Kawasaki Disease Reconsidered
New Insights and Expert Advice for a Challenging Disease

John Darby, MD
Stanford Shulman, MD
Nisha Tamaskar, MD
Brian Shirley, DO

Introductions

• Who are we?
  • John Darby, MD
    • Texas Children’s Hospital / Baylor College of Medicine
    • Hospitalist
  • Nisha Tamaskar, MD
    • Texas Children’s Hospital / Baylor College of Medicine
    • Hospitalist Fellow
  • Stanford Shulman, MD
    • Lurie Children’s Hospital / Northwestern University School of Medicine
    • Infectious Disease Physician
    • KD Guru
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Disclosures

• None of the presenters have any relevant financial relations to disclose

• We do not intend to discuss an unapproved/investigative use of a commercial product/device in our presentation
Introductions

• Who are you?

Objectives

• At the conclusion of this activity, participants will be able to…
  • Compare Kawasaki Disease practice patterns
  • Recognize features of classic and incomplete presentations of Kawasaki Disease and formulate a robust differential diagnosis
  • Identify potential complications of Kawasaki Disease and prepare management plans
Structure of the workshop

• Section 1 (PHM):
  • Classic Presentations of KD
  • Pathophysiology and Epidemiology

• Section 2 (ID):
  • Incomplete Presentations of KD and KD syndromes
  • Differential Diagnosis of KD

• Section 3 (Rheumatology):
  • Treatment of KD
  • Complications of KD

Themes

• Recognize practice variation

• Cases and audience questions
  • Polleverywhere login:

• Time for questions

• Who’s missing? Cardiology
Audience Question 1

To whom are patients with KD primarily admitted in your hospital?

A) Hospital Medicine (General Medicine)
B) Infectious Disease
C) Rheumatology
D) Cardiology
E) Other
Audience Question 2

Is any subspecialty/department automatically consulted when a patient is diagnosed with KD?

A) No, unless things get complicated, most patients are managed only by the general service
B) Yes, ID
C) Yes, Rheumatology
D) Yes, Cardiology
E) Yes, other

Audience Question 3

In patients with classic KD with no complications, in addition to the PCP, who follows patients with KD after discharge?

A) PCP only
B) ID
C) Rheumatology
D) Cardiology
E) Multiple services
Epidemiology

• Annual US incidence ~20 per 100,000 children <5yrs old

• 80-90% of cases occur in children 6mo-5yrs old
  • Peak 18-24 mo

• Rare beyond late childhood
  • Older children may experience delays in diagnosis

• Boys > Girls

Epidemiology

• Japan:
  • 10x increased risk of KD for children with an affected sibling
  • 2x increased risk of KD for children with a previously affected parent

• North America: case reports of families with multiple affected members
Pathophysiology

- Definite immune perturbations: cytokine cascade stimulation and endothelial cell activation
- Advanced treatments are immunomodulators

Who Owns KD?

- Pathophysiology: Vasculitis → Rheumatology?
  - Definite immune perturbations: cytokine cascade stimulation and endothelial cell activation
  - Advanced treatments are immunomodulators
Who Owns KD?

• Etiology: Infection? → Infectious Disease?
  • Age distribution
  • Winter–spring seasonality
  • Community outbreaks with wave-like geographic spread
  • Laboratory features
  • However…no identifiable infectious cause yet

Who Owns KD?

• Consequences: Coronary Aneurysms → Cardiology?
Audience question 4

• How many patients with KD do you see a month?

A) <1
B) 1
C) 2 – 4
D) >4
Audience question 5

• Which of the following is NOT a feature associated with typical KD?
  A) Erythematous, peeling groin rash
  B) Refusal to bear weight
  C) Erythema multiforme rash
  D) Bulbar conjunctival injection
  E) Posterior pharyngitis

Audience question 6

• All of the following are laboratory findings of typical KD EXCEPT:
  • A) Normal peripheral white count with left shift
  • B) Leukocytosis > 15K
  • C) Hypernatremia
  • D) CSF pleocytosis
  • E) Albumin < 3.0 mg/dL
  • F) Elevated serum transaminases
Classic Presentations

• Diagnostic Criteria
  • Fever
  • Conjunctival injection
  • Rash
  • Mucositis
  • Extremity changes
  • Lymphadenopathy

• Supporting Findings
  • Cardiovascular findings
    • Tachycardia, coronary artery changes, etc
  • GI Complaints
  • Irritability
  • Anorexia
  • Arthritis
Fever

• Most consistent manifestation of KD

• High spiking and with peak typically >39 C (102 F)\(^1\)

• Minimally responsive to antipyretics

• Present daily for >5 days

• Can last for 3 – 4 weeks if untreated

Conjunctival injection

• Bilateral

• Typically begins shortly after onset of the fever

• Involves the bulbar conjunctivae (sparing the limbus)

• Non-exudative, painless
Rash

• “Non-specific, diffuse maculopapular eruption.”

• Scarlatiniform rash, erythroderma, erythema-multiforme-like rash

• Rash is typically extensive

• Accentuated in the perineal region and early desquamation may occur

• (Urticarial exanthema)

• (Fine micropustular eruption)
Mucositis

• Strawberry tongue

• Redness and/or swelling of the lips

• Dryness, fissuring, peeling, cracking and bleeding of the lips

• Absence of oral ulcerations and pharyngeal exudates
Extremity Changes

• Erythema of the palms and soles

• Painful induration of the hands or feet

• Periungual desquamation of the fingers and toes
  • Begins within 2 – 3 weeks after onset of fever

• Deep transverse grooves across the nails (Beau’s lines)
  • 1 to 2 months after onset of fever
Lymphadenopathy

- Least common of the clinical features
- Typically unilateral and anterior cervical triangle
- $\geq 1$ lymph node that is $>1.5$ cm in diameter
- Firm and nonfluctuant
- Not associated with marked erythema of the overlying skin
- Non tender or slightly tender
Cardiac Findings

- Leading cause of long term morbidity and mortality in KD
- Coronary arteries
  - Arteritis, aneurysm, giant aneurysm
- Pericardium
  - Pericardial effusion
- Myocardium
  - Tachycardia, myocarditis, depressed cardiac output\(^1\)\(^2\)
- Valves

Non-cardiac findings

- Arthritis and arthralgia
  - Small interphalangeal joints, large weight-bearing joints
- Gastrointestinal complaints
  - Diarrhea, vomiting, and abdominal pain
  - Acute acalculous distention of the gallbladder (hydrops)
- Irritability
- Rhinorrhea and Cough

**Laboratory Findings**

- Leukocytosis with neutrophils and bands
- Elevated ESR and CRP (ESR ≥ 40 mm/h, CRP ≥ 3.0 mg/dL)
- Anemia for age
- Hypoalbuminemia (Albumin < 3.0 mg/dL)
- Hyponatremia
- Thrombocytosis
- Elevated serum transaminases
- Elevated GGT
- Sterile pyuria (≥ 10 WBC/high-powered field)

**Audience question 4**

- All of the following are laboratory findings of typical KD EXCEPT:
  - A) Normal peripheral white count with left shift
  - B) Leukocytosis > 15K
  - C) Hypernatremia
  - D) CSF pleocytosis
  - E) Albumin < 3.0 mg/dL
  - F) Elevated serum transaminases
Incomplete Presentations and Additional Kawasaki Syndromes

Stanford T. Shulman, M.D.
Virginia H. Rogers Professor of Pediatric Infectious Diseases
Case 3

- 8 month old male presents with 6 days of fever, bilateral non-exudative conjunctival injection and history of a fleeting macular truncal rash.
  - Labs: WBC 16, 73% Neutrophils, Hgb 9.8 g/dL, platelets 350K, ESR 47 mm/hr, CRP 13 mg/dL, albumin 2.8 g/dL, ALT 80

- Diagnosis?
  - A) Complete KD
  - B) Incomplete KD
  - C) Rubeola
  - D) JIA

Incomplete (Atypical) KD

- Children (often infants) with fever plus fewer than four other diagnostic criteria
- Does not refer to unusual clinical features
- Extremely difficult diagnostic dilemmas
- Patients appear to have same laboratory profile as classic cases
- Overdiagnosis and underdiagnosis
Incomplete (Atypical) KD

- At least 5 days of fever plus <4 classic KD features
- Risk for coronary disease = classic KD
- Especially seen in <1 year olds
- Inflammatory markers (ESR ≥ 40, CRP ≥ 3.0 mg/dL) are most useful for screening
- Maintain “high index of suspicion”
<table>
<thead>
<tr>
<th><strong>AHA Algorithm: Supplemental Criteria</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>• Albumin ≤3.0 gm/dl</td>
</tr>
<tr>
<td>• Anemia for age</td>
</tr>
<tr>
<td>• Elevated ALT</td>
</tr>
<tr>
<td>• Platelets ≥450,000/mm3 after day 7</td>
</tr>
<tr>
<td>• WBC ≥15,000/mm3</td>
</tr>
<tr>
<td>• Pyuria (≥10 WBC/HPF)</td>
</tr>
<tr>
<td>• (Hyponatremia)</td>
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<table>
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<th><strong>KD Syndromes</strong></th>
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<tr>
<td>• Lymph Node predominant</td>
</tr>
<tr>
<td>• Kawasaki Shock Syndrome</td>
</tr>
<tr>
<td>• KD in infants &lt;1 year of age</td>
</tr>
<tr>
<td>• KD in children &gt;8 years of age</td>
</tr>
<tr>
<td>• How about adenovirus?</td>
</tr>
</tbody>
</table>
Kawasaki ("Kawashocki") Shock Syndrome

- Hypotension plus more typical KD symptoms, which may develop during course
- Older girls often affected
- Compared to usual KD patients, higher CRP levels, lower initial albumin, sodium, and platelets, more IVIG resistance, possibly higher rates of CA abnormalities

KD in infants < 1 year of age

- Particularly high risk for CA abnormalities
  - Boys <6 months are highest risk
- Manifestations often subtle
  - Often lack full diagnostic criteria (incomplete)
- Standard treatment effective (IVIG, ASA)
Kawasaki Disease in Children >Eight Years

- About 5% of all Kawasaki Disease patients
- Predominance of white males
- Frequently delayed diagnosis and therapy
  - GI and joint manifestations common
  - Meningismus observed
  - These features serve as distractions from diagnosis
  - Coronary abnormalities more common

Differential Diagnosis

- Drug Reactions
- JIA
- Viral infections
Differential Diagnosis

- Drug Reactions
  - History of drug use
  - Much lower inflammatory markers than KD
  - Hives not in KD
  - Target lesions (E. multiforme) in KD

- JIA
  - Fever, Rash, Joints (±), high ESR/CRP
  - Often apparent in follow-up, little or transient response to IVIG/ASA
Differential Diagnosis

- Viral infections
  - Fever rarely persists > 6 days
  - Much lower inflammatory markers than KD

Case 4

- 8 month old male presents with 6 days of fever, bilateral non-exudative conjunctival injection and history of a fleeting macular truncal rash.
  - Labs: WBC 16, 73% Neutrophils, Hgb 9.8 g/dL, platelets 350K, ESR 47 mm/hr, CRP 13 mg/dL, albumin 2.8 g/dL, ALT 80.
  - Respiratory viral panel is positive for adenovirus.

- Diagnosis?
  - A) Acute Adenovirus infection
  - B) Incomplete KD
  - C) Rubeola
  - D) Typical KD
Differential Diagnosis

- Adenovirus can mimic KD
  - Exudative conjunctivitis, rash, elevated LFT
  - Adeno often reactivates with intercurrent febrile illnesses (+ PCR)
  - Less impressive ESR/CRP levels than KD

KD vs Adenovirus infection

<table>
<thead>
<tr>
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<th>KD - Like ADENOVIRAL infection</th>
<th>KD with Adenovirus detection</th>
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<tbody>
<tr>
<td>Tongue / Lip involvement</td>
<td>63%</td>
<td>93%</td>
</tr>
<tr>
<td>Rash</td>
<td>47%</td>
<td>93%</td>
</tr>
<tr>
<td>Hands / Feet</td>
<td>27%</td>
<td>85%</td>
</tr>
<tr>
<td>Unilateral Cervical LN</td>
<td>6%</td>
<td>40%</td>
</tr>
<tr>
<td>&lt;4 KD Criteria</td>
<td>96%</td>
<td>15%</td>
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## KD vs Adenovirus infection

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<tr>
<td>ESR &gt; 40</td>
<td>57%</td>
<td>80%</td>
</tr>
<tr>
<td>CRP &gt; 7.0</td>
<td>14%</td>
<td>50%</td>
</tr>
<tr>
<td>WBC &gt; 15K</td>
<td>16%</td>
<td>50%</td>
</tr>
<tr>
<td>Plt &gt; 450 (after 7 d of fever)</td>
<td>4%</td>
<td>35%</td>
</tr>
<tr>
<td>Pyuria (&gt; 10/HPF)</td>
<td>2%</td>
<td>50%</td>
</tr>
<tr>
<td>Adenovirus Cycle Threshold</td>
<td>25</td>
<td>35</td>
</tr>
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### Treatment and Complications

Joel Brian Shirley, DO

Pediatrics
KD – Management Review

PEDIATRICS Vol. 114 No. 6 December 2004

• Intravenous Immune Globulin (IVIG)
  • 2 grams/kg administered as a single infusion over 8 to 12 hours
  • Administer within 10 days of fever onset (within 7 days where possible)
  • Administer after 10th day if: persistent fever or aneurysms and ↑CRP and/or ESR

• Aspirin
  • 80 – 100 mg/kg per day divided in 4 doses
  • Administer along with IVIG
  • Decrease to 3 – 5 mg/kg per day at 48 – 72 hours after fever cessation
    • Continue this dose for 6 – 8 weeks from illness onset in children with no coronary changes
Case 5

- 10 month old Hispanic male with Kawasaki Disease
- Received IVIG and aspirin
- Febrile to 101.0 degrees 38 hours after completion of IVIG

Audience Poll

Which of the following options would you choose as next course of action?

a. Retreat with IVIG alone
b. Retreat with IVIG + steroid (IV methylprednisolone, PO prednisone)
c. Administer steroid alone (IV methylprednisolone, PO prednisone)
d. Administer TNFa inhibitor alone (infliximab, etanercept)
e. Observe
KD – Initial Therapy Nonresponder

• Failure to respond generally defined as persistent or recrudescent fever ≥36 hours after completion of initial IVIG

• ~15% of patients with KD initially treated with IVIG & aspirin fail to respond

• Persistent or recrudescent fever is single strongest risk factor for development of coronary artery aneurysms

KD – Initial Therapy Nonresponder

• Various retrospective studies demonstrate risk factors for nonresponsiveness to initial therapy:
  • ↑ CRP (≥10mg/dL)
  • ↑ AST and ALT
  • ↑ % bands
  • Early diagnosis (on or before day 4 suggesting more aggressive disease)
  • < 1 year of age
  • Sodium ≤ 133 mmol/L
  • Platelet count ≤ 300,000/mm³

• Note: scoring systems have high sensitivity in Japanese population, but they have NOT been reliable predictors in multiethnic populations
KD – Initial Therapy Nonresponder

• Children who fail initial therapy for KD:
  • No prospective randomized trials have evaluated optimal therapy

  • Several retrospective studies indicate retreating with IVIG is effective

  • **Recommendation**: retreat IVIG as a single infusion of 2 grams/kg for a total cumulative IVIG of 4 grams/kg

Case 6

• 10 month old Hispanic male with Kawasaki Disease

• Received IVIG and high dose aspirin
  • Fever and irritability persist

• Retreated with IVIG
  • Fever persists, CRP rises higher

• Now What?
Audience Poll

Which of the following options would you choose?

a. Retreat with IVIG
b. Administer steroid (IV methylprednisolone, PO prednisone)
c. Administer TNFα inhibitor (infliximab, etanercept)
d. Ask for help

Case 7

• 10 month old Hispanic male with Kawasaki Disease

• Initial echocardiogram demonstrates early coronary artery dilatation in the LAD and RCA

• What now?
Audience Poll

Which of the following options would you choose?

a. Administer IVIG alone

b. Administer IVIG + steroid (IV methylprednisolone, PO prednisone)

c. Administer IVIG + TNFα inhibitor (infliximab, etanercept)

d. Ask for help

Salvage Therapy

• Despite multiple doses of IVIG, about 5% of patients remain febrile

• As fever continues, coronary artery aneurysm risk increases

• Various salvage agents have been used in small studies, yet proven benefit has not been firmly established

• Disclaimer: Therapy when IVIG refractory is case dependent and there is considerable variability among institutions for which is used. The following are more common agents
Steroid Pulse Therapy

Original Article

Re-treatment for immune globulin-resistant Kawasaki disease: A comparative study of additional immune globulin and steroid pulse therapy

KANOKO HASHINO, MASAHIRO ISHII, MOTOFUMI IEMURA, TEIJI AKAGI AND HIROHISA KATO

Department of Pediatrics and the Cardiovascular Research Institute, Kame University School of Medicine, Kame, Japan
Infliximab Therapy

ORIGINAL ARTICLES

Infliximab for Intravenous Immunoglobulin Resistance in Kawasaki Disease: A Retrospective Study

Mary Beth Sun, MD, Kimberly Gauveau, ScD, June C. Burns, MD, Elena Corinnides, MD, Adriana H. Tramoulet, MD, MAS, Virginia E. Watson, MD, Annette Baker, RN, MSN, PNP, David R. Fulton, MD, Robert P. Sandef, MD, and Jane W. Newburger, MD, MPH

J Rheumatol, 2012

Infliximab Therapy

Efficacy and Limitation of Infliximab Treatment for Children with Kawasaki Disease Intractable to Intravenous Immunoglobulin Therapy: Report of an Open-label Case Series

MASAKI MORI, TOMOYUKI IMAGAWA, RYOKI HARA, MASAKO KIKUCHI, TAKUMA HARA, TOMO NOZAWA, TAKAKO MIYAMAE, and SHUMPEI YOKOTA

J Rheumatol, 2012
Clinical Trials Ongoing

• **Anakinra** in Infants and Children With Coronary Artery Abnormalities in Acute Kawasaki Disease
  • Completion December 2020

• A Randomized, Double Blind, Placebo Controlled Study of the Effects of *Etanercept* in Children Presenting With Kawasaki Disease
  • Completion July 2016

• Others: cyclosporine and plasma exchange

Case 8

• 3 yo African American Female with fever for 6 days and clinical stigmata for KD
  • Initial Labs:
    • CRP 4 mg/dL, ESR 45 mm/hr
    • WBC 16,000/mm³, Hgb 10.3 g/dL, Platelets 325,000/mm³
    • Albumin 2.3mg/dL

• Received IVIG and aspirin but high fever persists
  - retreatment with IVIG

• Fever continues…
Case 8 continued

• Clinical status evolves:
  • Prominent abdomen
  • Seizure x 2
  • Petechiae on palate and trunk
  • Abdomain US: hepatosplenomegaly
  • CBC: WBC 2.5, Hgb 7.2, Plts 20
  • ↑ PT/PTT/Ddimer
  • ↑ ferritin
  • ↑ AST/ALT
  • ↓ Fibrinogen

KD Complications

• Macrophage Activation Syndrome (1-2% of patients)
  • Severe, potentially fatal condition caused by excessive activation of macrophages and T cells → overwhelming inflammatory reaction.
  • Characterized by:
    • Persistent fever
    • Hepatosplenomegaly and liver disease
    • Lymphadenopathy
    • Severe cytopenias
    • Coagulopathy consistent with DIC
    • Hyperferritinemia and hypofibrinogenemia
    • Hemophagocytosis in bone marrow, liver, spleen or lymph glands
Case 9

- 9 month old AA male, presented to ED for fever of 11 days and features of Kawasaki Disease
  - ECHO: LAD and RCA ectasia
- Diagnosis: Kawasaki disease
- Appropriate therapy initiated
- Persisting fever and inflammation
- LAD and RCA aneurysm (D14)
- Pulsatile nodes bilateral axilla (Day 15)

KD Complications

- Peripheral Artery Aneurysms
  - Occurs in approximately 2% of untreated patients
  - Most commonly involves axillary, iliac, brachial, and mesenteric vessels
  - As can be seen with coronary circulation, peripheral vessels may develop stenotic/thrombotic complication
    - Distal ischemia >> gangrene in most severe cases
Questions?

References


