

## KAWASAKI DISEASE

### Introduction and History

Tomisaku Kawasaki encountered his first case of the disease that would bear his name in 1961, published his first case report in 1967 and published his first English-language article in 1974. Pediatricians in Hawaii independently recognized the disease in the early 1970s. Though it is unclear whether the disease existed in Japan prior to the 1960s, it is now known to be the leading cause of acquired heart disease in children in North American and Japan (surpassing Rheumatic Fever).

- Epidemiology:
  - Japan = 112 cases per 100,000 children less than 5yo
  - US = 4248 hospitalizations annually in 2000, with a median age of 2yo
  - Recurrence rate in Japan of 3%
  - Increased risk in the child or sibling of a patient with KD in Japan
  - More common in winter and spring
  - Males to female = 1.5:1; 76% are less than 5yo
  - Virtually all deaths secondary to cardiac sequelae (peak at 15-45d after fever)
  
- Etiology: the cause of KD is unknown, though there are several hypotheses
  - Infectious Cause:
    - supported by age distribution, seasonal predilection, epidemic cycles, outbreaks in community
    - rare in infants and older patients, possibly due to immune protection
    - likely a genetic predisposition towards the symptomatic infection
  - Bacterial Superantigenic Toxin
    - Reported expansion of certain T-cell receptors
    - However, recent prospective study demonstrates no difference between KD and matched febrile controls
  - Immune Response to various microbial agents
    - C/W lack of one documented organism
  
- Pathology: involvement of coronary arteries, but also aneurysms in extraparenchymal muscular arteries such as the femoral, iliac, renal, etc.

### Diagnosis

The diagnosis of KD is reliant upon identifying certain clinical criteria, though certain labs and other clinical findings can lend support to the diagnosis. The following table lists the clinical criteria for Kawasaki, the supportive laboratory findings, and other clinical findings.

A mnemonic for the classic clinical criteria is FEBRILE:

Fever

Extremities/erythema/edema

Buccal mucosa

Rash

I(gnore)

Lymphadenopathy

Eyes

Classic Clinical Criteria	Supportive Clinical Findings	Laboratory Findings
Fever for at least five days <i>plus</i> four of the principle features:  Changes in extremities Acute: Erythema of palms, soles edema of hands, feet Subacute: periungal peeling Polymorphous exanthem Bilateral non-exudative bulbar conjunctivitis Changes in lips/oral cavity: Erythema, cracked lips, Strawberry tongue, diffuse Injection of mucosa Cervical adenopathy usually unilateral, > 1.5cm	<b>Cardiovascular</b> Congestive Heart Failure Myocarditis, pericarditis Coronary artery abnormalities Aneurysms of medium non-coronary arteries Raynaud's phenomenon Peripheral gangrene <b>Musculoskeletal</b> Arthritis, arthralgia <b>Gastrointestinal</b> Diarrhea, vomiting, abd pain Hepatic dysfunction Hydrops of gallbladder <b>Central Nervous System</b> Extreme irritability Aseptic meningitis Sensorineural hearing loss <b>Genitourinary</b> Urethritis/meatitis <b>Other</b> Erythema, induration @ BCG Anterior uveitis Desquamating groin rash	Leukocytosis with neutrophilia Elevated ESR, CRP Anemia Abnormal plasma lipids Hypoalbuminemia Hyponatremia Thrombocytosis after week 1 Sterile pyuria Elevated serum transaminases Elevated serum GGTP CSF pleocytosis Synovial leukocytosis

\*\* Patients with fever for five days, but less than four of the principal criteria can be diagnosed if an Echo demonstrates coronary artery aneurysms.

\*\* Patients with four or more of the principal criteria, a diagnosis can be made on day four of fever.

#### Incomplete (atypical) Kawasaki:

- clinical scenario of fever for five days with 2 or 3 of the principal criteria
- more common in infants; associated with higher risk of aneurysms
- possess similar laboratory findings as classic KD
- Differential includes: systemic JIA onset, Adenovirus
- Echocardiography should be considered in any infant <6mo with fever  $\geq$  7days, laboratory evidence of inflammation and no other reason for fever

#### Differential Diagnosis

Scarlet Fever	Stevens-Johnson Syndrome
Staphylococcal Scalded Skin Syndrome	Juvenile Rheumatoid Arthritis
Toxic Shock Syndrome	Rocky Mountain Spotted Fever
Bacterial cervical lymphadenitis	Leptospirosis
Drug hypersensitivity reactions	Mercury Hypersensitivity Reaction
Viral infections (measles, adeno, entero, EBV)	

### Risk of Aneurysms

Untreated, 15-25% of all patients with KD will get coronary artery aneurysms. With treatment, 5% demonstrate at least transient dilation, and 1% develop giant aneurysms.

In Japan, the Harada scoring system is used to determine the risk of coronary artery aneurysms and the subsequent need for IVIG. Patients must fulfill four of the following criteria within 9 days of onset:

1. WBC > 12000 mm<sup>3</sup>
2. Platelets < 350000/mm<sup>3</sup>
3. CRP > 3+
4. Hematocrit < 35%
5. Albumin < 3.5g/dL
6. Age < 12mo
7. Male sex

However, none of the scoring systems are perfect, therefore IVIG is recommended in all patients.

### Treatment

- IVIG: well-established to reduce the risk of coronary artery aneurysms, although it is due to an unknown mechanism (generalized anti-inflammatory effect)
  - Demonstrated to have a dose response effect; higher dose single infusion is better
  - First dose effective in 90%, second dose in 67% of nonresponders
  - 2g/kg in single infusion within 10 days of onset of illness, preferably by day 7
  - Treatment before day 5 is no better for aneurysms, but may be associated with need for repeat treatment with IVIG
  - Defer measles and varicella immunizations for 12 months after IVIG
  - **Refractory Kawasaki:**
    - Fever persisting for > 36h after IVIG
    - approx .3-4% will not respond after two doses
    - treat with a third dose of IVIG or
    - initial data suggests a role for steroids in refractory cases
    - 30mg/kg/day of methylprednisolone for 1-3 days
    - Other experimental choices: plasma exchange, cyclophosphamide, infliximab
- Aspirin
  - Used for potent anti-inflammatory and antiplatelet effects
  - 80-100 mg/kg/day divided into four doses during acute phase (with IVIG)
  - Decrease to low-dose (3-5mg/kg/day) when either:
    - Afebrile for 48-72 hours
    - Until 14 days of illness and afebrile for >48 hours
  - Low dose continued until no coronary artery involvement demonstrated at 6-8 weeks
  - May continue indefinitely in presence of coronary involvement
  - Should receive Influenza vaccine annually if taking ASA
- Steroids
  - Initial study indicated steroids were detrimental as initial therapy, but subsequent studies have shown neither good nor bad effects
  - Recent studies have shown a shorter fever duration with steroids, but no difference in aneurysms than IVIG
  - The use of steroids, therefore, is not currently well-established, but a multicenter study is being performed
  - See Refractory Kawasaki (above) for more details

- Coronary Disease
  - Thrombosis prevention: ASA, other antiplatelet agents (mild to moderate disease)  
Heparin in rapidly expanding aneurysms  
Warfarin and ASA in giant aneurysms
  - Thrombosis treatment: Streptokinase, tPA, urokinase (but no randomized, controlled trials in children)
  - Surgical treatment: Arterial and venous grafts (arterial with higher patency rates)
  - Catheterization: Balloon angioplasty, rotational ablation, stent placement  
Like surgical therapy, reserved for patients with ischemic sx

### Natural History and Follow-Up

Aneurysms resolve in 1-2 years after onset in 50-67% of patients.

Smaller aneurysms have higher incidence of regression. Also associated with regression are: age <1yo, fusiform aneurysms, location in distal coronary.

### Long Term Risk Stratification

Risk Level	Description	Medical Tx	Physical Activity Restrictions	Follow-up and Testing	Invasive Testing
Level I	No coronary changes ever	None after 6-8wks	None after 6-8wks	CV risk assess at 5yr intervals	None
Level II	Transient coronary changes (6-8wks)	None after 6-8wks	None after 6-8wks	CV risk assess at 3-5yr intervals	None
Level III	Small-medium coronary artery aneurysm/major coronary artery	Low dose ASA until aneurysm regression	<11yo=none after 6-8wks 11-20yo guided by stress test	Annual cardio f/u with Echo, ECG Bienn. Stress test	Angiography if ischemia on prior testing
Level IV	1 or more large or giant coronary artery aneurysm or complex aneurysms in same artery	Long-term antiplatelet and warfarin or LMWH	Contact and high-impact sports to be avoided Other activity guided by stress test	Biannual f/u with Echo, ECG; annual stress test	Angio @ 6-12mo or sooner
Level V	Coronary artery obstruction	Long-term low dose ASA; warfarin or LHMH if giant aneurysm persists	Contact and high-impact sports to be avoided Other activity guided by stress test	Biannual f/u with echo, ECG; annual stress test	Angio recommended

### References

Freeman AF, Shulman ST. Refractory Kawasaki disease. *Pediatr Infect Disease J.* 2004;23: 463-464.

Newburger JW, et al. Diagnosis, treatment, and long-term management of Kawasaki disease: a statement for health professionals from the committee on rheumatic fever, endocarditis, and Kawasaki disease, Council on cardiovascular disease in the young, American Heart Association. *Pediatrics.* 2004;114: 1708-1733.

Newburger JW, Fulton DR. Kawasaki Disease. *Current Opinion in Pediatrics.* 2004;16:508-514.

Rowley AH. Incomplete (atypical) Kawasaki disease. *Pediatr Infect Disease J.* 2002;21: 563-565.