# Kawasaki Disease

**Definition**

1. **Kawasaki disease is an acute febrile vasculitic syndrome of early childhood who present with fever, rash, conjunctival injection, cervical lymphadenitis, inflammation of the lips and oral cavity, and erythema and edema of the hands and feet**
2. **Cardiac involvement occurs in 20 – 25% of patients, and the mortality rate is 0.1 – 2%**
3. **Kawasaki disease is the leading cause of acquired heart disease in children in the developed world and may be a risk factor for adult ischemic heart disease**

**Pathophysiology**

1. **The etiology of Kawasaki disease is unknown**
2. **Increasing evidence supports an infectious etiology**
3. **Most of the pathology of the disease is induced by a medium vessel arterial vasculitis**
    a. **Initially, neutrophils are present in great numbers, but the infiltrate rapidly switches to mononuclear cells, T lymphocytes, immunoglobulin A (IgA)–producing plasma cells**
    b. **Inflammation involves all 3 layers of vessels**
    c. **Eosinophils are preferentially accumulated in microvessels**

**Mortality/Morbidity**

1. **The mortality rate is reported to be 0.1 – 2 %**
2. **Approximately 20 – 25% of untreated patients develop cardiac problems, including coronary artery aneurysms (CAAs), acute myocardial infarction (MI) secondary to true coronary artery obstruction, myocarditis, congestive heart failure (CHF), pericarditis with pericardial effusion, mitral or aortic insufficiency, and dysrhythmias**
3. **Aneurysms develop in fewer than 5 – 10% of patients treated with intravenous gamma globulin before the 10th day of illness**
4. **Approximately 5% may have aortic or mitral regurgitation due to valvulitis, transient papillary muscle dysfunction, or MI**
5. **Arthritis persists in some children**
6. **Kawasaki disease appears to be a rare cause of adult cardiac dysfunction**

**Race**

1. **The prevalence of Kawasaki disease is highest among Japanese; is intermediate among blacks, Polynesians, and Filipinos; and is lowest among whites**

**Sex**

1. **Kawasaki disease is more common in males than in females, with a male-to-female ratio of 1.5:1**
2. **Arthritis appears more common in girls than in boys**

**Age**

1. **Approximately 90 – 95% of cases occur in children younger than 10 years**
2. **In the United States, the peak incidence is in children aged 18 – 24 months**
3. **In Japan, the incidence peaks in children aged 6 – 12 months**
4. **The earliest reported case in Japan occurred in a 20-day-old newborn.**
5. **Kawasaki disease in adults is rare. Kawasaki-like syndromes have been reported in adult HIV-infected patients**

**History**

1. **Acute stage (1 – 11 d)**
    a. **High fever (temperature >104℉), Irritability, N onexudative bilateral conjunctivitis (90%), Anterior uveitis (70%), Perianal erythema (70%), Acral erythema and edema that impede ambulation, Strawberry tongue and lip fissures, Hepatic, renal, and gastrointestinal dysfunction, Myocarditis and pericarditis, Lymphadenopathy (75%), generally a single, enlarged, nonsuppurative cervical node measuring approximately 1.5 cm**
2. **Subacute stage (11 – 30 d)**
    a. **Persistent irritability, anorexia, and conjunctival injection, Decreased temperature, Thrombocytosis, Acral desquamation, Aneurysm forms**
3. **Convalescent/chronic phase (≥30 d)**
    a. **Expansion of aneurysm, Possible MI**
    b. **A tendency for smaller aneurysms to resolve on their own (60% of cases)**

**Physical**

1. **Patients with classic Kawasaki disease must have 5 of the following symptoms, with fever an absolute criterion:**
    a. **Fever, lasting more than 5 days and refractory to appropriate antibiotic therapy**
    b. **Polymorphous erythematous rash**
    c. **Nonpurulent bilateral conjunctival injection**
    d. **Oropharyngeal changes, including diffuse hyperemia, strawberry tongue, and lip changes (e.g., swelling, fissuring, erythema, bleeding)**
    e. **Peripheral extremity changes, including erythema, edema, induration, and desquamation**
    f. **Nonpurulent cervical lymphadenopathy**
2. **Other findings may include the following:**
    a. **General: Irritability**
    b. **Cardiac: Coronary aneurysms, pericardial effusion, myocarditis, CHF**
    c. **Neurologic: Stiff neck secondary to aseptic meningitis, facial palsy, cerebral infarction**
    d. **Renal: Sterile pyuria, proteinuria, nephritis, acute renal failure**

e. **Musculoskeletal: Joint involvement (arthralgias or arthritis)**
f. **Pulmonary: Pleural effusion, infiltrates**
g. **GI: Abdominal pain, diarrhea, hepatitis, obstructive jaundice, hydrops, pancreatitis, gall bladder distention**
h. **Tissues: Meatitis, vulvitis, urethritis**
i. **Ophthalmologic: Conjunctivitis, uveitis**
j. **Dermatologic: Peripheral extremity gangrene, pustules, erythema multiforme–like lesions, perianal desquamation, macules, papules, measleslike rash, scarlet fever–like erythema, and induration at the site of Bacille bilié de Calmette-Guérin (BCG) inoculation (commonly observed in Japan)**
k. **Up to 10 – 45% of published cases have incomplete or atypical clinical presentations. The 2 most commonly missing findings are cervical lymphadenopathy and polymorphous rash**
l. **Mucous membrane changes, on the other hand, are the most common manifestations of Kawasaki disease, occurring in more than 90% of patients with either typical or atypical forms of the disease**

**Lab Studies**

1. **No specific laboratory test exists; however, certain abnormalities coincide with various stages**
    a. **Mild-to-moderate normochromic anemia is observed in the acute stage along with a moderate-to-high WBC count with a left shift, which is a predominant sign of immature and mature granulocytes**
    b. **Many of the acute phase reactant markers, such as the erythrocyte sedimentation rate (ESR), C-reactive protein, and serum $\alpha$-1-antitrypsin are elevated**
    c. **Culture results are all negative**
2. **Antineutrophil cytoplasmic antibodies, antiendothelial cell antibodies, antinuclear antibody, and rheumatoid factors: These are within the reference range**
3. **Platelets**
    a. **Thrombocytosis typically develops during the second or third week of illness, with an average of 700,000 per microliter**
    b. **Thrombocytopenia is associated with severe coronary artery disease and MI**
4. **Acute Phase Reactants**
    a. **ESR, C-reactive protein, and alpha 1-antitrypsin are elevated**
    b. **Serum complement is within the reference range or elevated**
5. **Liver Enzymes**
    a. **Mild elevations in transaminase values are observed in 40% of affected patients; elevated alanine aminotransferase (ALT) can indicate a more serious course**
    b. **Elevated bilirubin values occur in 10% of affected patients**

6. **Urinalysis**
    a. **Mild-to-moderate sterile pyuria of urethral origin and proteinuria may occur**
7. **Cardiac enzymes**
    a. **Levels of cardiac enzymes (e.g., creatine kinase [CK], creatine kinase-MB [CK-MB], cardiac troponin, and lactate dehydrogenase [LD-1 greater than LD-2]) are elevated during an MI**
8. **Rapid antigen test**
    a. **Test results for adenovirus are negative**

**Imaging Studies**

1. **Radiography**
    a. **Obtain a chest radiograph to rule out cardiomegaly or subclinical pneumonitis**
    b. **Chest radiography should be performed to assess baseline findings and to confirm clinical suspicion of CHF**
2. **Echocardiography**
    a. **This is the study of choice to evaluate for CAAs**
    b. **During the acute stage, obtaining a baseline echocardiogram is important to rule out CAAs and evidence of myocarditis, valvulitis, or pericardial effusion**
    c. **In children, ensure that pediatric cardiologists perform this study because they are familiar with coronary artery diameters**
    d. **Diffuse dilatation of coronary lumina can be observed in 50% of patients by the 10th day of illness**
    e. **Echocardiography should be repeated in the second or third week of illness and 1 month after all other laboratory results have normalized**
    f. **If the echocardiographic findings are abnormal at any point, refer the child to a pediatric cardiologist for a complete cardiac workup and follow-up care**
3. **Ultrasonography**
    a. **Gall bladder ultrasonography may be necessary if any suggestion of liver or gall bladder dysfunction is present**
    b. **Obtain a scrotal ultrasound in males to evaluate for epididymitis**
    c. **Although epididymitis is generally an inflammatory process that affects boys aged 9 – 14 years, it can be observed in younger males with Henoch-Schönlein purpura and Kawasaki disease**
4. **Magnetic resonance angiography (MRA)**
    a. **Free-breathing 3-dimensional (3D) coronary MRA accurately defines CAA in patients with Kawasaki disease**
    b. **This technique may provide a noninvasive alternative when the image quality of transthoracic echocardiography is**

insufficient, thereby reducing the need for serial radiographic coronary angiography in this patient group

**Other Tests**

1. Electrocardiography
    a. Obtain an ECG to evaluate for various conduction abnormalities
    b. Children with Kawasaki disease may also have acute infarction. Tachycardia, a prolonged PR interval, ST-T wave changes, and decreased voltage of R waves may indicate myocarditis
    c. Q waves or ST-T wave changes may indicate an MI

**Procedures**

1. Lumbar puncture may reveal cerebrospinal fluid pleocytosis
2. A select group of patients may require cardiac catheterization and angiography

**Medical Care**

1. The main goal of treatment is to prevent coronary artery disease and relieve symptoms
2. Full doses of salicylates (aspirin) and intravenous gammaglobulin are the mainstays of treatment
3. Admit all patients to the hospital for intravenous gammaglobulin and observation until fever is controlled
4. Closely monitor cardiovascular function
5. Patients with small aneurysms must take aspirin
6. Dipyridamole is indicated in patients with larger aneurysms
7. Patients taking long-term aspirin therapy should receive an influenza vaccination to protect against Reye syndrome

**Medication**

1. The pathophysiology in Kawasaki disease involves inflammation
2. The patient's own immune system probably causes the vasculitis that leads to morbidity and mortality in Kawasaki disease
3. Early and aggressive intervention improves outcome
4. Standard treatment includes aspirin and intravenous immunoglobulin to treat inflammation and prevent consequences of coronary artery disease
5. Other anticoagulants or antiplatelet agents (eg, warfarin, dipyridamole) are occasionally used

**Drug Category**

1. Immunomodulatory Agents
    a. Intravenous immune globulin (IVIG) is a purified preparation of gamma globulin; It is derived from large pools of human plasma and is comprised of 4 subclasses of antibodies, approximating the distribution of human serum
    b. Drug Name
        i. Immune globulin, intravenous (Gammagard, Gamimune)

ii. Generally recommended as first line but is not the sole therapy
iii. Dose: 400 mg/kg/d IV as a single daily infusion for 4 d Alternatively, 2 g/kg IV infused over 12 h once as single dose

2. Nonsteroidal Anti-inflammatory Agents
    a. Used to decrease inflammation, inhibit platelet aggregation, and improve complications of venous stases and thrombosis
    b. Adequate anti-inflammatory therapy requires that aspirin be combined with gamma globulin
    c. PO absorption of aspirin may decrease in Kawasaki disease to <50% (compared to typical bioavailability of 85 – 90%). This altered bioavailability may explain why higher doses required to achieve a salicylate serum concentration >20 mg/dL
    d. Drug Name
        i. Aspirin (Anacin, Ascriptin, Bayer Aspirin, Bayer Buffered Aspirin)
        ii. Dose: 80 – 100 mg/kg/d PO divided qid for 2 wk initially; then 5 – 10 mg/kg PO qd for 6 – 8 wk until sedimentation rate and platelet count are within the reference range, typically used for 6 – 12 wk
3. Antiplatelet Agents
    a. Dipyridamole (Persantine): A platelet-adhesion inhibitor that possibly inhibits RBC uptake of adenosine, itself an inhibitor of platelet reactivityBesides aspirin, dipyridamole may be used to prevent microthrombus formationDose: Not established; limited data indicates 3 – 6 mg/kg/d PO divided tid

Complications: Cardiovascular

1. Significant heart failure or myocardial dysfunction (unlikely to occur once fever is resolved)
2. Diffuse coronary artery ectasia and aneurysm formation, giant aneurysm (internal luminal diameter $\geq$8 mm)
3. MI
4. Myocarditis (common but rarely causes CHF)
5. Valvulitis, usually mitral (only occurs in 1% of patients and rarely requires valve replacement)
6. Pericarditis with small pericardial effusions (occurs in 25% of patients with acute illness)
7. Systemic artery aneurysms
8. Rupture of CAA with hemopericardium

Other Complications

1. Extreme irritablity, especially in younger infants
2. Aseptic meningitis
3. Arthritis
4. Mild hepatic dysfunction, rarely jaundice

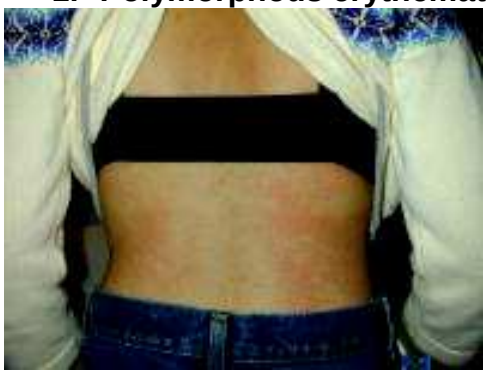
5. **Gallbladder hydrops (diagnosed by means of ultrasonography but usually resolves without surgical intervention**
6. **Diarrhea**
7. **Pneumonitis**
8. **Otitis mediaErythema and induration at the site of BCG inoculation (reported in Japan)**
10. **Bowel ischemia and necorosis**

**Prognosis**

1. **With prompt treatment, the prognosis is good. The current mortality rate is 0.1 – 2 %**

**Pictures**

1. **Polymorphous erythematous rash**



2. **Peeling and erythema of the fingertips**

3. **Strawberry tongue**