KAWASAKI DISEASE: CLINICAL PRESENTATION AND DIAGNOSIS

Preeti Jaggi, M.D
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• I do not intend to discuss an unapproved/investigative use of a commercial product/device in my presentation.
PROBLEMS WITH DIAGNOSING KD

- Transient signs and symptoms
- Mimicking features from other diseases
- Sometimes subjective signs
- Incomplete KD: 5 days of fever with 2-3 clinical features
  - Infants <6 months: <2-3 KD-like features
  - Echocardiography should be considered with fever of ≥7 days duration, systemic inflammation, and no other explanation for the febrile illness” ¹

¹ Newburger, Circulation, 2004 AHA Guidelines
OBJECTIVES

- Identify specific factors to help distinguish KD from other mimicking illnesses
  - KD/Viral detection, Adenovirus
  - KD vs. Lymphadenitis/Deep neck infection
  - KD vs. Systemic Onset JIA
  - KD-shock vs. TSS
KAWASAKI DISEASE BY AGE

n=1374
n=1374
EVALUATION SUSPECTED INCOMPLETE KD

Fever ≥ 5d and 2-3 clinical criteria

Assess clinical characteristics

Consistent with KD

Assess Lab Tests

CRP < 3 mg/dl and ESR < 40

Follow Daily

Inconsistent with KD

KD unlikely

CRP ≥ 3 mg/dl and/or ESR ≥ 40

< 3 Supp Labs

ECHO

≥ 3 Supp Labs

Treat & ECHO

Fever
EVALUATION OF 2004 AHA INCOMPLETE KD ALGORITHM

- KD patients with coronary abnormalities at 4 US centers from 1981 to 2006 (n=195).
- 137 patients met classic KD definition
- 53 additional patients had incomplete KD

Number of clinical criteria present at the time of initial evaluation for 195 patients with KD and CAAs.


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ADENOVIRUS BY PCR: Positive
RHINOVIRUS RNA BY PCR: Positive
METAPNEUMOVIRUS PCR: Positive

NP VIRAL DETECTION IN KAWASAKI DISEASE

<table>
<thead>
<tr>
<th>Location</th>
<th>Year</th>
<th>Method</th>
<th>n</th>
<th>Rate</th>
<th>Viruses</th>
</tr>
</thead>
<tbody>
<tr>
<td>Jordan-Villegas, TX</td>
<td>2008</td>
<td>DFA/VC</td>
<td>251</td>
<td>8.8%</td>
<td>HRV, AdV, Flu A or B, PIV</td>
</tr>
<tr>
<td>Shike, CA</td>
<td>2005</td>
<td>VC; subset PCR</td>
<td>70</td>
<td>5.7%</td>
<td>RSV, PIV, AdV</td>
</tr>
<tr>
<td>Leuin, CA</td>
<td>2013</td>
<td>DFA</td>
<td>59</td>
<td>10.2%</td>
<td>AdV, PIV, RSV</td>
</tr>
<tr>
<td>Location</td>
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<td>n</td>
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<td>Viruses</td>
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<tr>
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<td>2013</td>
<td>DFA</td>
<td>59</td>
<td>10.2%</td>
<td>AdV, PIV, RSV</td>
</tr>
<tr>
<td>Chang, Taiwan</td>
<td>2014</td>
<td>VC/PCR</td>
<td>226</td>
<td>7.5%</td>
<td>EV(n=4/40), AdV(n=7/18), Flu A(n=2/4), HRV</td>
</tr>
<tr>
<td>Year</td>
<td>Method</td>
<td>n</td>
<td>Rate</td>
<td>Viruses</td>
<td></td>
</tr>
<tr>
<td>-------------</td>
<td>------------</td>
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<td>-------</td>
<td>----------------------------------------------</td>
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<tr>
<td>Jordan-Villegas, TX</td>
<td>2008</td>
<td>DFA/VC</td>
<td>251</td>
<td>8.8%</td>
<td>HRV, HAdV, Flu A or B, PIV</td>
</tr>
<tr>
<td>Leuin, CA</td>
<td>2013</td>
<td>DFA</td>
<td>59</td>
<td>10.2%</td>
<td>HAdV, PIV, RSV</td>
</tr>
<tr>
<td>Chang Taiwan</td>
<td>2014</td>
<td>VC/PCR</td>
<td>226</td>
<td>7.5% 52.7%</td>
<td>EV(n=4/40), HAdV(n=7/18), Flu A(n=2/4), HRV</td>
</tr>
<tr>
<td>Kim, Korea</td>
<td>2012</td>
<td>PCR</td>
<td>55</td>
<td>32.7%</td>
<td>HRV, HAdV, Coronavirus</td>
</tr>
<tr>
<td>Dominguez CO</td>
<td>2015</td>
<td>Multiplex PCR</td>
<td>192</td>
<td>41.9%</td>
<td>HRV, HAdV, RSV</td>
</tr>
</tbody>
</table>
ADENOVIRUS

- Peak age of incidence of disease is 6 months-5 years
- Conjunctivitis (Follicular or Keratoconjunctivitis)
- Prolonged Fever
- Fever without focus
- Leukocytosis
- High inflammatory markers
- Can be found incidentally
  - 0.6% of healthy children by culture and up to 11% by PCR

<table>
<thead>
<tr>
<th>Year</th>
<th>Method</th>
<th>n</th>
<th>Adenovirus</th>
</tr>
</thead>
<tbody>
<tr>
<td>Shike, CA</td>
<td>2005 Viral culture; PCR</td>
<td>70</td>
<td>2.8%, 1 additional patient by PCR</td>
</tr>
<tr>
<td>J-Villegas, TX</td>
<td>2008 DFA/VC</td>
<td>251</td>
<td>2.4%</td>
</tr>
<tr>
<td>Kim Korea</td>
<td>2012 Multiplex PCR (HBoV/CV)</td>
<td>55</td>
<td>7.3%</td>
</tr>
<tr>
<td>Leuin, CA</td>
<td>2013 DFA</td>
<td>59</td>
<td>3.4%</td>
</tr>
<tr>
<td>Jaggi, OH</td>
<td>2013 PCR</td>
<td>51</td>
<td>8.8%</td>
</tr>
<tr>
<td>Dominguez, CO</td>
<td>2015 Multiplex PCR</td>
<td>192</td>
<td>4.7%</td>
</tr>
</tbody>
</table>
**PHARYNGOCONJUNCTIVAL FEVER**

**EPIDEMIOLOGICAL STUDIES OF A RECENTLY RECOGNIZED DISEASE ENTITY**

*Joseph A. Bell, M.D., Wallace P. Rowe, M.D., Joseph I. Engler, M.D., Robert H. Parrott, M.D.*

- Fever: 103 or 104° F, lasted from 1 to 10 days (median 5-6 d)

- The sore throat was generally quite mild and was described more as a discomfort or scratchiness. Examination generally showed nothing striking except that the posterior oral pharynx was frequently injected and prominently studded with glary lymph follicles.

- The conjunctivitis was of the mild follicular type, frequently monocular.

- Nontender, preauricular lymphadenopathy was occasionally noted.

- A purulent exudate was almost nonexistent, but a scanty, serous exudate, with some slight matting together of the eyelids and excessive lacrimation, was not uncommon.
Viral Testing in Work-up for KD

1. Never get or ignore viral testing in work-up of KD.
   *Would this lead to over-treatment for KD in some patients?

2. Selective viral testing
   *Do we have a choice?

3. Can we be better stewards of intravenous immunoglobulin in the absence of a definitive diagnostic test for KD?
ADENOVIRUS VS. KD SCLERAL INJECTION

- Often begins unilaterally
- Tearing or pus discharge
- Scleral hemorrhage/Cornea
- Blurry vision, foreign body sensation
- Photophobia uncommon
- Preauricular lymph node

- Bilateral
- Non-exudative
- Bulbar >tarsal
- Spares the limbus
- Iridocyclitis or anterior uveitis
ADENOVIRUS DISEASE WITH SOME KD-LIKE SYMPTOMS (N=62)

- 89% had less than 4 clinical features of KD
- Common KD-like features: 73% conjunctivitis, 65% with mucosal, 52% rash
- Less common KD-like features: 15% with extremity changes, 13% unilateral node
- Median duration of fever at time of evaluation: 5 days

ALL SPECIES BUT ESPECIALLY SPECIES C CAN BE INCIDENTALLY DETECTED

- Pediatric tonsil or adenoid tissue (n=203)
- The presence of viral DNA peaked at 4 years of age and declined thereafter
- Infectious virus was detected infrequently
- Species C Adenoviruses can establish latent infections in mucosal lymphocytes

Garnett, J Virology 2009
<table>
<thead>
<tr>
<th>Adenovirus + from NP</th>
<th>Complete KD n=10</th>
<th>Adenovirus Disease n=51</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>ESR: ≥40mm/h</td>
<td>7 (70%)</td>
<td>29 (57%)</td>
<td>NS</td>
</tr>
<tr>
<td>CRP (mg/dL), Median, IQR</td>
<td>8.1(4.4-20)</td>
<td>3.6 (2.1-5.7)</td>
<td>0.038</td>
</tr>
<tr>
<td>Albumin: ≤3.0g/dl</td>
<td>1 (10%)</td>
<td>3 (6%)</td>
<td>0.026</td>
</tr>
<tr>
<td>ALT: &gt;45 IU/L</td>
<td>7 (70%)</td>
<td>1 (2%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Pyuria: &gt;10/HPF</td>
<td>6 (60%)</td>
<td>1 (2%)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

Song, IDSA 2015 and Jaggi, CID 2013
## COMPLETE KD VERSUS ADENOVIRUS DISEASE

<table>
<thead>
<tr>
<th>Virologic Characteristics</th>
<th>Complete KD n=10</th>
<th>KD-like Acute HAdV Disease n=51</th>
<th>( p ) value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adenovirus Species</td>
<td>5C (63%) 2B (25%)</td>
<td>8C (25%) 21B (66%)</td>
<td>0.030</td>
</tr>
<tr>
<td>Viral Burden (PCR threshold cycle)</td>
<td>36.8 (25.2-38.5)</td>
<td>25.3 (21.9-29.4)</td>
<td>0.019</td>
</tr>
<tr>
<td>Culture Positive from NP</td>
<td>2 of 8 (25%)</td>
<td>29 of 32 (91%)</td>
<td>0.005</td>
</tr>
</tbody>
</table>
ADENOVIRUS VS. KAWASAKI DISEASE

- If child appears to have classic, complete KD features with detectable Adenovirus, incidental Adenovirus shedding may be occurring.
- For those with an incomplete presentation and who have detectable Adenovirus, species identification and viral burden MAY be helpful.
NECK SWELLING PREDOMINANT KD

ACUTE BACTERIAL LYMPHADENITIS
RETROPHARYNGEAL INFLAMMATION
## KD VS. PURULENT NECK INFECTIONS

<table>
<thead>
<tr>
<th></th>
<th>Acute bacterial lymphadenitis</th>
<th>Retropharyngeal Phlegmon</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Epidemiology</strong></td>
<td>2-4 years</td>
<td>1-4 years</td>
</tr>
<tr>
<td><strong>Signs/symptoms</strong></td>
<td>Superficial erythema, warmth</td>
<td>Torticollis, drooling</td>
</tr>
<tr>
<td><strong>Fever</strong></td>
<td>Yes</td>
<td>Yes</td>
</tr>
</tbody>
</table>
NODE DOMINANT PRESENTATION OF KD

- 7 year period, San Diego
- 1st medical encounter with fever and cervical adenopathy **before** the appearance of other clinical criteria.
- 57 children with node-first KD presentation (NFKD), 287 typical KD, and 78 bacterial lymphadenitis
- Compared with typical KD, NFKD were older (4.2 vs. 2.0 years), had more severe inflammation (CRP 13.7 vs. 7.4), similar rates of CAA and resistance to IVIG
<table>
<thead>
<tr>
<th>Parameter</th>
<th>NFKD (n=57)</th>
<th>Bacterial cervical adenitis (n=78)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>WBC $\times 10^9$</td>
<td>16.4 (12.4-18.8)</td>
<td>19.0 (14.0-24.3)</td>
<td>0.01</td>
</tr>
<tr>
<td>ESR mm/h</td>
<td>79 (64-112)</td>
<td>48 (31-69)</td>
<td>0.0001</td>
</tr>
<tr>
<td>C-reactive protein (mg/dL)</td>
<td>13.7 (7.1-21.8)</td>
<td>6.1 (3.1-12.1)</td>
<td>0.0001</td>
</tr>
<tr>
<td>ALT</td>
<td>27 (19-76)</td>
<td>22 (19-24)</td>
<td>0.47</td>
</tr>
</tbody>
</table>
KD Lymph Node(s) Appearance

A  B  C

Copyright ©2002 American Academy of Pediatrics
Cervical Bacterial Lymphadenitis

KD Lymph Node(s) Appearance

KD MIMICKING RETROPHARYNGEAL INFECTION

- 6 yo with a 2-day history of fever and 1 day history of anterior neck pain, torticollis, and odynophagia. 3x 2 cm node on the left, Lateral neck X-ray showed widening of the retropharyngeal space. Ampicillin-sulbactam started
- HD 2, continued with high fever. A contrast CT scan-2.8-cm low-density mass without wall enhancement in the retropharyngeal space. Therapy changed to clindamycin
- HD 3: patient taken to the OR but no fluid aspirated.
- HD 4: Maculopapular rash and non-purulent conjunctivitis appeared and KD was suspected.

RETROPHARYNGEAL EDEMA IN KD

Retropharyngeal edema (arrows) in NFKD

KD VS. SYSTEMIC ONSET JUVENILE ARTHRITIS
SYSTEMIC ONSET JUVENILE IDIOPATHIC ARTHRITIS (SoJIA)

- Arthritis in >1 joint for at least 3 days
- Preceded by or accompanied by fever for at least 2 weeks duration
- At least one other sign/symptom (evanescent rash, generalized lymphadenopathy, HSM, or serositis).
- Delay may occur between the onset of fever and arthritis
- Leukocytosis, anemia, elevated inflammatory markers
- Coronary artery dilation (not aneurysm) has been described in SoJIA

Petty et al., Int League of Associations for Rheumatology classification of JIA. J Rheum 2004; Binstadt, Pediatrics 2005
SOJIA MIMICKING KD

- 5 y/o male with 7 days fever, mucosal change, and rash. C-reactive protein 16.1 mg/dL, ESR 72 mm/h, normocytic anemia, WBC 18,400/mm³, platelet 495,000/mm³
- 2 doses of IVIG for presumed incomplete KD on hospital days 2 and 4, infliximab on hospital day 6
- 1 day after discharge, readmitted for fever, bilateral foot pain. ALT of 211 IU/L, albumin of 2.7 g/dL, ferritin at 8506 ng/mL, hemoglobin 4.6 g/dL. Pain/limitation of hip and ankle range of motion.
- A BM biopsy showed hemophagocytosis. On follow-up, he developed right knee swelling 2 months after diagnosis.
KD FOLLOWED BY SOJIA

- 2 cases
- Reviewed PHIS database for diagnosis code of SoJIA following KD
- Listed at least once 3 months after and within 6 months after KD diagnosis.
- Literature Review

Dong et al., J Pediatrics 2015
SOJIA AFTER TREATMENT FOR PRESUMED KD (N=15): CASE REPORTS

► Median age: 2 years
► Rash was present in all patients
► Conjunctivitis was the least common KD symptom reported (3 of 15 patients).
► Median fever: 13 days at time of presentation.
► 13 of 15 patients were diagnosed as incomplete KD at time of treatment with IVIG

Dong et al., J Pediatrics 2015
## SOJIA VS. KD: PHIS DATABASE

<table>
<thead>
<tr>
<th></th>
<th>Sole KD (n=6720)</th>
<th>Presumed KD/SoJIA (n=10)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (y, IQR)</td>
<td>2 (1-4 IQR)</td>
<td>3 (2-5.75 IQR)</td>
<td>NS</td>
</tr>
<tr>
<td>LOS for initial admission (d)</td>
<td>3 (2-4 IQR)</td>
<td>8 (4-11 IQR)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Repeat IVIG</td>
<td>1437 (21.4%)</td>
<td>5 (50%)</td>
<td>.027</td>
</tr>
<tr>
<td>Corticosteroid</td>
<td>566 (8.4%)</td>
<td>10 (100%)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>TNF-inhibitors</td>
<td>196 (2.9%)</td>
<td>2 (20%)</td>
<td>.024</td>
</tr>
<tr>
<td>Anti-cytokine therapies</td>
<td>2 (0.03%)</td>
<td>1 (10%)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>MAS</td>
<td>17 (0.3%)</td>
<td>3 (30%)</td>
<td>&lt;.001</td>
</tr>
</tbody>
</table>
KAWASAKI DISEASE VS. SOJIA

**KD**
- Relatively shorter duration of illness on presentation
- More likely to have conjunctivitis

**SoJIA**
- Often receive multiple doses of IVIG, other therapy
- Less likely to have conjunctivitis

**Commonalities**
- Incomplete
- Refractory disease
- MAS
- Uveitis
- Coronary dilation
KD SHOCK SYNDROME

- More likely female
- Higher incidence of GI symptoms (abdominal pain)
- More likely to have an incomplete presentation
- More likely to have IVIG resistance
- Higher likelihood of CAL
- Prolonged myocardial dysfunction
- Larger proportions of bands, higher inflammatory markers and lower hemoglobin, platelet counts, coagulopathy

Gamez-Gonzalez 2013, Dominguez 2008, Kanegaye 2009
<table>
<thead>
<tr>
<th></th>
<th>SA-TSS</th>
<th>KD-Shock</th>
</tr>
</thead>
<tbody>
<tr>
<td>Isolation of organism</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>Hypotension</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Rash</td>
<td>Yes (required)</td>
<td>Yes</td>
</tr>
<tr>
<td>GI (vomiting, diarrhea)</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Mucous membrane</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Renal impairment</td>
<td>Cr elevation or pyuria</td>
<td>Pyuria</td>
</tr>
<tr>
<td>Musculoskeletal</td>
<td>Myalgia/CPK elevation</td>
<td>Myalgia</td>
</tr>
<tr>
<td>CNS</td>
<td>Disorientation</td>
<td>Aseptic meningitis</td>
</tr>
<tr>
<td>Thrombocytopenia/Coagulopathy</td>
<td>Yes</td>
<td>Can be seen</td>
</tr>
<tr>
<td>Anemia</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>Elevated ALT/low albumin</td>
<td>Yes/No</td>
<td>Yes/Yes</td>
</tr>
</tbody>
</table>
KD WITH SHOCK VERSUS TOXIC SHOCK SYNDROME

- 10 year retrospective review, China
- TSS (SA): fever, rash, hypotension and three organs involved (GI, mucosal, renal, hepatic, hematologic or CNS)
- TSS: (GAS): isolation of GAS from sterile/non-sterile site, hypotension, and 2 or more systems: renal, hepatic, coagulopathy, ARDS, skin rash, soft tissue necrosis

Lin, PIDJ 2015
<table>
<thead>
<tr>
<th></th>
<th>KD Shock (n=17)</th>
<th>TSS (n=16)</th>
<th>p value</th>
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<tbody>
<tr>
<td>Age (mean months)</td>
<td>36.8 ± 41</td>
<td>113 ± 55</td>
<td>.001</td>
</tr>
<tr>
<td>Total fluid ml/kg</td>
<td>10.9 ± 18</td>
<td>29.7 ± 33</td>
<td>.048</td>
</tr>
<tr>
<td>Max dopamine dose</td>
<td>7.3 ± 5.5</td>
<td>12.3 ± 7.5</td>
<td>0.035</td>
</tr>
<tr>
<td>Hg g/dL</td>
<td>10 (7.9-13.8)</td>
<td>13.7 (8.3-18.4)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Platelet count 10³/microliter</td>
<td>312 (116-518)</td>
<td>184 (31-629)</td>
<td>0.021</td>
</tr>
<tr>
<td>Cr, mg/dL</td>
<td>0.45 (0.3-1.8)</td>
<td>1.53 (0.5-3.89)</td>
<td>0.001</td>
</tr>
<tr>
<td>Albumin, g/dL</td>
<td>2.45 (1.6-3.0)</td>
<td>2.6 (1.7-3.1)</td>
<td>NS</td>
</tr>
<tr>
<td>Severe TR or moderate MR</td>
<td>9 (52.9%)</td>
<td>0 (n=7)</td>
<td>0.22</td>
</tr>
<tr>
<td>Pericardial effusion</td>
<td>2 (11.8%)</td>
<td>0 (n=7)</td>
<td>NS</td>
</tr>
<tr>
<td>CAL</td>
<td>9 (52.9%)</td>
<td>0 (n=7)</td>
<td>0.02</td>
</tr>
</tbody>
</table>
NCH CASE

- 6 year old, Caucasian boy presented with 5 days of fever, bilateral conjunctivitis, swollen hands/feet, macular rash, hypotension, diarrhea.
- Received 60 mL/kg of fluid, 15 mcg/kg/min dopamine
- Laboratory abnormalities: Cr 1.39 mg/dL, albumin 2.0 mg/dL, ALT 52 IU/L, thrombocytopenia (79,000), WBC greater than 15,000.
NCH CASE

- Initial echocardiogram: No MR or TR, pericardial effusion, depressed LV function
- Required 2 doses of IVIG
- Hydropic gallbladder
- Periungual peeling, Max Z score of 3.69 of the proximal LAD
KD VS. TOXIC SHOCK?

- Male
- Abdominal symptoms
- Platelet count was fairly low
- No TR/MR, trivial pericardial effusion
- No CAL initially
- Got 60 mL/kg of fluid
- Elevated creatinine
Median duration of symptoms
KD associated shock syndrome: 4-5 days
Toxic shock syndrome: <2 days
SUMMARY

- Incomplete KD more common in extremes of age
- Adenovirus characteristics may help distinguish incidental detection from cause of illness in those with KD-like features
- KD can mimic lymphadenitis and retropharyngeal infection. Cluster of nodes suggests KD.
- Incomplete and refractory KD, specifically lacking conjunctivitis and with MAS should prompt consideration of SoJIA
- KD should be on the differential for patients with shock.
1984
• Furoshu et al. IVIG for KD
• CAA: 25% aspirin alone (n=40) vs. 3% IVIG/aspirin (n=45)

1986
• IVIG for KD 400 mg/kg/day x 4d vs. aspirin alone
• CAA: 23% aspirin alone vs. 8% in IVIG/aspirin group

1991
• IVIG single dose 2 g/kg vs. 400 mg/kg
• CAA: 7.2% (multiple) vs 3.9% (single)
• All children received aspirin

Treatment by the 10th day of fever
2007
- Single dose of methylprednisolone and IVIG vs. IVIG alone
- Similar days of fever, rates of retreatment

Newburger et al. NEJM 2007

2012
- Primary treatment **for high risk patients** in Japan
- Prednisone, IVIG/aspirin vs. IVIG/aspirin
- Reduced incidence of coronary aneurysm


2013
- Randomized, placebo controlled trial using infliximab for primary treatment of Kawasaki disease

Tremoulet AH et al. Lancet. 2014
PRACTICE CHANGE

- When evaluating for incomplete Kawasaki disease, realize the limitations of a one time assessment; may need to see the child multiple times before determining it is not Kawasaki disease.

- Have a high index of suspicion for Kawasaki disease in the under 6 month olds.