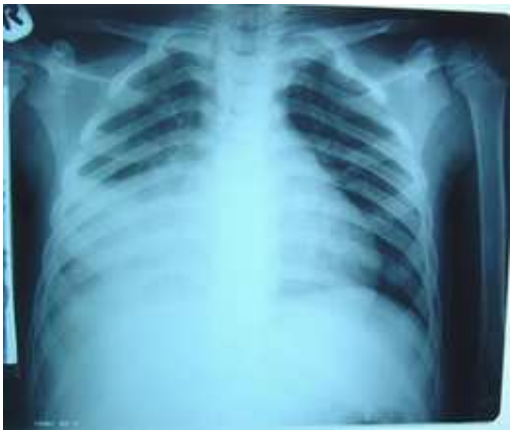
H) Beau'sline



I) Fissure of lips



J) Cervical Lymphadenopathy



K) Lobar Pneumonia and Typical (KD)

Figure 4. Iranian Patients With Kawasaki Disease: A Collection of Pictures

Involvement of medium sized arteries throughout the body (2% systemic arteries aneurysms). Renal, paraovarian, paratesticular, mesenteric, pancreatic, iliac, hepatic, and splenic involvement. Axillary aneurysm, gangrene, Brachial Plexus, and veins

Respiratory*:* Bronchitis, interstitial nodules, rhinorhea, cough, pneumonitis, right lower lobe pneumonia (In an 8-year old boy from Iran with gall bladder stone).

GI Involvement 50%: Oropharyngeal stomatitis (100% dry lips and cherry red) –Sialoductitis Adenitis 1%-diarrhea 19%-vomiting 19%-ischemic enteritis, hepatitis, cholangitis, abdominal pain: 13%-hydropse: 15%- bowel infarction, appendicitis, pancreatitis (reported in Iran)- organomegaly: 3%-paralytic ileus: 1%- mild jaundice: 1-10%, mild ALT increase <40%- albumin decrease, and perianal inflammation.

Urinary tract: Interstitial nephritis, cystitis, prostatitis, strile pyuria, urethral proteinuria.

CNS:

- Aseptic meningitis (<2yrs., 6% in Iran) (convulsion 6% < 4yrs.) neuritis, visual and hearing loss (20-35db examination on day 7 and 30), facial nerve and palate paralysis.

Lymphadenitis (Cervical and noncervical): Splenitis, HPS (hemophagocytic or macrophage activating syndrome), hemolytic anemia, lymphoid neoplastic disease (reported in Iran) neuroblastoma . Thrombocytopenia was also observed.

***Skin, Nails, Hair*:** perineal rash, Beau's lines, BCG scar Redness, hair loss.

Eyes: Bilateral rectus nerve palsy, 90% conjunctivitis (83% with anterior uveitis within first week)

Ears: tympanitis.

Joint 1/3: Arthritis synovial effusion > 100,000 WBC – PMN dominant .Poly articular involvement, small joints in acute phase, large joints in subacute phase

Organs Infarction in Subacute Phase:

- Lasting for days: Fever, rash, and lymphadenopathy resolve and irritability, anorexia, and conjunctivitis persist.

-Inflammatory changes appear to resolve completely in these nonvascular tissues.

DIFFERENTIAL DIAGNOSIS

The differential diagnoses of Kawasaki disease include:

- Streptococcal infection (including scarlet fever, toxic shock-like syndrome)
- Staphylococcal infection (such as toxic shock syndrome or scalded skin syndrome)
- Measles, rubella, roseola infantum, Epstein Barr virus, influenza A and B, adenovirus
- *Mycoplasma pneumoniae*
- Stevens-Johnson syndrome
- Systemic idiopathic juvenile arthritis

One of the difficulties of securing the diagnosis is that the clinical features of Kawasaki disease may appear sequentially rather than at the same time, and the feature most commonly identified is desquamation, which occurs late in the disease when cardiac complications may have occurred.

Many of the differential diagnoses can be ruled out clinically; few have a fever that persists for more than five days (23, 24).

The child with Kawasaki disease is very irritable and inconsolable (which may be due to an aseptic meningitis); however, this may be seen in other infections especially in measles. Another clinical sign is the presence of erythema and induration at the BCG immunisation sites as there is cross reactivity between the heat shock proteins and the T cells of patients with Kawasaki disease (25).

The rash, oral and peripheral changes of **scarlet fever** are similar to Kawasaki disease, but the lymphadenopathy is more extensive and conjunctivitis is not seen. The rash in scarlet fever normally begins on day 2–3 of the illness, starting in the groin or axilla and rapidly spreading to the trunk, arms and legs. Seven to 10 days later desquamation occurs. The high fever associated with scarlet fever lasts 5–6 days. Scarlet fever responds readily to penicillin treatment or erythromycin in those allergic to penicillin.

Toxic shock and toxic shock-like syndromes are both associated with an ill child who may have erythema of the hands and feet, a diffuse non-specific

rash over the face, trunk and limbs that desquamates, mucositis with oral involvement and non-exudative conjunctivitis. The patient needs urgent treatment with antibiotics and supportive therapy. The initial presentation of Kawasaki disease is not with shock.

Scalded skin syndrome is included as a differential diagnosis as there is a macular erythema that starts on the face and becomes more widespread; however, the epidermolytic toxin of *Staphylococcus aureus* (phage type II but occasionally I or III) causes bullae by separating intraepidermal layers, with the upper layers falling off. There is no mucosal involvement.

Measles mimics Kawasaki disease as there are many common features, namely the rash, non-exudative conjunctivitis, high temperature and generalised lymphadenopathy. In over half the cases of Kawasaki disease there is a solitary enlarged cervical lymph gland.

The temperature in measles may exceed 40°C but tends to fall after day 5 of the illness. Koplik spots are not seen in Kawasaki disease and the morbilliform rash of measles begins from the ears and hairline and starts to fade by day 4; after day 7 brownish staining may be seen due to capillary hemorrhage. Desquamation in severely affected cases of measles can occur but is not seen in the hands and feet.

Rubella characteristically involves the cervical, suboccipital and post-auricular glands, which may appear up to a week before the onset of the rash. The rash comprises fine pink macules that coalesce on the face and trunk, spreading to the extremities, lasting for up to five days. The temperature in children is rarely above 37.4°C.

Roseola infantum has a sudden onset of fever up to 40°C, which lasts for 3–5 days. As defervescence occurs, a generalised macular or maculopapular rash appears on the trunk and neck which lasts for 1–2 days; it may also spread to the legs and arms. Cervical lymphadenopathy is seen with the suboccipital, posterior auricular and posterior cervical nodes being enlarged. The short duration of fever and absence of mucosal involvement exclude Kawasaki disease.

Epstein Barr virus causes infectious mononucleosis that predominantly affects older children, although an anginose form affecting the tonsils is seen in preschool children, which is associated with fever and sore throat with cervical lymphadenopathy, and the clinical picture is that of acute streptococcal tonsillitis. There is not commonly a rash in this form of Epstein Barr virus infection.

Infectious mononucleosis starts with anorexia, malaise and low grade fever that lasts for 1–3 weeks. There is often notable enlargement of cervical lymph glands and splenomegaly is common. Rashes are seen in 10–15% of cases, the most common being a widespread maculopapular rash. Laboratory testing readily differentiates this condition from Kawasaki disease.

Influenza A in young children causes fever above 39°C, upper respiratory tract symptoms, and fleeting morbilliform rashes. The duration of the fever is 3–5 days at the most.

Adenovirus infection occurs mostly in children younger than 5 years and can have a number of presentations including pharyngoconjunctival fever with pharyngitis, headache, myalgia and unilateral or bilateral follicular conjunctivitis, with exudation.

Mycoplasma pneumoniae, which may have a role in Stevens-Johnson syndrome causes upper and lower respiratory tract disease and is associated with a polymorphous rash and fever. There may also be generalised lymphadenopathy but rarely is there conjunctivitis, erythema of palms and feet or oral involvement.

Stevens-Johnson syndrome is characterised by erythema multiforme and causes erosive lesions at mucosal sites such as the conjunctivae and the oral

cavity. The rash usually fades within 10 days but there is a risk of superadded infection, which may cause widespread lymphadenopathy.

Systemic juvenile idiopathic arthritis may present with swinging fevers, systemic upset, and arthritis. The arthritis may not be present at the onset of the symptoms and varies from monoarticular to more commonly polyarticular involvement. Temperature may exceed 40°C and last for at least two weeks. There must be one or more of the following extraarticular features: generalised lymphadenopathy (painless rather than painful in Kawasaki disease), rash (classically described as a macular pink fleeting rash), hepatomegaly (not a characteristic feature of Kawasaki disease) or serositis.

Recommended investigations in combination with clinical assessment to exclude Kawasaki disease are given in table 1 (26).

Acute Management

Without treatment, coronary artery abnormalities develop in about 15 to 25 percent of patients with Kawasaki disease. Fortunately, with prompt therapy this percentage decreases to about 5 percent for any abnormality (including transient abnormalities) and 1 percent for giant coronary artery aneurysms. In the United States, children with Kawasaki disease are treated initially with a single dose of IVIG (2 g per kg) and high-dose aspirin (80 to 100 mg per kg per day, divided into four doses).Therapy should be initiated within 10 days of fever onset if possible; however, children who present after 10 days of fever still should be treated if fever or other signs of persistent inflammation are present, including an elevated ESR or CRP level.

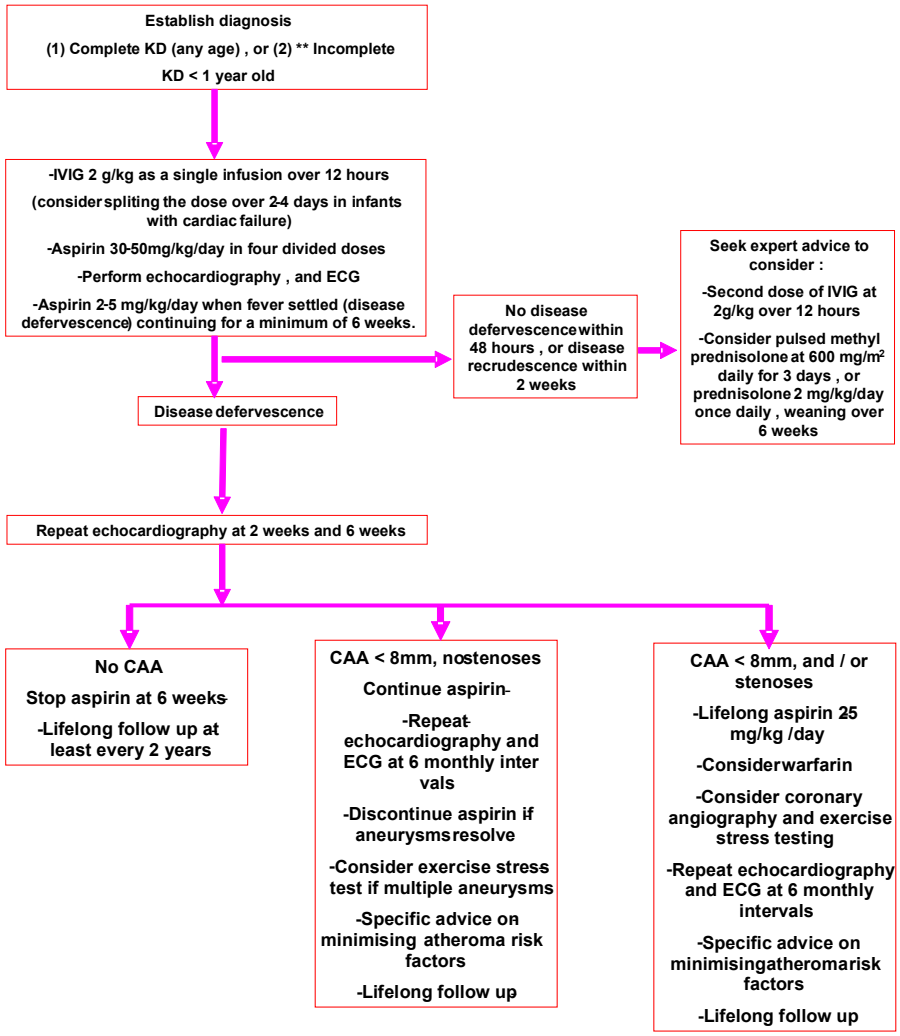
High-dose aspirin is administered initially for its anti-inflammatory effect. Variation exists among medical centers concerning when the aspirin dose should be reduced, either 48 to 72 hours after defervescence or 14 days after the onset of symptoms and when the child has been afebrile for at least 48 to 72 hours. Low-dose aspirin (3 to 5 mg per kg per day, given as a single dose) has an antiplatelet effect and should be continued until six to eight weeks after disease onset if there are no coronary artery abnormalities or indefinitely if abnormalities are present.

In general, ibuprofen should be avoided in children taking aspirin because it may antagonize the antiplatelet effect of aspirin. Reye's syndrome is a risk for patients taking high-dose aspirin during influenza or varicella infection and is a possible but remote risk in patients receiving low-dose aspirin. Therefore, children on long-term aspirin therapy should receive annual influenza vaccination. Also, parents should be told to contact their physician if symptoms of influenza or varicella arise, because alternative agents to aspirin may be considered.

About 85 to 90 percent of patients respond promptly to initial therapy of IVIG and high-dose aspirin; however, others have persistent or recurrent fever beyond 36 hours of therapy and require further treatment.[12] In most centers, patients who fail to respond to the first dose of IVIG are given a second dose of 2 g per kg. Steroids have been investigated as an alternative to a second IVIG course, but because their effects on coronary artery aneurysms are controversial, most experts recommend withholding steroids unless fever persists after at least two courses of IVIG. Other therapies, including pentoxifylline (Trental), infliximab (Remicade; a monoclonal antibody against tumor necrosis factor a), plasma exchange, ulinastatin (a human trypsin inhibitor used in Japan; not available in the United States), abciximab (Reopro; a monoclonal platelet glycoprotein IIb/IIIa receptor inhibitor), and cytotoxic agents such as cyclophosphamide (Cytoxan), have been used in small numbers of patients, but data are too limited for official recommendations.

Serial echocardiography, performed at a center experienced in examining the coronary arteries of children, is indicated for those with acute Kawasaki disease. The first echocardiogram should be obtained when the diagnosis is suspected, but treatment should not be delayed while waiting for the study to be completed. Echocardiography provides a baseline for coronary artery dimensions and morphology and assesses cardiac function. For children with an uncomplicated course (e.g., fever resolves with initial therapy, no coronary artery abnormalities are present), echocardiography should be repeated in two weeks and six to eight weeks after diagnosis (2). Some centers also obtain a 6- to 12-month follow-up study. In children with a complicated course (e.g., persistent fever, coronary or myocardial abnormalities), more frequent studies over a longer period may be indicated, and consultation with a pediatric cardiologist is needed. The role of other cardiac imaging modalities, such as cardiac magnetic resonance imaging and ultrafast computed tomography, is currently under investigation (Figure 5).

Figure 5 . Guideline for Life long follow up of Kawasaki disease



The acute management of patients with coronary artery abnormalities depends on the extent and severity of the lesion, and decisions are usually made in consultation with a pediatric cardiologist. Although low-dose aspirin is adequate for patients with mild disease (e.g., dilation; small, stable aneurysm), additional therapy such as antiplatelet agents and heparin may be required for patients with more severe disease because of the increased risk of thrombosis from the abnormal blood flow through coronary aneurysms.

Most patients with large or giant coronary artery aneurysms (i.e., internal diameter greater than 8 mm) are maintained on aspirin (or clopidogrel [Plavix]) and warfarin (Coumadin) to prevent thrombosis within the aneurysm and myocardial infarction. No randomized controlled trials have been performed in children to determine the optimal prevention and treatment of coronary thrombosis, but a combination of therapies targeting different levels of the coagulation cascade is used most often. Abciximab has shown promise in restoring coronary artery blood flow after acute thrombosis, but further study is needed.

Long-term Management

Children who have Kawasaki disease without evidence of abnormalities on echocardiography appear to return to their usual state of health without any cardiac sequelae; however, some follow-up studies have demonstrated prolonged endothelial dysfunction and abnormal lipid profiles, even in children without demonstrable coronary abnormalities. Therefore, long-term surveillance studies are ongoing in this population.

About one half of the coronary artery aneurysms associated with Kawasaki disease resolve by echocardiography and angiography within one to two years, particularly those that are smaller and fusiform. Unfortunately, myointimal proliferation may lead to stenosis of the diseased coronary artery over time. Stenosis is most common in coronary arteries with giant aneurysms and occurs at the entrance to or exit from an aneurysmal area. Thrombosis leading to myocardial infarction in a stenotic or aneurysmal coronary artery is the leading cause of death in these children and occurs most often in the first year after illness onset. Therefore, serial imaging and stress tests are necessary in patients with significant coronary artery abnormalities, and cardiac catheterization with angiography is often performed to better delineate the morphology once the inflammation has resolved.

Decisions about interventions for individual patients usually should be made in consultation with a cardiac surgeon and an experienced adult interventional cardiologist. Excision of aneurysms has been unsuccessful, and deaths have resulted. Coronary artery bypass grafts, angioplasty, stents, rotational ablation, and cardiac transplantation have been performed with some success on small numbers of severely affected patients.

In the current AHA guidelines, a stratification system has been developed to categorize patients by their risk of myocardial infarction and to provide guidelines for management (2).

REFERENCES

1. Jennette JC, Falk RJ. Small-vessel vasculitis. *N Engl J Med* 1997; 337 (21): 1512- 23.
2. Kushner HI, Turner CL, Bastian JF, Burns JC. The narratives of Kawasaki disease. *Bull Hist Med* 2004; 78 (2): 410- 39.
3. Managoli S, Chaturvedi P. Kawasaki disease with coronary artery aneurysm and symptomatic pneumonia. *Indian Pediatr* 2003; 40 (11): 1106- 7.
4. Yanagawa H, Nakamura Y, Yashiro M, et al. Results of the Nationwide. *Pediatrics* 1998; 102: 65-72.
5. Kawasaki T. Acute febrile mucocutaneous syndrome with lymphoid involvement with specific desquamation of the fingers and toes in children. *Arerugi* 1967; 16 (3): 178- 222.

6. Burns JC, Kushner HI, Bastian JF, Shike H, Shimizu C, Matsubara T, et al. Kawasaki disease: A brief history. *Pediatrics* 2000; 106 (2): E27.
7. Numazaki K .Kawasaki disease and Chlamydia pneumonia, *Journal of Infect and chemotherapy* 1996. 2; 4: 264-5.
8. Barron KS. Kawasaki disease: etiology, pathogenesis, and treatment. *Cleve Clin J Med* 2002; 69 Suppl 2: SII69- 78.
9. Benseler SM, McCrindle BW, Silverman ED, Tyrrell PN, Wong J, Yeung RS. Infections and Kawasaki disease: implications for coronary artery outcome. *Pediatrics* 2005; 116 (6): e760- 6.
10. Siadati A ,Sabouni F .Kawasaki disease and coincidental infections. *Annual congress of Advances in pediatrics* 2006.
11. Siadati A, Sabouni F. Many faces of Kawasaki disease; 18th International congress of pediatrics; 2006.
12. Unresolving pneumonia. Archives of disease in childhood, BMA copyright 2003.
13. Mammishi S. Rahmati B. Kawasaki disease, 18th Internation Congress of Pediatrics; 2006.
14. Lee KY, Han JW, Lee HS, Hong JH, Hahn SH, Lee JS, et al. Epidemiologic study of Kawasaki disease at a single hospital in Daejeon, Korea (1987 through 2000). *Pediatr Infect Dis J* 2004; 23 (1): 52- 5.
15. Maconochie. Kawasaki disease, Archives of Disease in Childhood, Education and Practice, 2005; 89 (1): ep 3.
16. Mahr A. Kawasaki disease, Orphanet Encydopedia, 2004, Orpha net /data/patho/GB/uk-Kawasaki, pdf.
17. Wein stein M. Inflammation at a previous. *CMAJ* 2006; 174 (4): 1506.
18. Falcini F, Simonini G, Calabri GB, Cimaz R. Multifocal lymphadenopathy associated with severe Kawasaki disease: a difficult diagnosis. *Ann Rheum Dis* 2003; 62 (7): 688- 9.
19. Shibuya N, Shibuya K, Kato H, Yanagisawa M. Kawasaki disease before Kawasaki at Tokyo university hospital. *Pediatrics* 2002; 110 (2 Pt 1): e 17.
20. Newburger JW, Takahashi M, Diagnosis, treatment and long term management. *Pediatrics* 2004; 114: 1708- 33 .
21. Baumer JH, Love SJ, Gupta A, Haines LC, Maconochie I, Dua JS. Salicylate for the treatment of Kawasaki disease in children. *Cochrane Database Syst Rev* 2006; (4): CD004175.
22. Rowley A, Shulman S. Infectious diseases and immunization. New developments in the search for the etiologic agent of Kawasaki disease . *Co pediatrics* 2007; 19(1): 71- 4 .
23. Hara T, Mizuno Y, Akeda H, Fukushige J, Ueda K, Aoki T, et al. Thrombocytopenia: a complication of Kawasaki disease. *Eur J Pediatr* 1988; 147 (1): 51- 3.
24. Parrillo S.J. Pediatrics, Kawasaki disease. *E Medicine* 2006; 16 .
25. Simonini G, Rose CD, Vierucci A, Falcini F, Athreya BH. Diagnosing Kawasaki syndrome: the need for a new clinical tool. *Rheumatology (Oxford)* 2005; 44 (8): 959- 61.
26. Brogan PA, Bose A, Burgner D, Shingadia D, Tulloh R, Michie C, et al. Kawasaki disease: an evidence based approach to diagnosis, treatment, and proposals for future research. *Arch Dis Child* 2002; 86 (4): 286- 90.