KAWASAKI DISEASE
New Paradigms
Michael A. Portman
KAWSASHIKI DISEASE

- Acute systemic vasculitis in children
- Predilection for the coronary arteries with aneurysm formation → clot, stenosis
- Cause unknown
- 7000 cases per year in the U.S.
- 400 cases with severe heart disease per year
IN Seattle Children’s KD Patient Series

7% of patients develop coronary artery aneurysms despite appropriate treatment

Patel AS, Bruce M, Harrington W and Portman MA

*Open Heart.* 2015;2:e000206
INCIDENCE IN JAPAN IS NOW 250 TO 300 PER 100,000 CHILDREN

INCIDENCE IN U.S IS ~ 20/100,000

BUT 70% OF KD PATIENTS ADMITTED TO SCH ARE NOT ASIAN
Diagnosed by Clinical Criteria

- Fever for > 5 days (Onset of Fever)
- At least 4/5 of the following:
  - Nonpurulent conjunctivitis
  - Cervical lymphadenopathy > 1.5cm (least common)
  - Erythematous rash
  - Mucositis – “strawberry tongue”
  - Extremity changes – swelling/peeling
- Don’t have to all be present at the same time!
- +/- Other diagnoses excluded
FORGET AGE QUALIFIER

- KD INCIDENCE RATE IS HIGHER IN CHILDREN YOUNGER THAN 5 YRS
- BUT STILL RETAIN HIGH SUSPICION FOR OLDER CHILDREN
- KD OFTEN MISSED OR DIAGNOSED LATE IN OLDER CHILDREN BECAUSE OF MISCONCEPTION
Kawasaki Disease
Conjunctivitis – NonPurulent, Oral Changes
CONJUNCTIVITIS

BULBAR  NO EXUDATE
ORAL CHANGES
Kawasaki Disease: Rash

- Polymorphous
  - NOT vesicular
- Typical Location
  - Truncal
  - Groin accentuation
RASH
KD-Swollen or Red Peripheral Extremities
RED PALMS AND SOLES
LYMPHADENOPATHY

- Anterior Cervical Lymph Node > 1.5 cm

Lymphadenitis with 4 days or more fever is KD until proven otherwise especially in infants

Ultrasound and/or CT are not helpful
## Non-specific findings in KD

### Frequency of Symptoms over Time

<table>
<thead>
<tr>
<th>Associated Findings and Events</th>
<th>At any Time During the Study Period</th>
<th>Within the 10 Days Prior to Diagnosis</th>
<th>During Hospitalization</th>
<th>Week 1 Follow-Up</th>
<th>Week 5 Follow-Up</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Number of Subjects</strong></td>
<td>198</td>
<td>198</td>
<td>198</td>
<td>198</td>
<td>198</td>
</tr>
<tr>
<td>Irritability</td>
<td>118 (60)</td>
<td>98 (50)</td>
<td>30 (15)</td>
<td>35 (18)</td>
<td>12 (6)</td>
</tr>
<tr>
<td>Vomiting</td>
<td>104 (53)</td>
<td>88 (44)</td>
<td>12 (6)</td>
<td>16 (8)</td>
<td>4 (2)</td>
</tr>
<tr>
<td>Cough</td>
<td>77 (39)</td>
<td>55 (28)</td>
<td>13 (7)</td>
<td>17 (9)</td>
<td>17 (9)</td>
</tr>
<tr>
<td>Decreased food/fluid intake</td>
<td>76 (38)</td>
<td>73 (37)</td>
<td>12 (6)</td>
<td>9 (5)</td>
<td>6 (3)</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>66 (33)</td>
<td>52 (26)</td>
<td>13 (7)</td>
<td>11 (6)</td>
<td>3 (2)</td>
</tr>
<tr>
<td>Rhinorrhea</td>
<td>63 (32)</td>
<td>37 (19)</td>
<td>6 (3)</td>
<td>15 (8)</td>
<td>23 (12)</td>
</tr>
<tr>
<td>Weakness</td>
<td>48 (24)</td>
<td>37 (19)</td>
<td>5 (3)</td>
<td>10 (5)</td>
<td>4 (2)</td>
</tr>
<tr>
<td>Abdominal pain</td>
<td>42 (21)</td>
<td>35 (18)</td>
<td>8 (4)</td>
<td>8 (4)</td>
<td>1 (1)</td>
</tr>
<tr>
<td>Joint pain</td>
<td>47 (24)</td>
<td>29 (15)</td>
<td>6 (3)</td>
<td>19 (10)</td>
<td>14 (7)</td>
</tr>
<tr>
<td>Diarrhea, vomiting or abdominal pain</td>
<td>140 (71)</td>
<td>120 (61)</td>
<td>31 (16)</td>
<td>30 (15)</td>
<td>8 (4)</td>
</tr>
<tr>
<td>Cough or rhinorrhea</td>
<td>99 (50)</td>
<td>69 (35)</td>
<td>16 (8)</td>
<td>22 (11)</td>
<td>30 (15)</td>
</tr>
</tbody>
</table>

*Source: J Pediatr. 2009 Apr; 154(4): 592–595.e2.*
GENERAL THEORY: AN ENVIRONMENTAL STIMULUS OR INFECTION TRIGGERS AN AUTO-INFLAMMATORY RESPONSE (KD)

PRESENCE OF A CO-EXISTING RESPIRATORY INFECTION OR POSITIVE VIRAL TEST OR + STREP DOES NOT RULE OUT KD
When to suspect incomplete KD?

- Child: $\geq 7$d fever + 2-3 criteria
- Infants $\leq 6$mo: 7d fever, lab evidence of inflammation and no other explanation of febrile illness → even if NO criteria
Incomplete KD (not atypical)

Supplemental lab data
- Elevated ALT
- Albumin <=3.0
- WBC >15k
- Anemia for age
- Plts>450k (after 7d)
- UA > 10 WBCs
KAWSASAKI SHOCK SYNDROME

- Subgroup of patients present with blood pressure lability and fever

- Require ICU - pressors to maintain BP

- Often only 1 or 2 criteria in addition to fever

- Usually older than 5 years

- Echo often ordered for cardiac function not for coronary dilatation
11-year-old young lady who was previously healthy.
6-day history of fever, neck and throat pain
right-sided cervical adenitis
She received a dose of ceftriaxone at her PMD's office 4 days previous
Overnight developed some further vomiting and diarrhea and conjunctival injection.
In the ED, hypotensive and received multiple fluid boluses.
Myalgias and fatigue, although currently she is not complaining of significant pain.

LAB, Hgb 10.6, WBC 30,000, UA sterile pyuria, CRP 24

IMPRESSION:
1. Systemic inflammatory response syndrome.
2. Hypotension.
3. Cervical lymphadenitis.
4. Hyponatremia and hyponatremic dehydration.

TREATMENT
Vasoactive for BP management
Antibiotics - NO Change

Two days later Echocardiogram
KD Treatment: Initial phase

- Intravenous Immune Globulin
  - Effective as a single, high dose (2 g/kg IV)
  - If given within 10 days of illness
  - Tx > 10d if persistent fever, aneurysms, or systemic inflammation
  - With IVIG, ~20% coronary artery inflammation and dilation ~8% aneurysms with ~4% “giant”
Aspirin

- Anti-inflammatory (moderate dose) and anti-platelet effects (low dose)
- No good data that ASA prevents CA dz
- ASA 30 to 50 mg/kg/d divided Q6h until afebrile for at least 48 hours; ? 14 days
- Low dose 3-5 mg/kg/d (max 81mg) until at least 6 wk cardio visit or normalization of coronary arteries

**NO IBUPROFEN – INTERFERES WITH ASPIRIN ANTIPLATELET ACTION**
DOSE - 2 GM/KG OVER 12 HOURS (Appropriate Rate Sheet)

DO NOT GIVE TOO FAST --- HYPOTENSION

Protocols in 1988-1992 over 4 days

Do Not Delay

Accurately record time of initiation and COMPLETION OF INFUSION
KD Parent and Child Stress

- Usually 5 to 7 days fever at home
- Very irritable Child
- Many sleepless nights
- Multiple physician and prolonged ER visits
- Difficult diagnosis, often trial of antibiotics
- Mysterious disease with uncertain outcome
- Potential Heart Disease
- IVIG --- another sleepless night with constant vital sign assessments
- Expectation for prompt therapy
Health Related Quality of Life Scores and Hospitalization

A. Pneumonia – Kawasaki Disease Matched Cohort

B. Cancer – Kawasaki Disease Matched Cohort

Kourtidou et al, Journal of Pediatrics, in press
BEHAVIOR WILL NOT RETURN TO NORMAL FOR 4 TO 6 WEEKS
SLEEPING IS A MAJOR PROBLEM
EXPECT CONTINUED IRRITABILITY
HANDS, FEET WILL HAVE SKIN PEELING
SKIN IS SENSITIVE FOR EXTENDED TIME PERIOD; EXPECT RASHES AND ECZEMA
HAVE THERMOMETER AT HOME AND TAKE TEMP IF YOU FEEL CHILD IS HOT

CALL PEDIATRICIAN OR CARDIOLOGIST FOR TEMP GREATER THAN 100.4°F

YOU MUST FOLLOW UP WITH CARDIOLOGIST WITHIN 2 WEEKS AFTER DISCHARGE EVEN IF YOUR CHILD APPEARS WELL

A NORMAL INITIAL ECHO DOES NOT GUARANTEE NO CORONARY INVOLVEMENT LATER
Recommended by AAP

NO LIVE IMMUNIZATIONS FOR 11 MONTH PERIOD AFTER IVIG INFUSION (MMR, VARICELLA)

WHY - NOT DANGEROUS EXCEPT IMMUNIZATION MAY NOT WORK

MAY GET INFLUENZA VACCINE, THOUGH NOT AT DISCHARGE
ASPIRIN AS ANTI-PLATELET

MAKE SURE DOSE FORMULATION IS REASONABLE, NO TINY FRACTIONS OF A PILL

- ASPIRIN IS THE MOST IMPORTANT TREATMENT FOR YOU CHILD. ASPIRIN PREVENTS CLOTS IN ARTERIES
- DO NOT STOP ASPIRIN UNTIL CARDIOLOGIST TELLS YOU
- IF YOU RUN OUT, YOU DO NOT NEED PRESCRIPTION, OVER THE COUNTER BABY ASA IS THE SAME
- DO NOT USE IBUPROFEN. IT INTERFERES WITH ASPIRIN PREVENTING CLOTS
KD Treatment Failure

Persistent or recurrent fever > 36 hours after COMPLETING IVIG

A single spike after 36 hours does not equate with persistent or recurrent

Substantially HIGHER RISK OF CAD
Coronary Aneurysms
Clot Formation or Scarring
REFRACTORY IVIG

- DOCUMENT FEVER AFTER 36 HOURS
- SECOND ROUND IVIG OR INFLIXIMAB
- NEITHER IS ABSOLUTELY PROVEN EFFECTIVE; NO PLACEBO CONTROLLED TRIAL
- WHICH IS BETTER?

KIDCARE STUDY
LIFE WITH SEVERE KD

- LIFE LONG HEART DISEASE
- RESTRICTED ACTIVITY
- MULTIPLE CARDIAC PROCEDURES
- ANTI-COAGULATION
- EARLY DEATH
CHALLENGES

- Understanding and defining risk factors
- Diagnosis: Need for a rapid simple test
- Treatment: IVIG often ineffective
- Prevention or healing of coronary artery aneurysm
- Anti-coagulation therapies are not optimal for children: Lovenox (2 daily injections); Warfarin provides unstable anti-coagulation
GENETIC - KD BANKING – 800 PATIENTS AND 450 TRIOS (BOTH PARENTS INCLUDED). We have defined some genes which influence susceptibility and treatment response but these do not fully explain differences in incidence among races so far

Role of Activating FcγR Gene Polymorphisms in Kawasaki Disease Susceptibility and Intravenous Immunoglobulin Response
Sadeep Shrestha, PhD; Howard Wiener, PhD; Aditi Shendre, MPH; Richard A. Kaslow, MD; Jianming Wu, PhD; Aaron Olson, MD; Neil E. Bowles, MD; Hitendra Patel, MD; Jeffrey C. Edberg, PhD; Michael A. Portman, MD


ENVIRONMENTAL - Is it all genetics responsible for higher Asian incidence?
• 2008 – Committee on Nutrition issues statement concerning isoflavones in soy formula

• Limited indication for use of soy formula in infants

• Estrogen-like compounds may affect sexual development
Soy and Kawasaki disease
Kawasaki disease and soy: potential role for isoflavone interaction with Fcγ receptors

Michael A. Portman¹,²

Kawasaki disease (KD) is a diffuse vasculitis occurring in children and showing predilection for the coronary arteries. The etiology remains unknown, although some risk factors for susceptibility have been defined. Asian ethnicity is a primary risk factor. Several theories have circulated regarding the differences in KD ethnic incidence. Those theories implicating genetic differences among populations as the cause for this discrepancy have dominated and are areas of active investigation by multiple research groups. Differences in diet between Asians and Westerners are touted as reasons for certain ethnic-related discrepancies in susceptibility to cardiovascular disease and cancer in adults. Surprisingly, these cultural dietary differences have not been previously considered as the source of the discrepancy in KD incidence among these ethnic populations. Recent data from genetic studies have highlighted the role of specific immunogenetic variations in the susceptibility to KD. Unique loci, such as the leukocyte antigen and CD40 loci, which might account for some but not all of the ethnic diversity in KD incidence (6). Although population density and climatic factors have been associated with KD outbreaks, these do not explain ethnic differences in KD incidence that persist throughout the world (3). Ethnic and cultural disparities in diet have not been previously considered as potential causes for the variation in KD incidence. Soy consumption in Asian cultures is substantially higher than that in the United States and Europe. Observational studies suggest that the Asian diet, which includes greater amounts of soy protein than do typical diets of non-Asian persons in the United States and Europe, may contribute to lower risk of cardiovascular disease and several cancers. These observations prompted the US Food and Drug Administration in 1999 to approve a health claim stating that diets that are low in saturated fat and high...
Scientific Basis of the Theory: Tyrosine Protein Kinase

Cell activation
(phagocytosis, cytokine release)
Epidemiology


Holman, Hawaii Med J, 2010
Original Research

Soy isoflavone intake is associated with risk of Kawasaki disease

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d Department of Epidemiology, University of Washington, Seattle, WA, USA
Epidemiology

Dietary Survey for Soy and Isoflavone Intake

KD patients and mothers (n ~ 200)
Maternal during pregnancy and nursing

Age matched Controls (n ~ 200)
Isoflavone Distribution by Ethnicity

Kawasaki Disease status among Caucasians

Kawasaki Disease status among Asians
Odds Ratios for Kawasaki Disease among Children

- **Reference**
- **Quantile 2 ≤ 16.6**: OR = 1.14 (0.63, 2.05)
- **Quantile 3 > 16.6**: OR = 2.23 (1.32, 3.75)
- **Quantile 2 ≤ 6.5**: OR = 0.97 (0.53, 1.75)
- **Quantile 3 > 6.5**: OR = 2.52 (1.49, 4.23)
Etanercept (Enbrel)
Etanercept (Enbrel)

- Multi-Center Clinical Trial
- Enrollment Complete (200) Placebo Controlled Double-Blinded Randomized
- Results to be presented next week at the Scientific Sessions of the American Heart Association
Etanercept (Enbrel)

PREVIEW

• IVIG RESPONSE RATE 90% IN ASIANS AND HISPANICS
• BUT 78% IN WHITE NON-HISPANICS
• AND 50% IN AFRICAN AMERICANS

ETANERCEPT REDUCED REFRACTORY RATE IN POPULATIONS LESS THAN RESPONSIVE TO IVIG
Etanercept Investigators
N.Chouetier, NYC; K Sexson, Houston; N Dahdah, Montreal; A Olson, Seattle

N.Chouetier, NYC
K Sexson, Houston
KAWASAKI DISEASE
INTERNATIONAL KAWASAKI DISEASE SYMPOSIUM
KYOTO, FEBRUARY 2012
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