KAWASAKI DISEASE
1967-2017
What have we learned?

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PEDIATRIC RHEUMATOLOGY

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CASE – 3 YEAR OLD WITH FEVER & RASH

A 3 year old white boy presents with abdominal pain, fever of 104°F and truncal rash. He was placed on oral amoxicillin and took 4 doses. Fever persisted, he is admitted to hospital on day 2 of illness. Physical examination is significant for bilateral scleral injection, edema of hands and feet, and a generalized maculopapular rash.
QUESTION #1 - Possible diagnoses would include all of the following except:

• Kawasaki Disease
• Streptococcal Infection
• Epstein Barr Virus Infection
• Adenovirus infection
• Varicella/Zoster

Case, cont.
He improves with intravenous hydration. Fever persists and he develops swelling of his knees. The blood culture obtained on admission grows *Staphylococcus aureus*. A blood culture obtained on day 4 of illness is sterile. He is started on aspirin and given a dose of intravenous immunoglobulin (IVIG). By day 8 of illness, he is afebrile and the rash has resolved. Erythrocyte sedimentation rate is 110 mm/hour, platelet count 440,000. Antibodies to Lyme and strep are negative. The child is sent home.
QUESTION #2 – For treatment of Kawasaki Disease, IVIG should be administered:

• After congestive heart failure symptoms have resolved
• After the fever subsides
• Only if a trial of corticosteroids has not been effective
• As soon as the diagnosis is made
• At the time of skin desquamation
**INTRODUCTION**

- disease or syndrome?
- acute vasculitis of young children
- distinct complication - coronary aneurysms
- there have been major advances in understanding this condition

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**KD - INTRODUCTION**

- effective therapy has been discovered
- insight into underlying immunologic processes
- establishment of general guidelines for diagnosis and management
- IVIG reduces discoverable aneurysms from 20% to 3% of cases
- mortality dropped from 2% to 0.1%

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**KAWASAKI DISEASE - HISTORY**

- 1967 - Dr. T. Kawasaki reports 50 Japanese children with MCLNS
- 1975 - coronary aneurysms reported
- 1976 - effect of aspirin (+), steroids (-)
- 1976 - outbreak in Hawaii
- 1984 - IVIG effective in anecdotal cases
- 1986 - clinical trial of IVIG shows efficacy
- 1991 - large single IVIG dose effective
KAWASAKI DISEASE - HISTORY

• 2007-2012 – controlled trials establish efficacy of adjunctive steroids in high risk KD
• 2000 – identification of oligoclonal IgA plasma cells in KD tissue samples
• 2005 – cytoplasmic inclusion bodies in ciliated bronchial epithelium that react with IgA antibodies that are present in the acute KD arterial wall.

Epidemiology

• Median age of affected children = 2.3 years
• 80% of cases in children < 4 yrs, 5% of cases in children > 10 yrs
• Males:females = 1.5-1.7:1
• Recurs in 3%
• Positive family history in 1% but 13% risk of occurrence in twins
• Overall U.S. in-hospital mortality ≈ 0.17%
• Increased cases in winter months

KAWASAKI DISEASE - EPIDEMIOLOGY

• Japan 5000 cases/yr. & US 4-8000/yr.
• Japan KD registry >250,000 cases
• leading cause acquired heart disease in kids
• Differing racial incidences
  • European/Hispanic 1/10,000
  • African ancestry 1.5/10,000
  • Asians 5 to 10/10,000
Table 1: Incidence of KD in various countries & Approximate Risk of Child Developing KD by Age 5y

<table>
<thead>
<tr>
<th>Country</th>
<th>Approximate Risk of Child Developing KD by Age 5y</th>
</tr>
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<tbody>
<tr>
<td>Japan</td>
<td>1 in 90</td>
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<tr>
<td>Korea</td>
<td>1 in 150</td>
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<tr>
<td>China</td>
<td>1 in 400</td>
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<tr>
<td>Taiwan</td>
<td>1 in 300</td>
</tr>
<tr>
<td>Continental USA</td>
<td>1 in 1000</td>
</tr>
<tr>
<td>Hawaii—Japanese American</td>
<td>1 in 95</td>
</tr>
<tr>
<td>Hawaii—Native Hawaiian</td>
<td>1 in 230</td>
</tr>
<tr>
<td>Hawaii—Chinese American</td>
<td>1 in 240</td>
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<tr>
<td>Hawaii—Other Asian</td>
<td>1 in 235</td>
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<tr>
<td>Hawaii—Caucasian</td>
<td>1 in 1000</td>
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<td>Canada</td>
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<tr>
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<tr>
<td>Australia</td>
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<td>Finland</td>
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<tr>
<td>Norway</td>
<td>1 in 3700</td>
</tr>
<tr>
<td>Chile</td>
<td>1 in 2600</td>
</tr>
</tbody>
</table>


**KD - DIAGNOSIS**

- Fever persisting 5 days or more
- Changes in periph. extremities
- Rash
- Conjunctival injection
- Mucosal changes
- Adenopathy (≥1.5 cm)

(for diagnosis: at least 5/6 should be present or 4/6 + coronary aneurysm)
Common features in the history of children with KD

- Prolonged intermittent high-spiking fevers
- Excessive irritability when compared with other previous febrile illnesses
- Refusal to bear weight or hold objects in hands
- Redness and swelling of hands and feet
- Redness and peeling of the skin in the groin area
- Red eyes, red lips and tongue
- Red rash on body, primarily on trunk, arms, legs
- Swollen glands in neck
- Vomiting, Diarrhea, Cough
- Redness at site of BCG injection

Laboratory findings – Kawasaki Disease

- Normal peripheral white blood cell count with left shift, or
- Increased WBC with predominance of neutrophils
- Elevated erythrocyte sedimentation rate (40 mm/h) and/or C-reactive protein (3.0 mg/dL)
- Anemia for age
- Albumin less than 3.0 mg/dL
- Hypoalbuminemia
- Thrombocytosis week 2-3
- Sterile pyuria (10 WBC/HPF)
- Elevated serum transaminases with or without elevated serum gamma glutamyl transpeptidase or bilirubin
- Cerebrospinal fluid pleocytosis, normal glucose and protein levels
- Leukocytosis in synovial fluid

Small coronary artery with segmental necrosis and inflammation in a patient with Kawasaki disease

**KEY POINTS - PATHOLOGY**

- KD vasculopathy primarily involves muscular arteries and is characterized by 3 linked processes:
  - (1) necrotizing arteritis
  - (2) subacute/chronic vasculitis
  - (3) LMP (luminal myofibroblastic proliferation)
- Large or giant coronary artery aneurysms ≥8 mm in diameter or with a Z score ≥10 do not “resolve,” “regress,” or “remodel.”
- They rarely rupture and virtually always contain thrombi (the oldest of which may calcify) that can become occlusive.
- Source: Diagnosis, Treatment, and Management of Kawasaki Disease, Circulation. 2017
KEY POINTS – PATHOLOGY (cont)

• Aneurysms with markedly damaged but partially preserved media may develop decreases in lumen diameter over time as the result of LMP or thrombi and can become progressively stenotic.
• Atherosclerotic features are not characteristic of KD vasculopathy even in late deaths or transplants.
• Pericarditis and myocarditis result from subacute/chronic inflammation, which is usually concentrated around coronary arteries.
• Source: Diagnosis, Treatment, and Management of Kawasaki Disease, Circulation. 2017

KD - EVALUATION

• blood culture, CBC, CRP, ESR
• measles IgM
• strep culture, ASO
• EKG, Chest X-ray
• echocardiogram
• other studies

KD - THERAPY

• baseline echo
• IVIG 2 g/kg over 10-12 hours
• aspirin 80-100 mg/kg/d, then 3-5 mg/kg until ESR and plt normalize
• delay measles vaccine
• further pharmacologic therapy based on degree of coronary involvement (AHA recommendations)
• Diagnosis, Treatment, and Management of Kawasaki Disease, Circulation. 2017
Factors associated with an increased risk of KD
- Asian ethnicity
- Age less than 5 years
- Parent or sibling with prior history of KD

Factors associated with higher risk of coronary artery abnormalities
- Age <12 months or >8 years
- Male gender
- Longer interval from disease onset to IVIG Rx
- Failure to respond to initial IVIG
- Laboratory features (albumin <3.0 mg/dL, anemia for age, elevated ALT, hyponatremia, thrombocytopenia)
**KAWASKI DISEASE – adjunct therapy**

- 2007-2012 – controlled trials establish efficacy of adjunctive steroids in high risk KD
- 10-20% of KD do not respond to initial dose of IVIG & high dose aspirin
- 1-2% fail to respond to second IVIG dose

**Options for treatment of refractory KD**

- Additional dose(s) of 2 g/kg of intravenous gammaglobulin
- IV methylprednisolone 30 mg/kg/d for 1 to 3 days
- Infliximab 5 mg/kg
- Other possible therapies: cyclosporine, methotrexate
- Therapies sometimes used in Japan: plasmapheresis, neutrophil elastase inhibitor
- Possible future therapies: statins, interleukin-1 inhibitors


**KD - GUIDELINES FOR LONG TERM FOLLOW-UP**

- **no coronary disease** - no specific recommendations
- **coronary disease**
  - restrictions on physical activity
  - follow-up echocardiograms
  - stress testing, based on extent of coronary involvement
KD - Complciations

- Review of 74 patients with late term complications of KD - mean age 24.7 yr
- Myocardial infarction/ chest pain (61%) arrhythmia (11%) sudden death (16%)
- Symptoms precipitated by exercise in 82%
- 1/3 ring calcifications on X-ray
- Risk of accelerated coronary disease still not known in KD patients
The Big Question:

What is the Etiology of Kawasaki Disease?
KD - POTENTIAL ETIOLOGIES

- bacteria (strep, staph, P.acnes)
- rickettsiae
- dust mites/rug shampoo
- parvovirus
- retrovirus
- staphylococcus aureus toxin

- Mercury
- Leptospira
- Retrovirus
- EBV/CMV
- Coronavirus
- Human bocavirus
- Persistent RNA virus

WE STILL DON’T KNOW
A new RNA virus? Rowley et al. PIDJ 2011

- IgA plasma cells are discovered in the arterial wall, producing antibody at the site of pathology [25, 34].
- DNA sequencing of CD80 regions of alpha genes in arterial wall shows an oligoclonal response (partial antibody sequences are present) [10].
- Synthetic versions of these antibodies are made using recombinant DNA technology [2].
- KD synthetic antibodies are inactivated and used in immunohistochemistry experiments on KD and control tissue [3].
- KD synthetic antibodies bind to antigen in KD but not control infant distal bronchial epithelium, and to a subset of macrophages in inflamed KD tissue [3].
- Light and electron microscopy studies show that the antigen is localized to cytoplasmic inclusion bodies with aggregates of viral proteins and viral acids [34].
- Inclusion bodies are present in 85% of acute and late-stage KD fatalities, and in 20% of older childhood and adult controls, and nucleic acid stains reveal that they contain RNA but not DNA, consistent with a persistent, ubiquitous RNA virus [25].

ATYPICAL (INCOMPLETE) KD

**POSSIBLE**
- young infant
- marked increase in acute phase reactants
- thrombocytosis & desquamation later
- hydrops of gall bladder
- persistent fever

**NOT LIKELY**
- normal ESR, Hb
- establishment of another diagnosis
- exudative conjunctivitis or pharyngitis
- mouth ulcers, generalized nodes
Key Points: Consider KD in the Differential Diagnosis of Certain Infants or Children

- Infants <6 months old with prolonged fever and irritability
- Infants with prolonged fever and unexplained aseptic meningitis
- Infants or children with prolonged fever and unexplained or culture-negative shock
- Infants or children with prolonged fever and cervical lymphadenitis unresponsive to antibiotic therapy
- Infants or children with prolonged fever and retropharyngeal or parapharyngeal phlegmon unresponsive to antibiotic therapy

* Source: Diagnosis, Treatment, and Management of Kawasaki Disease, Circulation. 2017

Case, cont.

He improves with intravenous hydration. Fever persists and he develops swelling of his knees. The blood culture obtained on admission grows *Staphylococcus aureus*. A blood culture obtained on day 4 of illness is sterile. He is started on aspirin and given a dose of intra-venous immunoglobulin (IVIG). By day 8 of illness, he is afebrile and the rash has resolved. Erythrocyte sedimentation rate is 110 mm/hour, platelet count 440,000. Antibodies to lyme and strep are negative. The child is sent home.
Case, continued

Over the next 8 weeks, he has episodes of nocturnal vague abdominal pain. His activity level is normal, he has had no recurrent rash and is behaving normally, except he refuses to jump. He has low grade fevers (maximum 101°F) and sedimentation rate is 40-70. Physical examination is normal.

QUESTION #3 – The next step in management should be:

- Restart aspirin therapy and repeat sedimentation rate in 1-2 weeks
- Give a second dose of IVIG
- Consider further diagnostic testing
- Repeat the echocardiogram
- Re-assure the mother and observe
OTHER DIAGNOSES TO CONSIDER – KD mimics

INFECTION DISEASES
• Measles, Rubeola, Scarlet Fever
• SSSS/Staph toxic shock
• Group A Beta-hemolytic Streptococcal infection
• Leptospirosis
• Rocky Mountain Spotted Fever
• EBV infection
• parvovirus
• other viral exanthems

OTHER
• Drug Eruptions
• Erythema Multiforme
• Stevens-Johnson Syndrome/Toxic epidermal necrolysis
• Acrodynia (Hg Toxicity)
• Juvenile Idiopathic Arthritis (systemic type)

TAKE HOME POINTS
• filling clinical criteria does not mean the patient has KD
• a normal echo/platelet count/ESR does not r/o KD, especially early in disease
• think of incomplete KD in patients with unexplained fever >10 d or very young infants
• be sure to consider acute bacterial infection in any child with focal musculoskeletal complaints (Staph aureus is never a contaminant)

FUTURE GOALS
• prevention of long term complications
• determination of etiologic agent(s)
• identification of specific treatment
• more accurate diagnostic tools
• establishment of guidelines for atypical cases
QUESTIONS?