Kawasaki Disease Update ---

*It’s getting curiouser and curiouser!*

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Disclosures

I have no financial relationships with the manufacturers or any commercial products and/or provider of commercial products or services discussed in this CME activity.

I do intend to discuss unapproved/investigative use of commercial products in this presentation.
Disclosures
Diagnostic Criteria
Circulation 2001;103:335-6

- Fever for 5 days or more
- Changes of the peripheral extremities
  - Red palms/soles; indurative edema (acute)
  - Membranous desquamation (subacute)
- Polymorphous exanthem
- Bilateral conjunctival injection w/o exudate
- Changes of the lips and oral cavity
  - Red, cracked lips; strawberry tongue; red oral mucosa
- Acute, non-purulent cervical adenopathy >1.5 cm
Fever plus 4 of the 5 other criteria allows for diagnosis.

Fever plus fewer than 4 of 5 other criteria can be diagnosed as KD if coronary artery disease is detected.

Other possible diagnoses should be excluded.

BUT: As many as 20% of KD patients are “incomplete” and may be missed.
Diagnostic Criteria

- Fever plus 4 of the 5 other criteria allows for diagnosis.
- Fever plus fewer than 4 of 5 other criteria can be diagnosed as KS if coronary artery disease is detected.
- Other possible diagnoses should be excluded. (Scarlet fever, measles, Adenovirus, EBV, STSS, leptospirosis, JIA, SJS/TEN)
- BUT: As many as 20% of KD patients are “incomplete” and may be missed.
Guidelines for Diagnosis, Treatment and Long-Term Follow-up

- Circulation 2004; 110:2747-2771
- Pediatrics 2004; 114:1708 – 1733
- [www.pediatrics.org/cgi/content/full/114/6/1708](http://www.pediatrics.org/cgi/content/full/114/6/1708)
CRP > 3
ESR > 40

Supplemental lab criteria:
Hgb low for age
WBC > 15,000
Platelets > 450k after 7 days
High ALT
≥ 10 WBC/HPF urine
Perivascular Echo-Brightness During Acute Phase

Normal Left Coronary Artery

Left Coronary Artery During Acute Kawasaki Syndrome
Patients reviewed from 4 centers from 1981-2006 with CAA (z score > 3) N=195 patients

- 137 (70%) met case definition and would have been treated on admit.
- 53 (27%) were incomplete and eligible for algorithm-all qualified for IVIG and would have been treated on admit.
- Overall application of the algorithm would have referred >190 patients (97%) for IVIG therapy.
New update from the 2004 edition

- Diagnosis Treatment and Long-term Management of Kawasaki Disease.
- Circulation March 29, 2017
Epidemiology
PIDJ 2010;29:483-488

A. Hospitalization Rate (NIS) vs. Hospitalization Rate (KID)

B. Hospitalizations per 100,000 people by region:
   - Northeast
   - Midwest
   - South
   - West

Kawasaki syndrome-associated hospitalization rates estimated using the Kids’ Inpatient Database (KID) and the Nationwide Inpatient Database (NIS), Healthcare Cost and Utilization Project (HCUP), and by region using the NIS.
## Kawasaki Incidence Rate, United States

Belay ED, CDC Atlanta Georgia

<table>
<thead>
<tr>
<th>Year</th>
<th>Rate (95%CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1997</td>
<td>17.6/100,000 (16.9-18.3)*</td>
</tr>
<tr>
<td>2000</td>
<td>17.1/100,000 (16.5-17.7)</td>
</tr>
<tr>
<td>2003</td>
<td>19.6/100,000 (17.6-21.6)</td>
</tr>
<tr>
<td>2006</td>
<td>20.8/100,000 (18.5-23.1)</td>
</tr>
</tbody>
</table>

*N.S.
KD Incidence Rate in Japan


Figure. Trend in incidence rates of Kawasaki disease by sex in Japan
# Incidence rates of KD

<table>
<thead>
<tr>
<th>Geographic Area</th>
<th>Incidence rate/100,000 &lt; 5y</th>
<th>Period</th>
</tr>
</thead>
<tbody>
<tr>
<td>Japan</td>
<td>264.8</td>
<td>2012</td>
</tr>
<tr>
<td>Korea</td>
<td>113.1</td>
<td>2006-2008</td>
</tr>
<tr>
<td>Taiwan</td>
<td>69.0</td>
<td>2003-2006</td>
</tr>
<tr>
<td>Beijing</td>
<td>55.1</td>
<td>2004</td>
</tr>
<tr>
<td>Shanghai</td>
<td>53.3</td>
<td>1997-2000</td>
</tr>
<tr>
<td>United States</td>
<td>19.0</td>
<td>2009</td>
</tr>
<tr>
<td>Hawaii</td>
<td>50.4</td>
<td>1996-2006</td>
</tr>
<tr>
<td>Canada</td>
<td>26.2</td>
<td>2004-2006</td>
</tr>
<tr>
<td>England</td>
<td>8.4</td>
<td>1998-2003</td>
</tr>
<tr>
<td>Finland</td>
<td>7.2</td>
<td>1992</td>
</tr>
<tr>
<td>Sweden</td>
<td>6.2</td>
<td>1990-1992</td>
</tr>
<tr>
<td>France</td>
<td>9.0</td>
<td>2005-2006</td>
</tr>
<tr>
<td>Italy</td>
<td>14.7</td>
<td>1981-1982</td>
</tr>
</tbody>
</table>
Etiologic Theories in the Past

- 1969  Leptospira (Kawasaki)
- 1973  Rickettsia-like bodies (Hamashima).
- 1975  Mercury poisoning or allergy (Cheek)
- 1982  House-dust mite (Furusho)
- 1982  Rug shampoo theory (Patriarca)
- 1982  BCG vaccine (Takayama)
- 1983  Propionibacterium (Kato).
- 1986  Retrovirus (Burns, Shulman).
- 1987  Retrovirus theory refuted.
- 1991  SPE and SST toxins acting as superantigen (Leung).
- 2005  Corona virus (Yale group)
### Possible Etiologies of KD: Infectious


<table>
<thead>
<tr>
<th>Agent</th>
<th>Status</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adenovirus</td>
<td>Lack of evidence</td>
</tr>
<tr>
<td>Measles virus</td>
<td>Lack of evidence</td>
</tr>
<tr>
<td>Rickettsial</td>
<td>Lack of evidence</td>
</tr>
<tr>
<td><em>Propionibacterium acnes</em></td>
<td>Lack of evidence</td>
</tr>
<tr>
<td><em>Streptococcus sanguis</em></td>
<td>Lack of evidence</td>
</tr>
<tr>
<td>Leptospira</td>
<td>Lack of evidence</td>
</tr>
<tr>
<td>Retrovirus</td>
<td>Lack of evidence</td>
</tr>
<tr>
<td>HSV, EBV or CMV</td>
<td>Lack of evidence</td>
</tr>
<tr>
<td>Staph or strep toxin</td>
<td>Not confirmed</td>
</tr>
<tr>
<td>Coronavirus NL-63</td>
<td>Not confirmed</td>
</tr>
<tr>
<td>Unknown RNA virus</td>
<td>Under investigation</td>
</tr>
</tbody>
</table>
Viral etiology of Kawasaki disease?

- Macrophages and CD8 T lymphocytes are prominent in inflammatory infiltrate of tissues in fatal cases. Brown JID 2001;184:940
- Sequenced IgA genes from tissue and found an oligoclonal (i.e. conventional antigen-driven) IgA response. Rowley JImmunol 2001;166:1334
- Synthesized antibodies in vitro and stained pathological tissue to identify antigen. Rowley JID 2004;190:856
A. H&E stain showing amphophilic ICI in ciliated bronchial epithelium

B. Synthetic antibody staining of ICI in ciliated bronchial epithelium

C. Methyl green pyronin stain indicating presence of RNA

D. Antibody stained antigen positive macrophages in myocardium
Rowley A et al PLOS ONE 2008; 3:e1582
A. Ciliated bronchial epithelium with electron-dense apical ICI
B. Alveolar macrophage with finely granular spheroid bodies
Detection of cytoplasmic inclusion bodies in KD bronchial epithelium by immunofluorescence

Hypothesized Pathogenesis
Adapted from Rowley et al NatRev:Microbiol2008;394-401
Day 6-8: Coronary arteritis with edematous dissociation of the tunica media

Day 10: Lymphocyte/macrophage & neutrophil infiltration of the arterial wall resulting in pan-vasculitis; proliferative granulomatous inflammation.

Day 12: Weakened arterial wall begins to dilate; aneurysms form.

Day 25: Inflammation begins to subside.

Day 40: Inflammatory cells are almost entirely gone.
- **Necrotizing arteritis** (NA): a synchronized, acute, self-limited inflammatory process subsiding after the first 2 weeks resulting in aneurysms, thromboses and ruptures within the first month.

- **Subacute/chronic vasculitis** (SA/C): an asynchronous inflammatory process with full range of intensities, intimately associated with LMP that can be active for months to years.

- **Luminal myofibroblastic proliferation** (LMP): proliferation of smooth muscle cell derived myofibroblasts and their matrix products associated with SA/C inflammation.
Necrotizing arteritis: a lytic, neutrophilic process beginning in intima, destroys arterial wall into adventitia, causes large sacular aneurysms that can thrombose or rupture, begins and ends within the first 2 weeks, consistent with innate immune response.
Subacute/chronic (SA/C) vasculitis: predominantly small lymphocytes, with plasma cells & eosinophils, can begin in the first 2 weeks or thereafter, starts in adventitia and progresses toward lumen, closely linked to luminal myofibroblastic proliferation (LMP), consistent with acquired immune response.
Luminal myofibroblastic proliferation (LMP): an asynchronous progressive intra-luminal stenosing lesion of smooth muscle cell-derived myofibroblasts, their matrix products, and SA/C inflammation; it is not granulation tissue nor does it show organization, “remodeling”, or re-canalization.
The importance of discharge instructions in KD

- 13-30% of patients fail IVIG Rx
- Of 40 pts who relapsed after Rx at CHLA, 47% relapsed after D/C from hospital
- 3 recent patients had break down in communication resulting in CAA formation.
- Families MUST be instructed to call if fever returns.
When to Consider Retreatment of Kawasaki Disease with Immune Globulin: Is Fever the Right Indicator?

Wilbert Mason MD MPH, Michael Smit MD, MSPH, Masato Takahashi MD
Children’s Hospital Los Angeles
Keck School of Medicine of the University of Southern California
Fever/Heart Rate in “resistant” patients

- Persistent fever and tachycardia: 15
- Diminished fever/persistent tachycardia: 11
- Persistent fever/resolved tachycardia: 1

Total: 27
6 y/o girl with KD transferred to CHLA after IVGG X 2 and pulsed steroids X 2 for an angiogram
Fever/Heart Rate in “resistant” patients

Of the 27 patients who had persistent/recurrent fever, 6 were discharged home when their fever normalized but had recurrence at home.

5 out of 6 were still tachycardic at the time of discharge.
Resting tachycardia is well described in KD and has been attributed to myocarditis in the early stage of the illness.

Tachycardia should be viewed as an indicator of myocardial inflammation in KD.

In that respect, it is as valid measure of the activity of the disease as is fever.

In this small convenience sample of KD patients, tachycardia was more prevalent in patients who had persistent disease following IVIG than was fever.

Several patients were discharged home when afebrile but still tachycardic only to return with relapsed fever.

Patients in the acute phase of KD are maintained on high dose aspirin that may decrease temperature masking ongoing inflammation.
Other Immune Modulators

Infliximab (Remicade®):
One case report of a 3 y/o treatment failure with giant coronary artery aneurysms who responded to one dose.

J Rheumatol 2004;31:808

Case series of 17 patients who failed standard Rx responded to infliximab 5 mg/kg.

J Pediatr 2005;146:662
196 patients randomized:

98 IVIG+asa+infliximab vs. 98 IVIG+asa+placebo

- Primary outcome: Rx resistance*
- Secondary outcomes: Z scores of proximal LAD & proximal RCA at 2 & 5 weeks, ESR, CRP, other labs

*Rx Resistance=Temp ≥ 38.0º between 36 hours and 7 days after end of IVIG therapy

Result of primary outcome:

Infliximab resistance 11 vs. placebo 11 (p=0.81)
<table>
<thead>
<tr>
<th>Outcome</th>
<th>Infliximab</th>
<th>Placebo</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Proximal LAD</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Change at week 2</td>
<td>-0.61</td>
<td>-0.31</td>
<td>0.045</td>
</tr>
<tr>
<td>Change at week 5</td>
<td>-0.8</td>
<td>-0.51</td>
<td>0.074</td>
</tr>
<tr>
<td>Proximal RCA</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Change at week 2</td>
<td>-0.29</td>
<td>-0.22</td>
<td>0.59</td>
</tr>
<tr>
<td>Change at week 5</td>
<td>-0.53</td>
<td>-0.29</td>
<td>0.14</td>
</tr>
<tr>
<td>CRP @ 24 hours</td>
<td>-628.58</td>
<td>-342.86</td>
<td>0.0003</td>
</tr>
<tr>
<td>ESR @ week 2</td>
<td>-23</td>
<td>-14</td>
<td>0.009</td>
</tr>
<tr>
<td>Other labs</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
</tr>
</tbody>
</table>
Other Possible Therapies

- Etanercept
- Anakinra
- Cyclosporin
- Steroids
- IL2 inhibitors
- Cytotoxic agents
Genes Involved in susceptibility to KD in Independent cohorts

<table>
<thead>
<tr>
<th>Gene</th>
<th>Chromosome Location</th>
<th>Genetic Methods</th>
<th>Validation Populations</th>
<th>Potential Significance</th>
<th>Reference and Year</th>
</tr>
</thead>
<tbody>
<tr>
<td>FCGR2A</td>
<td>1q23</td>
<td>GWAS</td>
<td>Europe, Taiwan, Korea, Chinese (Han)</td>
<td>Low-affinity receptor for Fc fragment of IgG</td>
<td>Khor et al 2011</td>
</tr>
<tr>
<td>CASP3</td>
<td>4q34-35</td>
<td>Linkage analysis</td>
<td>Japan, Euro-USA Taiwan, Korea, China</td>
<td>Apoptosis in immune cells and cardiomyocytes</td>
<td>Onouchi et al 2010</td>
</tr>
<tr>
<td>HLA class II</td>
<td>6p21.3</td>
<td>GWAS</td>
<td>Japan, Korea, Taiwan</td>
<td>Activation marker for immune cells</td>
<td>Onouchi et al 2012</td>
</tr>
<tr>
<td>BLK</td>
<td>8p23-22</td>
<td>GWAS</td>
<td>Japan, Korea, Taiwan</td>
<td>B-cell receptor signal transduction</td>
<td>Onouchi et al 2012</td>
</tr>
<tr>
<td>IPTKC</td>
<td>19q13.2</td>
<td>Linkage analysis</td>
<td>Japan, Korea, China, USA Europe</td>
<td>Neg. regulator of calcineurin NFAT pathway</td>
<td>Onouchi et al 2008</td>
</tr>
<tr>
<td>CD40</td>
<td>20q12-13.2</td>
<td>GWAS</td>
<td>Japan, Korea</td>
<td>Incr. translation</td>
<td>Onouchi et al 2012</td>
</tr>
</tbody>
</table>
Update on Kawasaki Disease

Genetics:
- Response to IVIG and coronary outcomes (Gene expression studies)
  - FCy3B
  - sTNFR-1 and sTNFR-2
  - G-CSF
  - IL-6
  - PRV-1
Implication of Kawasaki disease

- KD is the most common cause of acquired heart disease in children in the developed world.
Cardiovascular findings in acute phase Kawasaki disease

- **Physical findings c/w myocarditis**: tachycardia disproportionate to body temperature, gallop sounds, hypotension, rarely shock.

- **Echo findings**: mild LV dilatation, decrease in LV systolic and diastolic function, pericardial effusion, Doppler evidence of mitral and/or aortic insufficiency (usually mild)

- **Coronary dilatation 30-50%**: starting about Day 9~10.
Giant coronary artery aneurysm = > 8 mm internal diameter of CA

Echocardiogram

Angiogram
Coronary Artery Complications
Kurume, Japan 1973-1993


Acute Kawasaki disease
N= 594

- Normal coronary artery
  N=448 (75.4%)

- Coronary aneurysm
  N=146 (24.6%)

  - Regression
    N=72 (12%)  
    (49% of aneurysms)

  - Persistent
    N=60 (10.1%)  
    (41% of aneurysms)

  - Developed stenosis
    N=14 (2%)  
    (10% of aneurysms)
3-month-old girl died of myocardial infarction 3 weeks after the onset of KD

*Arrow:* aneurysmal left coronary artery filled with clot
High Risk Group

- Patients whose diagnosis and IVIG therapy was delayed beyond Day 10.
- Patients under 1 year of age at onset.
- Patients who failed to respond to initial IVIG treatment.
- Patients with recurrent Kawasaki disease
- Male gender
- Patients with prolonged fever, high CRP, low albumin, anemia
Biomarkers

- BNP and NT-proBNP may predict coronary artery aneurysms and/or IVIG failure. *Pediatr Cardiol* 2009;30:810-817
- Periostin, a secreted matricellular protein, may indicate arterial damage from the etiologic agent and/or host response. *PIDJ in press*

Currently there are no biological markers that with sufficient sensitivity or specificity to establish a diagnosis of KD.
Retrospective cohort study (NCKP): 546 KD patients vs. 2218 matched controls

- Current age ≥ 15 yrs
- Age ≤ 5 yrs at diagnosis
- 79% received IVIG

KD identified by database N=671

- Unconfirmed KD N=66
- Confirmed KD N=605

Follow-up time
- F/U time < 1yr N=59
- F/U time ≥ 1yr N=546
Coronary artery outcomes \( (N=546) \)

- No lesions: 436 (79.9%)
- Transient ectasia: 19 (3.5%)
- Persistent ectasia: 3 (0.5%)
- Transient aneurysm: 23 (4.2%)
- Persistent aneurysm: 25 (4.6%)
- Unknown: 40 (7.3%)
### Long term cardiovascular outcomes

**Pediatrics 2014;133:e305-e312**

<table>
<thead>
<tr>
<th>Age of onset</th>
<th>Age of event</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>2 y/o male aspirin &amp; IVIG w/o CAA</td>
<td>5 y/o</td>
<td>Died of coronary disease</td>
</tr>
<tr>
<td>5 y/o male aspirin, IVIG and persantine</td>
<td>11 y/o</td>
<td>Sudden death w/o thrombosis or AML#</td>
</tr>
<tr>
<td>13 y/o male treated w steroids and antibiotics</td>
<td>26 y/o</td>
<td>ACS* due to CAA thrombosis; CABG**</td>
</tr>
<tr>
<td>4 y/o male with persistent CAA</td>
<td>32 y/o</td>
<td>Developed ACS</td>
</tr>
<tr>
<td>KD as a child-age?</td>
<td>19 y/o</td>
<td>Developed ACS</td>
</tr>
</tbody>
</table>

*ACS= acute coronary syndrome
#AMI=acute myocardial infarction
**CABG=coronary artery bypass graft*
Progression of coronary aneurysms to stenotic lesions.

Regression of A Large Fusiform LCA Aneurysm

CHLA: 186 KD patients seen and 34 had CAA; 1 died, 3 were LTF/U and 3 were false +. 18/27 remaining patients (66.7%) showed regression. Circulation 1987;75:387-94
Natural history of coronary artery changes and anticoagulant therapies

Total group

- Normal coronary arteries (60%)
  - Low-dose aspirin
    - For 6-8 weeks

- Transient ectasia (30%)
  - Low-dose aspirin
    - Until regression

- Small-medium aneurysms [< 6 mm] (5-10%)
  - Low-dose aspirin
    - For long duration
    - (Check for resistance)

- Large aneurysms [≥ 6 mm] (<2%)
  - LMWH → Warfarin
    - And low-dose aspirin
    - (Check for resistance)

- Giant aneurysms (> 8 mm) [< 1%]
Imaging studies (why? and how often?)

- Myocardial perfusion imaging under resting and stress
- MRI or multi-detector CT scan
- Cardiac cath and angio (associated with interventions)
- Intravascular ultrasound (IVUS)
Angio/echo Silent Lesion - Intravascular ultrasound
Coronary artery interventions and surgery

- Catheter intervention (Japanese data)
  - Balloon dilatation
- Problems with calcific lesions
  - Rotablation
- Coronary artery bypass graft (CABG) with internal thoracic artery
  - Dr. Kitamura’s data: Close to 90% 20-year graft survival
Rotational Artherectomy (Rotablation) of calcified LAD coronary artery
Sato K et al Cardiov Revasc Med 2014

LAD coronary artery: A-C various views; D Fluoroscopy of giant CAA
Rotational Artherectomy (Rotablation) of calcified LAD coronary artery
Sato K et al Cardiov Revasc Med 2014
Long Term Management

- Importance of effective anticoagulation; increasing recognition of the role of thrombosis in long-term outcomes
  - Caution regarding reduced bone mineral density in those on chronic warfarin
  - Possible need to monitor response to antiplatelet therapy
- Stenosis, obstructions and systemic vascular disease-who is at risk
- Importance of transition to adult care
Long Term Management

- The emergence of a growing population of adults who have had KD during childhood
  - Retrospective diagnosis
  - Importance of engaging adult cardiologists
  - Who needs follow-up?
  - Who is at risk for what?
  - Monitoring serum lipids?
  - SEE Circulation article from 2017 for NEW recommendations for long term management
Thank you - Questions?

Cowasocky

- 146 patients (24.6%) had CAA
- Followed by sequential angiography
- 49.3% showed complete resolution 6-18 months later and 54.8% showed regression
- Overall, 28 patients (4.7% of all the KD patients) showed progression to CA stenosis
- Giant CAA were seen in 26 patients (4.4%)
  - 20 boys & 6 girls
  - 12/16 progressed to stenosis or complete obstruction; 8/12 suffered AMI and 4 died
- None of the patients with giant CAA showed regression