Kawasaki Disease: Updates on Diagnosis, Treatment, and Management

Kristin C. Lombardi, M.D.
Assistant Professor of Pediatrics, Clinical Educator
The Warren Alpert Medical School of Brown University
Pediatric Cardiologist, Hasbro Children’s Hospital
Objectives

Review the clinical manifestations of Kawasaki Disease (KD)

Discuss the role of echocardiography in management of KD and describe cardiac complications

Define primary treatment of KD

Discuss treatment options for IVIG-resistant KD patients
Kawasaki Disease

Acute, self-limited febrile illness of unknown cause that primarily affects children <5 years of age

Most common cause of acquired heart disease in children in developed countries
History

1961: Tomisaku Kawasaki saw first case of KD

1967: Kawasaki published first report of 50 patients with KD (Japanese)

   Debate: rash and fever connected to subsequent cardiac complications??

1974: Kawasaki published the first report in English

1975: First reported U.S. cases (Hawaii) by Melish and Hicks (pediatricians)

1984: High dose IVIG introduced by Furusho and Furukawa
History

1986: U.S. multicenter trial demonstrates efficacy of high dose IVIG

1988: Committee on Infectious Diseases of the AAP endorsed IVIG treatment as recommended therapy for KD

1999: Description of atypical/incomplete KD

2000: Potential role for steroids, other anti-inflammatory, anti-platelet drugs

2004: AAP/AHA Statement on diagnosis, treatment and long term management


2017: AHA Scientific Statement: Diagnosis, Treatment, and Long-Term management of Kawasaki Disease

Epidemiology

Markedly more prevalent in Japan and in children of Japanese ancestry

- Annual incidence of 240-260 cases/100,000 kids <5 yrs (based on 2011, 2012 data)

In U.S. race-specific incidence rates estimated:

- Americans of Asian descent: 30/100,000
- Non-Hispanic African Americans: 16/100,000
- Caucasians: 20/100,000

Overall incidence in U.S. estimated at 25/100,000 kids <5 yrs of age
Epidemiology

More common during winter and early spring
Males more common than females (1.5:1)
75% children <5 years old
  • Peak incidence 1-2 years old
Recurrence of ~ 1 - 3%
  • Highest in first 2 years after initial episode
Familial occurrence
  • In Japan, within 1 year after onset of first case in a family, the rate in a sibling is 2.1% (10-fold higher relative risk than Japanese population in general)
  • Risk of concordance in identical twins is 13%
Etiology

Etiology remains unknown

Clinical and epidemiological features strongly suggest an infectious cause

• Age distribution
• Winter-spring seasonality
• Occurrence of community outbreaks
• Laboratory features

Higher rates of KD in siblings of index cases and twins are consistent with a genetic predisposition
2004: American Heart Association published guidelines for diagnosis, treatment, and long-term management of KD

2017: Scientific Statement for Health Professionals from AHA which incorporates:

- Algorithm to ensure capture of incomplete KD during appropriate time
- Improved management for IVIG-refractory patients
- Greater specification of long-term management based on initial and current coronary artery involvement
Diagnosis

• No specific “diagnostic test” or pathognomonic clinical feature so **clinical criteria** have been established to assist with diagnosis
Fever ≥5 days

≥4 of the 5 clinical features

- Non-purulent conjunctivitis
- Extremity changes (early, late)
- Polymorphous exanthem
- Oral changes (lips, oropharynx, strawberry tongue)
- Cervical lymphadenopathy
Quiz question #1

If a patient has $\geq 4$ clinical features on exam, he/she can be diagnosed with Kawasaki Disease on day 4 of fever.

A. True
B. False
Fever

• Usually high-spiking and remittent
• Peak temp usually >39 C (102 F) and in many cases >40 C (104 F)
• If not treated – fever persists for mean of 11 days but may continue 2-3 weeks
• With appropriate therapy, fever usually resolves within 2 days
Non-purulent conjunctivitis

- Injected bulbar vessels
- Limbus spared
- Not exudative
- Painless, no photophobia
Extremity changes

Early: Erythema of the palms and soles; painful induration

Late: Desquamation of fingers and toes (periungal)
Polymorphous exanthem

Usually within 5 days of fever

Most common: nonspecific diffuse maculopapular eruption

Occasionally urticarial

Rash extensive and involves trunk and extremities; typically worse in diaper area; can have desquamation

Bullae or vesicles have not been described
Oral changes

Lips: erythema, dryness, fissuring, peeling, cracking
Tongue: strawberry
No oral ulcerations or exudates
Cervical lymphadenopathy

Least consistent feature of KD

When present – tends to involve primarily the anterior cervical nodes

 Usually unilateral

Classic criteria: at least 1 node that is >1.5 cm in diameter

Nodes often firm and non-fluctuant, non-tender
Other clinical findings

Cardiac:
- Hyperdynamic precordium, tachycardia, and/or an innocent flow murmur

Non-cardiac:
- Systemic inflammation in medium-sized arteries and in multiple organs and tissues
  - Liver (hepatitis)
  - Lung (interstitial pneumonitis)
  - GI tract (abdominal pain, vomiting, diarrhea, gallbladder hydrops)
  - Meninges (aseptic meningitis, irritability)
  - Urinary tract (pyuria)
  - Arthritis or arthralgia in first week of illness
Laboratory findings

**Leukocytosis** typical during acute stage
- 50% of patients have WBC > 15,000

**Anemia** may develop

**Elevated ESR, CRP**
- Usually returns to normal by 6-10 weeks

**Thrombocytosis** typical during later phases
- Platelets 500,000-1,000,000; normal by 4-8 wks
  - Thrombocytopenia rarely seen; risk factor for coronary aneurysms
Laboratory findings

Mild to moderate elevations in serum transaminases

U/A: intermittent mild to moderate sterile pyruia in 33% of patients
Cardiac findings

Coronary aneurysms

• Major sequelae of KD are related to cardiovascular system

  • Echo for all patients with suspected KD

  • Initial echo should be done as soon as diagnosis is suspected but **initiation of treatment should not be delayed in waiting for echo!!**

  • Initial echo establishes baseline of coronary artery morphology, LV function, valvular function, effusion
Coronary aneurysms

Develop 10 - 20 days from onset of fever

- 25% of untreated patients
- 4% of those treated with high dose IVIG
- Resolution in 50%; thrombosis/rupture in 1% (2 years post illness)
  - Development of coronary stenosis or occlusion over time
- Large or giant aneurysms (≥ 8 mm or with Z-score ≥ 10) pose greatest risk

Risk factors

- More prominent inflammatory response (prolonged fever, WBC, ESR)
- Thrombocytopenia
- Males (~ 1.3)
- Age extremes (< 6 months, >7 years)
Coronary aneurysms

• Principal cause of death from KD: myocardial infarction due to thrombotic occlusion in an aneurysmal or stenotic coronary artery

• Highest risk of MI is in the first year after onset of disease

• Coronary arteries may be predisposed to accelerated atherosclerosis in patients with KD
Suspected incomplete KD
Evaluation of Suspected Incomplete Kawasaki Disease

Children with fever ≥5 days and 2 or 3 compatible clinical criteria OR Infants with fever for ≥7 days without other explanation

Assess Laboratory Tests

CRP<3.0 mg/dL and ESR<40 mm/hr
- Serial clinical and laboratory re-evaluation if fevers persist
- Echocardiogram if typical peeling develops

CRP≥3.0 mg/dL and/or ESR≥40 mm/hr
- NO
- YES

3 or more Laboratory Findings:
1) Anemia for age
2) Platelet count of ≥450,000 after the 7th day of fever
3) Albumin ≤3.0 g/dL
4) Elevated ALT level
5) WBC count of ≥15,000/mm³
6) Urine ≥10 WBC/hpf

OR
Positive echocardiogram
Common pitfalls in diagnosis

- Children may present with only fever and unilateral enlarged cervical node – get started on abxs for presumed bacterial lymphadenitis– rash and mucosal changes follow which are thought to be reaction to abxs.

- **KD should be considered in differential diagnosis of every child with fever of at least several days’ duration, rash, and nonpurulent conjunctivitis** (esp children <1 year old, in whom diagnosis is frequently missed).
Initial Therapy

Aspirin

Acute phase: Moderate- (30-50 mg/kg/day) to high-dose (80-100 mg/kg/day) aspirin until afebrile

- NO evidence that it reduces coronary artery aneurysms
- US typically used high dose, and Japan/Western Europe typically used moderate dose; NO DATA to suggest that either is superior

Once afebrile for 48-72 hrs: 3-5 mg/kg/day for 6-8 weeks (assuming no coronary artery changes)

- If coronary artery changes – may continue aspirin indefinitely
Initial Therapy

**IVIG**

- 2 g/kg IV in a single infusion (within first 10 days of illness)
  - Reasonable to give it >10\(^{th}\) day if persistent fever without other explanation OR coronary artery abnormalities together with ongoing systemic inflammation (elevated ESR, CRP)
  - Defer measles and varicella immunizations for 11 months after receiving IVIG
What about Reye Syndrome?

Reye syndrome is a risk in children who receive aspirin while infected with varicella or influenza; also reported in patients taking high-dose aspirin for a prolonged period of time after KD.

- Presents with confusion, seizures, LOC (swelling in liver, brain)
- Low-dose therapy used as antiplatelet not associated with development of Reye syndrome
- If present with influenza AND KD – consider alternative antipyretic drug (such as tylenol)
Treatment if Fail Initial Therapy

〜10-20% of patients with KD fail to defervesce with initial IVIG therapy

• Failure: persistent or recrudescent fever >36 hours after completion of initial IVIG infusion
• Increased risk of developing coronary artery abnormalities

Retreat with IVIG 2 g/kg

Steroids

• High-dose pulse steroids (usually methylprednisolone 20-30mg/kg IV for 3 days, with or without a subsequent course and taper of oral prednisone) may be considered as alternative to 2nd infusion of IVIG – OR – in addition to 2nd infusion
• Administration of a longer (2-3 week) tapering course of prednisolone or prednisone may be considered
Treatment if Fail Initial Therapy

**Infliximab**

- May be considered as an alternative to a 2\textsuperscript{nd} infusion of IVIG or corticosteroids for IVIG-resistant patients

**Cyclosporine**

- May be considered in refractory KD in whom 2\textsuperscript{nd} IVIG, infliximab, or course of steroids has failed
**Risk stratification**

<table>
<thead>
<tr>
<th>Classification</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>No involvement at any timepoint (Z score always &lt;2)</td>
</tr>
<tr>
<td>2</td>
<td>Dilation only (Z score 2 to &lt;2.5)</td>
</tr>
<tr>
<td>3</td>
<td>Small aneurysm (Z score ≥2.5 to &lt;5)</td>
</tr>
<tr>
<td>3.1</td>
<td>Current or persistent</td>
</tr>
<tr>
<td>3.2</td>
<td>Decreased to dilation only or normal luminal dimension</td>
</tr>
<tr>
<td>4</td>
<td>Medium aneurysm (Z score ≥5 to &lt;10, and absolute dimension &lt;8 mm)</td>
</tr>
<tr>
<td>4.1</td>
<td>Current or persistent</td>
</tr>
<tr>
<td>4.2</td>
<td>Decreased to small aneurysm</td>
</tr>
<tr>
<td>4.3</td>
<td>Decreased to dilation only or normal luminal dimension</td>
</tr>
<tr>
<td>5</td>
<td>Large and giant aneurysm (Z score ≥10, or absolute dimension ≥8 mm)</td>
</tr>
<tr>
<td>5.1</td>
<td>Current or persistent</td>
</tr>
<tr>
<td>5.2</td>
<td>Decreased to medium aneurysm</td>
</tr>
<tr>
<td>5.3</td>
<td>Decreased to small aneurysm</td>
</tr>
<tr>
<td>5.4</td>
<td>Decreased to dilation only or normal luminal dimension</td>
</tr>
</tbody>
</table>
Lifestyle and cardiovascular risk factors

Debate about whether long-term pathological vascular process in arteries of patients after KD represents a new distinct vasculopathy or if it has common features of atherosclerosis

- Pathology suggests distinct process (thrombosis, chronic inflammation, luminal myofibroblastic proliferation)
- Studies in patients note endothelial dysfunction, arterial stiffness
Lifestyle and cardiovascular risk factors

• Several reports document that HDL levels are decreased acutely after KD
  • Usually improve after convalescence from disease but can persist especially in patients with severe/ongoing coronary artery aneurysms

• Currently unclear if there is increased risk for CVD in patients with history of KD, but due to the fact that KD can affect coronary arteries → not unreasonable to check lipids at some point in childhood, and even consider empiric statin in those with aneurysms
## Table 11. Long-Term Thromboprophylaxis and Medical Therapy Algorithm

<table>
<thead>
<tr>
<th>Risk Level</th>
<th>Low-Dose ASA</th>
<th>Anticoagulation (Warfarin or LMWH)</th>
<th>Dual Antiplatelet Therapy (ASA+Clopidogrel)</th>
<th>β-Blocker</th>
<th>Statin</th>
</tr>
</thead>
<tbody>
<tr>
<td>1: No involvement</td>
<td>6–8 wk then discontinue</td>
<td>Not indicated</td>
<td>Not indicated</td>
<td>Not indicated</td>
<td>Not indicated</td>
</tr>
<tr>
<td>2: Dilation only</td>
<td>Continuation after 6–8 wk is reasonable</td>
<td>Not indicated</td>
<td>Not indicated</td>
<td>Not indicated</td>
<td>Not indicated</td>
</tr>
<tr>
<td>3.1: Small aneurysm, current or persistent</td>
<td>Continue</td>
<td>May be considered</td>
<td>May be considered as an alternative to anticoagulation</td>
<td>Not indicated</td>
<td>Empirical therapy may be considered</td>
</tr>
<tr>
<td>3.2: Small aneurysm, regressed to normal or dilation only</td>
<td>Continue, but discontinuation may also be considered</td>
<td>Not indicated</td>
<td>Not indicated</td>
<td>Not indicated</td>
<td>Empirical therapy may be considered</td>
</tr>
<tr>
<td>4.1: Medium aneurysm, current or persistent</td>
<td>Continue</td>
<td>May be considered</td>
<td>May be considered as an alternative to anticoagulation</td>
<td>Not indicated</td>
<td>Empirical therapy may be considered</td>
</tr>
<tr>
<td>4.2: Medium aneurysm, regressed to small aneurysm</td>
<td>Continue</td>
<td>Not indicated</td>
<td>May be considered</td>
<td>Not indicated</td>
<td>Empirical therapy may be considered</td>
</tr>
<tr>
<td>4.3: Medium aneurysm, regressed to normal or dilation only</td>
<td>Continue</td>
<td>Not indicated</td>
<td>May be considered</td>
<td>Not indicated</td>
<td>Empirical therapy may be considered</td>
</tr>
</tbody>
</table>
Long-term Thromboprophylaxis and Medical Therapy Algorithm

<table>
<thead>
<tr>
<th>Risk Level</th>
<th>Low-Dose ASA</th>
<th>Anticoagulation (Warfarin or LMWH)</th>
<th>Dual Antiplatelet Therapy (ASA+Clopidogrel)</th>
<th>β-Blocker</th>
<th>Statin</th>
</tr>
</thead>
<tbody>
<tr>
<td>5.1: Large and giant aneurysm, current or persistent</td>
<td>Continue</td>
<td>Reasonably indicated</td>
<td>May be considered in addition to anticoagulation</td>
<td>May be considered</td>
<td>Empirical therapy may be considered</td>
</tr>
<tr>
<td>5.2: Large or giant aneurysm, regressed to medium aneurysm</td>
<td>Continue</td>
<td>Reasonably indicated</td>
<td>May be considered as an alternative to anticoagulation</td>
<td>May be considered</td>
<td>Empirical therapy may be considered</td>
</tr>
<tr>
<td>5.3: Large or giant aneurysm, regressed to small aneurysm</td>
<td>Continue</td>
<td>May be considered</td>
<td>May be considered as an alternative to anticoagulation</td>
<td>May be considered</td>
<td>Empirical therapy may be considered</td>
</tr>
<tr>
<td>5.4: Large or giant aneurysm, regressed to normal or dilation only</td>
<td>Continue</td>
<td>Not indicated</td>
<td>May be considered as an alternative to anticoagulation</td>
<td>Not indicated</td>
<td>Empirical therapy may be considered</td>
</tr>
</tbody>
</table>

ASA indicates acetylsalicylic acid or aspirin; and LMWH, low-molecular-weight heparin. Green indicates a Class I recommendation (should be performed); yellow indicates a Class IIa recommendation (it is reasonable to perform); orange indicates a Class IIb recommendation (may be considered); and red indicates a Class III recommendation (should not be performed).
Long-Term Assessment and Counseling Algorithm

- Based on risk level
- Suggests frequency of cardiology assessment
- Type and frequency of additional cardiology assessment (stress echo, stress MRI, stress with nuclear perfusion)
- Physical activity counseling
- Reproductive counseling
What about physical activity?

Currently no evidence to support aggressive activity restrictions

KD patients, regardless of extent of coronary artery abnormalities, have been shown to be <50% as active as their peers

• Associated with lower confidence in physical activity and lower physical functioning

Important to provide exercise guidance based on testing (exercise stress tests, stress-echo, Holters), with preference for lower-intensity competitive sports for those with persistent aneurysms

If on Warfarin or Lovenox → need to restrict from activities involving risk of bodily contact, trauma, injury
Differential Diagnosis

- Measles
- Other viral infections (adenovirus, enterovirus)
- Staphylococcal and streptococcal toxin-mediated diseases (scarlet fever and toxic shock syndrome)
- Drug hypersensitivity reactions (Stevens-Johnson syndrome)
- Systemic onset juvenile idiopathic arthritis
- Rickettsial disease (Rocky Mountain spotted fever)
In the future...

Etiology??
- Definitive lab test
- Vaccine

Long-term follow-up??
- Other issues that develop
Post-lecture questions
Question #1

High-dose aspirin (80-100 mg/kg/day) in the acute phase of illness is superior to moderate-dose aspirin (30-50 mg/kg/day)

A. True
B. False
Question #2

All the following criteria support the diagnosis of Kawasaki disease, **except**: 

A. Platelet count >1,000,000  
B. Fever for 5 days  
C. Cervical lymphadenopathy  
D. Erythema and edema of the hands or feet  
E. Bilateral conjunctival injection
Question #3

Which of the following is a supplemental lab finding used in the diagnosis of Kawasaki Disease?

A. Hyperalbuminemia
B. Thrombocytopenia
C. Leukopenia
D. Sterile pyuria
Supplemental lab criteria

- Albumin $\leq 3.0$
- Anemia for age
- Elevation of alanine aminotransferase (ALT)
- Platelets after 7 days $\geq 450,000$
- WBC $\geq 15,000$
- Urine $\geq 10$ WBC
Thank you!