How ’bout Them Steroids: 
The Role of Corticosteroids in Kawasaki Disease

Pharmacotherapy Grand Rounds

Meenakshi R. Ramanathan, Pharm.D.  
PGY1 Pharmacy Resident  
Department of Pharmacy, CHRISTUS Santa Rosa Health System, San Antonio, TX  
Division of Pharmacotherapy, The University of Texas at Austin College of Pharmacy  
Pharmacotherapy Education and Research Center,  
The University of Texas Health Science Center at San Antonio

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Learning Objectives:
1. Describe the clinical presentation of Kawasaki disease
2. Explain the primary treatment options for Kawasaki disease
3. Evaluate the literature for evidence of corticosteroids in Kawasaki disease
4. Develop an evidence-based approach for treatment of Kawasaki disease
Kawasaki Disease (KD)

I. Introduction\textsuperscript{1,2,3}
A. Definition: Acute vasculitis syndrome of unknown etiology that primarily affects small- and medium-sized arteries, particularly the coronary arteries\textsuperscript{1}
B. First reported in 1967 by Dr. Tomisaku Kawasaki in Japan\textsuperscript{2}
C. First reported case outside of Japan was in 1976 in Hawaii\textsuperscript{3}
D. Originally named “mucocutaneous lymph node syndrome”
E. Leading cause of acquired heart disease in North American and Japanese children, which may lead to serious cardiovascular sequelae in adulthood
F. KD aroused much interest because it produced sudden death due to coronary arteritis accompanied by aneurysms and thrombotic occlusion

II. Epidemiology\textsuperscript{1,2,4}
A. Affects children worldwide in all races
B. Annual estimated incidence (cases per 100,000 children ≤ 5 years of age)
   1. Japan: 184.6\textsuperscript{2}
   2. United States\textsuperscript{4}
      a. American Asian and Pacific Island: 32.5
      b. African American: 16.9
      c. Hispanic: 11.1
      d. Caucasian: 9.1
      e. American Indian and Alaskan natives: 4.3
C. More common during winter and early spring months
D. Boys > girls ~ 1.5 to 1.7:1\textsuperscript{2}
E. 76% of children < 5 years old at diagnosis\textsuperscript{2}
F. Peak age of incidence at 13 and 24 months of age\textsuperscript{2}

III. Pathophysiology\textsuperscript{2}
A. Etiology unknown, though suspected to be an infectious agent
   1. Self-limiting disease, generally nonrecurring
   2. Age of infected children (generally < 5 years of age)
   3. Seasonality of cases (winter-spring seasonality)
   4. Occurrence of community outbreaks with a wave-like geographic spread and apparent epidemic cycles
B. Signs and symptoms
   1. Fevers (independent predictor for poor prognosis with KD)
   2. Leukocytosis
   3. Increases in c-reactive protein (CRP) and erythrocyte sedimentation rate (ESR)
   4. Rash
   5. Cervical lymphadenopathy
   6. Conjunctivitis
C. Mechanism of immune system activation
   1. Theory #1: Bacterial superantigen leads to massive stimulation of T lymphocytes
   2. Theory #2: Oligoclonal IgA immune response is occurring rather than a polyclonal one
      a. IgA plasma cells infiltrating the coronary arteries
      b. Detection of viral-like cytoplasmic inclusion bodies in ciliated bronchial epithelial cells
   3. Theory #3: T-cell activation may determine susceptibility and severity of KD
      a. Polymorphism in the inositol 1,4,5-triphosphate 3-kinase C (ITPKC) gene on chromosome 19q13.2, which acts as a negative regulator of T-cell activation and may contribute to immune hyperreactivity in KD
      b. This polymorphism was significantly associated with KD susceptibility and increased risk of coronary artery abnormalities in both Japanese and American children
IV. Diagnosis\textsuperscript{2,5,6}
   A. Diagnostic pearls
   1. Clinical diagnosis
      a. Generally high fevers, unresponsive to antibiotics and antipyretics
      b. Clinical features may not all be present at one time; a complete history is needed
      c. KD mimics many other acute disease states in children, such as streptococcal and staphylococcal
toxin-mediated disease and infections with viruses such as adenovirus and enterovirus
   B. Diagnostic criteria
      1. Classic criteria\textsuperscript{5,6}
         a. Presence of $\geq 5$ days of fever
         b. $\geq 4$ of 5 principal clinical features
            i. Changes in extremities
               a. Acute: erythema of palms, soles; edema of hands, feet
               b. Subacute: periungual peeling of fingers, toes in weeks 2 and 3
            ii. Polymorphous exanthema
            iii. Bilateral bulbar conjunctival injection without exudates
            iv. Changes in lips and oral cavity: erythema, lips cracking, strawberry tongue, diffuse
                injection of oral and pharyngeal mucosa
            v. Cervical lymphadenopathy ($>1.5$-cm diameter), usually unilateral
      2. Echocardiographic criteria\textsuperscript{5}
         a. Presence of $\geq 5$ days of fever
         b. $< 4$ of 5 principal clinical features
      2. Presence of coronary artery abnormalities on two-dimensional echocardiography or coronary
         angiography
   V. Laboratory and cardiac findings\textsuperscript{2,5}
   A. Laboratory findings
      1. Increased erythrocyte sedimentation rate (ESR)
      2. Increased c-reactive protein (CRP)
      3. Leukocytosis with neutrophil predominance
      4. Anemia
      5. Thrombocytosis
      6. Hypoalbuminemia
      7. Increased serum transaminases
      8. Sterile pyuria
   B. Cardiac manifestations\textsuperscript{2,5}
      1. Coronary artery abnormalities
      2. Myocarditis
      3. Valvular regurgitation
      4. Gallop rhythm
      5. Wall motion abnormalities
      6. Pericarditis
      7. Valvulitis
      8. KD shock syndrome
   C. Coronary artery abnormalities\textsuperscript{5}
      1. Definition
         a. Japanese Ministry of Health criteria\textsuperscript{5}
            i. Lumen $> 3$ mm in children $< 5$ years old
            ii. Lumen $> 4$ mm in children $> 5$ years old
            iii. Internal diameter of a segment measures $\geq 1.5$ times that of an adjacent segment
         b. de Zorzi criteria: $z$ score $> 2.5$ (a coronary dimension that is $\geq 2.5$ SDs above mean for that body
            surface area)\textsuperscript{5}
2. Diagnosis
   a. Two-dimensional echocardiography\textsuperscript{5}
      i. Preferred imaging modality for cardiac assessment (evidence level C)\textsuperscript{5}
      ii. Noninvasive
      iii. High sensitivity and specificity for detecting abnormalities in proximal left main coronary artery (LMCA) and right coronary artery (RCA)
   b. Coronary angiography
3. Coronary artery aneurysms (CAA)
   a. Background
      i. Develop in as many as 25\% of untreated children\textsuperscript{2,4,5}
      ii. Most serious complication
      iii. Can lead, over time, to ischemic heart disease, myocardial infarction, and rarely, death
   b. Formation\textsuperscript{7-11}
      i. Big picture: direct cell-mediated attack of endothelial cells that are infected with an as yet unidentified infectious agent may underlie the vascular injury
      ii. Detailed overview
         a. Blood vessel damage appears to result from an aberrant immune response leading to endothelial cell injury and vessel wall damage
         b. Attack of anti-endothelial cell antibodies and circulating immune complexes
         c. Disruption of vascular endothelial function by an influx of active neutrophils into affected coronary artery (central to the pathogenesis of acute KD)
         d. Influx of large mononuclear cells and lymphocytes (mostly CD8 T cells) and immunoglobulin-A plasma cells
         e. Destruction of internal elastic lamina occurs, followed by myofibroblast proliferation, leading to formation of a CAA
   f. American Heart Association classification\textsuperscript{5}
      i. Small (< 5 mm internal diameter)
      ii. Medium (5 to 8 mm internal diameter)
      iii. Giant (8 mm internal diameter)
   g. Regression\textsuperscript{12}
      i. Occurs usually within 1 – 2 years of disease onset
      ii. Proposed mechanism of regression: intimal proliferation of aneurysm

VI. Clinical Phases\textsuperscript{2}
   A. Acute
      1. Begins with onset of fever and ends with its resolution
      2. Lasts 11 days on average, but may be less if therapy is instituted
   B. Subacute
      1. Begins with the resolution of fever and ends when all clinical features resolve
      2. Begins 10 days into the illness and lasts 2 weeks long
      3. Characterized by thrombocytosis and periungual desquamation of the fingers and toes
   C. Convalescent
      1. Begins when many clinical features resolve and continues until the laboratory findings return back to normal, specifically the erythrocyte sedimentation rate and platelet count
      2. Generally takes 4 – 8 weeks to resolve
      3. Characterized by nail abnormalities
VII. Treatment\textsuperscript{2,5}  
A. Approach  
1. Acute phase aimed at reducing inflammation in the coronary artery wall and preventing coronary thrombosis  
2. Long-term therapy for those persons who develop coronary aneurysms for the prevention of myocardial ischemia or infarction  

B. Primary treatment\textsuperscript{2,4,5,13}  
1. Intravenous immune globulin (IVIG) 2 g/kg as a single infusion (evidence level A)\textsuperscript{2,5}  
   a. Should be added within the first 10 days of illness  
   b. Can also be added after the 10\textsuperscript{th} day in patients with persistent fever, aneurysms, and ongoing systemic inflammation  
   c. How does it help?  
      i. Reduces fever duration  
      ii. Reduces incidence of coronary artery aneurysms when given within a few days of the onset of disease  
   d. Proposed mechanism of action\textsuperscript{5}  
      i. Modulation of cytokine production  
      ii. Neutralization of bacterial superantigens or other etiologic antigens  
      iii. Augmentation of T-cell suppressor activity  
      iv. Suppression of antibody synthesis  
      v. Provision of anti-idiotypic antibodies  
2. Aspirin (ASA) 80 – 100 mg/kg/day PO in 4 divided doses (evidence level B)\textsuperscript{2,5}  
   a. Keep until afebrile for at least 48-72 hours  
   b. Purpose: anti-inflammatory effect  
3. Once afebrile for 48-72 hours, decrease ASA dose to 3-5 mg/kg/day (evidence level B)\textsuperscript{2,5}  
   a. Maintain until 6 – 8 week echocardiogram is normal; if abnormal, continue ASA  
   b. Purpose: mitigate hypercoagulable state and platelet activation that contribute to risk of thrombosis in inflamed coronary arteries  

C. IVIG Resistance\textsuperscript{1,7,14,15}  
1. Rates of resistance and aneurysms  
   a. Although a majority will respond to the first dose of IVIG therapy, another 11.6% - 23% of patients will have persistent or recurrent fever\textsuperscript{14}  
   b. These patients are at the greatest risk of developing coronary artery lesions  
   c. Despite receiving high-dose IVIG within the first 10 days of illness, approximately 5% of children with KD have subsequent coronary aneurysms and 1% have giant aneurysms\textsuperscript{15}  
2. Treatment of IVIG resistance  
   a. Re-treat with second dose of IVIG if fever persists > 48 hours from completion of IVIG  
   b. IVIG 2 g/kg as a single infusion (evidence level C)\textsuperscript{2,5}  

D. Pharmacotherapy treatment options\textsuperscript{2,5}  
1. Corticosteroids  
2. Infliximab  
3. Pentoxifylline  
4. Cyclophosphamide  
5. Cyclosporine A  
6. Methotrexate  
7. Abciximab
Corticosteroids (CS)

I. Background
A. Corticosteroid therapy was used as initial treatment for KD prior to IVIG\textsuperscript{1,11}
   1. Initially thought to suppress vasculitis that precedes vascular remodeling
   2. Rational for CS use in KD\textsuperscript{2}
      a. Reduce fever
      b. Decrease inflammatory response in KD patients, which may reduce coronary artery abnormalities
D. Three schools of thought for treatment of KD\textsuperscript{14}
   1. More aggressive treatment for all KD patients: adding CS as primary treatment
   2. More aggressive treatment for patients expected to be unresponsive to initial treatment: adding CS to patients who are at high risk of coronary artery abnormalities
   3. Treatment for patients refractory to initial treatment: adding CS only when conventional therapy fails
B. CS have been used in other forms of vasculitis\textsuperscript{4,16}
   1. Polyarteritis nodosa
   2. Churg-Strauss syndrome
   3. Wegener’s granulomatosis
   4. Behcet’s disease
   5. Giant cell arteritis
   6. Systemic lupus erythematosus
II. Mechanism of action\textsuperscript{10,17,18}

Source: http://www.rise.duke.edu/phr150/Performance/howitworks.html
A. Genomic pathway
1. Binds to the steroid receptor in the cytoplasm of the target tissue
2. Steroid-receptor complex moves into the nucleus, where it binds to glucocorticoid-responsive DNA sequences (also known as glucocorticoid response elements)
3. Steroid-receptor complex then recruits either co-activator or co-repressor proteins, such as cytokines, chemokines, inflammatory enzymes and adhesion molecules to modify the structure of the chromatin
4. Decreasing gene transcription, and therefore, inhibiting IL-1, IL-2, IL-3, and IL-6, γ-interferon, and tumor necrosis factor α (TNF-α) synthesis

B. Non-genomic pathway
1. Interfere with important signal transduction pathways involved in immune activation including the mitogen-activated protein kinase (MAPK) and mitogen-activated protein(MAP)-extracellular signal-regulated kinase (Erk) signaling pathways
2. These pathways are critical to lymphocyte activation and also matrix metalloproteinase (MMP) upregulation

C. Other
1. Interfere with cell migration and recognition
2. Interfere with cytotoxic effector mechanisms

III. Acute adverse effects

A. Hematologic
1. Increased total white blood count
2. Decreased lymphocytes, monocytes, eosinophils
3. Promotes blood coagulation

B. Metabolic abnormalities
1. Increased gluconeogenesis (hyperglycemia, glycosuria, “steroid diabetes”)
2. Increased serum lipids (triglycerides and cholesterol)
3. Reduced protein synthesis and protein catabolism

C. Increased susceptibility to infection

D. Aggravation of existing psychiatric problems
The Controversy

I. Concerns of corticosteroid use in KD\textsuperscript{1,12,20}
   A. Possible worsening incidence of coronary artery abnormalities
      1. Impair vascular remodeling of damaged vessel walls
      2. Prevent coronary artery aneurysm regression via intimal proliferation
   B. Cytokines involved in the reconstruction of the inflamed coronary vessel wall may also be inhibited
   C. Procoagulant effect may put patient at risk for thrombosis, especially in the subacute phase

II. Studies that demonstrated worsening coronary artery abnormalities
      1. Prospective study (n=92)
      2. Prednisolone (PSL) monotherapy (n=17) compared to four other treatment modalities
         a. ASA
         b. Cephalexin
         c. PSL + ASA
         d. PSL + warfarin
      3. Rates of CAA highest in PSL monotherapy arm: 11/17 cases (64.7%)
         a. ASA: 4 / 36 cases (11%)
         b. Cephalexin: 5 / 25 cases (20%)
         c. PSL + ASA: 0 / 7 cases (0%)
         d. PSL + warfarin: 2 / 7 cases (28.6%)
      4. Significant limitations in interpreting results
         a. No comparison of baseline characteristics (including echocardiography)
         b. Uncontrolled, non-randomized
         c. Small sample size
      1. Retrospective chart review (n=80) between 1990 and 2008
      2. Nineteen patients received CS in the acute phase of KD
      3. CAA z scores were similar at baseline in the coronary arteries
      4. CAA z score worsened over time in the CS group in comparison to the non-CS group

<table>
<thead>
<tr>
<th>Table 1. Adjusted CAA z-score</th>
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<tbody>
<tr>
<td>Group</td>
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<tr>
<td>-------</td>
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<tr>
<td>LAD, NON-CS</td>
</tr>
<tr>
<td>LAD, CS</td>
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<tr>
<td>RCA, NON-CS</td>
</tr>
<tr>
<td>RCA, CS</td>
</tr>
<tr>
<td>LMCA, NON-CS</td>
</tr>
<tr>
<td>LMCA, CS</td>
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</table>

5. Significant limitations of interpreting results
   a. Retrospective nature
   b. Small sample size
   c. Study spanned a 17 year period
   d. Treatment with CS was at the discretion of the physician

III. The role of CS in the American Heart Association guidelines: steroid treatment should be restricted to children in whom ≥ 2 infusions of IVIG have been ineffective in alleviating fever and acute inflammation (evidence level C)\textsuperscript{5}

Studies of Corticosteroids in the Primary Treatment of Kawasaki Disease

V. Newburger J, et al. (2007)
VI. Kobayashi T, et al. (2012)

<table>
<thead>
<tr>
<th>Purpose</th>
<th>To investigate the role of corticosteroids in the initial treatment of KD</th>
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<tbody>
<tr>
<td>Design</td>
<td>Multicenter, prospective, randomized, non-blinded trial</td>
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</table>
| Patients | • Inclusion criteria: clinical diagnosis of KD  
          • Exclusion criteria  
            o Previous diagnosis of KD  
            o Presence of coronary artery abnormality  
            o Initial consultation after 9 days from the onset of illness (day 1 = first day of fever) |
| Outcomes | • Primary: Detection of a CAA at follow-up evaluations during the first month of illness  
          • Secondary  
            o Duration of fever after initial treatment  
            o Time to normalization of CRP level  
            o Incidence of initial treatment failure and recurrence |
| Methods | • September 2000 and March 2005  
         • 178 patients from 12 hospitals  
         • Interventions  
           o Group 1: IVIG 1g/kg/day for 2 consecutive days, given over 12 hours  
           o Group 2: IVIG 1 g/kg/day for 2 consecutive days, given over 12 hours plus prednisolone sodium succinate (PSL) 2 mg/kg/day, three times daily, given intravenously (IV) until fever resolved and continued orally until the C-reactive protein (CRP) normalized (<0.5 mg/dL)  
           o All patients received ASA 30 mg/kg/day + dipyridamole 2 mg/kg/day, decreased down to 5 mg/kg/day after CRP normalized  
           o Additional therapy was given for patient with persistent fever lasting more than 24 hours (initial treatment failure) or recrudescence fever associated with KD symptoms after an afebrile period (recurrence)  
         • Definitions  
           o Afebrile = < 37.5°C for more than 24 hours  
           o Coronary artery abnormality: Japanese Ministry of Health criteria or when the luminal contour was clearly irregular |
| Results | • Baseline characteristics were similar between the groups  
         • Duration of steroid administration, 18 – 100 days (median, 23 days) |

### Table 2. Primary endpoints

<table>
<thead>
<tr>
<th></th>
<th>IVIG group (n=88)</th>
<th>IVIG + PSL group (n=90)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Coronary artery dilatation until 1 month, no. (%)</td>
<td>10 (11.4)</td>
<td>2 (2.2)</td>
<td>0.017</td>
</tr>
<tr>
<td>Coronary artery dilatation at 1 month, no. (%)</td>
<td>3 (3.4)</td>
<td>0 (0.0)</td>
<td>0.119</td>
</tr>
<tr>
<td>Giant coronary aneurysm, no. (%)</td>
<td>0 (0.0)</td>
<td>0 (0.0)</td>
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</table>

### Table 3. Secondary endpoints

<table>
<thead>
<tr>
<th></th>
<th>IVIG group (n=88)</th>
<th>IVIG + PSL group (n=90)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Duration of fever after treatment, days*</td>
<td>1 (0 to 15)</td>
<td>0 (0 to 8)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Duration to normalization of CRP level, days*</td>
<td>9.0 (4 to 42)</td>
<td>8.0 (3 to 20)</td>
<td>0.001</td>
</tr>
</tbody>
</table>
| Need for additional therapy  
  Initial treatment failure, no. (%) | 16 (18.2) | 5 (5.6) | 0.10 |
| Recurrence, no.(%) | 2 (2.2) | 4 (4.4) | 0.682 |

* Data expressed as median (range)

### Conclusions

A combination of CS and IVIG improved clinical course and coronary artery outcome without causing untoward effects in children with acute KD

### Strengths

• Multi-centered, prospective, randomized design  
• Large sample size  
• Appropriate exclusion criteria

### Limitations

• No mention of blinding design  
• May not be able to generalize to outside of Japan: different definition for treatment failure and afebrile, differences in regimen between the US and Japan, dipyridamole not normally used in KD  
• Japanese Ministry of Health Criteria may underestimate the true incidence of CAA in KD patients

| **Purpose** | To determine whether the addition of intravenous methylprednisolone (IVMP) to conventional primary therapy for KD reduces the risk of coronary artery abnormalities |
| **Design** | Multicenter, randomized, double-blind, placebo-controlled trial |
| **Patients** | **Inclusion criteria** |
| | - Patients between days 4 and 10 of illness (day 1 = first day of fever) |
| | - Must satisfy one of the following eligibility requirements |
| | ▪ Patient met four or more principal clinical criteria |
| | ▪ Patient had a coronary artery z score of ≥ 2.5 + 2 principal clinical criteria (for younger than 6 months) or 3 principal clinical criteria (for patients 6 months of age or older) |
| | ▪ Coronary aneurysm + 1 principal clinical criterion |
| | **Exclusion criteria:** previous treatment with IVIG, treatment with CS, other than the inhaled forms, in the previous 2 weeks, presence of a disease known to mimic KD, previous diagnosis of KD, or contraindication to CS or ASA use |
| **Outcomes** | Primary: z scores for the coronary arteries at week 5 after randomization |
| | Secondary: coronary artery abnormalities, cardiac complications, time to hospital discharge, days of fever, percentage of patients retreated with IVIG, adverse events |
| **Methods** | **Eight centers in North America from December 2002 – December 2004** |
| | **Patients with ≤ 10 days of fever** |
| | ▪ Group 1 (n=101): IVMP (30 mg/kg) |
| | ▪ Group 2 (n=98): placebo |
| | All patients received conventional therapy with: |
| | ▪ IVIG 2 g/kg over 10 hours |
| | ▪ ASA 80-100 kg/day until they were afebrile for 48 hours and 3-5 mg/kg/day thereafter |
| | **Temperature of 38.3°C or higher ≥ 36 hours after completion of initial IVIG, received IVIG 2 g/kg** |
| | **Third treatment with IVIG 2 g/kg with persistent fever ≥ 36 hours after IVIG retreatment** |
| | **Continued fever after third dose of IVIG was treated at the discretion of the center physicians** |
| | **Two-dimensional echocardiography and labs** |
| | ▪ Taken at baseline, median days 8 and 36 |
| | ▪ Diameters of coronary arteries |
| | **Temperatures were taken daily prior to ASA** |
| | ▪ Children were hospitalized until they had been afebrile > 12 hours |
| | ▪ Parents were responsible for recording temperatures after discharge |
| | ▪ Subgroup analysis: gender, age (< or ≥ 1), days of illness (< or ≥ 7), presence of coronary artery abnormalities at baseline |
| | **Adverse events were classified according to severity, expectedness, and attributability** |
| **Results** | **Baseline characteristics similar between groups** |
| | No significant difference: |
| | ▪ Maximum z score at week 1 (p=0.76) or week 5 (p=0.76) |
| | ▪ Secondary outcomes, including adverse events (IVMP n=37 vs. placebo n=24, p=0.18) |
| | ▪ Subgroup analysis for coronary artery outcome at week 5 |
| | **Post-hoc analysis: to explore effect of IVMP on coronary outcomes based on severity of illness** |
| | ▪ 27 patients IVIG non-responders versus 127 IVIG responders |
| | ▪ Improved efficacy of IVMP specifically in IVIG non-responders |
| | ▪ Lower mean maximum z score at week 1 in favor of IVMP |
| | ▪ Percentage of patients with coronary artery abnormalities at weeks 1 and 5 in favor of IVMP |
| **Conclusions** | Addition of a single-pulsed dose of IVMP is not recommended for routine use in primary treatment of KD |
| **Strengths** | A larger-scale, double-blind, placebo-controlled clinical trial |
| | Used currently recommended IVIG + ASA in all patients |
| | Incidence of coronary abnormalities taken at baseline, 1 and 5 weeks |
| **Limitations** | Failure to exclude KD patients with previous coronary artery abnormalities |
| | Evaluated only one type of corticosteroid (IVMP) |
| | Data was not collected past 5 weeks after randomization |
| | Underpowered for subgroup analyses and for detection of between-group differences in the number of adverse events |

<table>
<thead>
<tr>
<th>Purpose</th>
<th>To assess whether addition of prednisolone (PSL) to intravenous immunoglobulin (IVIG) with aspirin (ASA) would reduce the incidence of coronary artery abnormalities in patients with severe KD</th>
</tr>
</thead>
</table>
| Design   | • Multi-center, prospective, randomized, open-label, blinded trial  
• Patients and treating physicians were unmasked to group allocation |
| Patients | • Inclusion criteria  
  o Japanese diagnostic guidelines for KD  
  o Risk score of ≥ 5 points on the Kobayashi scoring system to predict initial non-response to IVIG  
• Exclusion criteria  
  o History of KD  
  o Diagnosed at ≥ 9 days of illness  
  o Patients with coronary artery abnormalities prior to enrollment  
  o Patients who received steroids 30 days before the study  
  o Patients who received IVIG 180 days before the study  
  o Concomitant severe medical disorders (e.g. immunodeficiency, chromosomal anomalies, congenital heart diseases, metabolic diseases, nephritis, collagen disease)  
  o Other suspected infectious diseases (e.g. sepsis, septic meningitis, peritonitis, bacterial pneumonia, varicella, and influenza) |
| Outcomes | • Primary: incidence of coronary artery abnormalities during the study period (echocardiography)  
• Secondary  
  o Incidence of coronary artery abnormalities at week 4 after enrollment  
  o z scores of coronary arteries  
  o Incidence of need for additional rescue treatment  
  o Duration of fever after enrollment  
  o Serum c-reactive protein (CRP) at 1 and 2 weeks after enrollment  
  o Serious adverse events |
| Methods  | • September 29, 2008 – December 2, 2010  
• 248 patients in 74 hospitals in Japan  
• Cohorts  
  o Group 1: IVIG 2g/kg for 24 hours + ASA 30 mg/kg/day until afebrile and decreased to ASA 3-5 mg/kg/day for at least 28 days after fever onset (n=123)  
  o Group 2: Same regimen as group 1 + PSL 2 mg/kg/day given over 15 days after concentrations of CRP normalized (n=125) |
| Results  | • Decreased incidence of coronary artery abnormalities with IVIG + ASA + PSL group  
  o 4 (3%) vs. 28 (23%); HR 0.20, 95% CI 0.12 – 0.28, P<0.0001  
• Adverse event rate was similar between groups  
  o IVIG + ASA = 1 patient with high cholesterol and 1 with non-occlusive thrombus  
  o IVIG + ASA + PSL = 2 patients with high cholesterol and 1 patient with neutropenia |
| Conclusions | Addition of PSL to the standard regimen of IVIG improves coronary artery outcomes in patients with severe KD in Japan |
| Strengths | • Multi-center, prospective, randomized, blinded study design  
• Large sample size across many hospitals in Japan |
| Limitations | • Open-label study design  
• Patients and treating physicians were unmasked to group allocation |

**Purpose**
To summarize clinical trials that compared the incidence of coronary abnormality between IVIG and CS therapy and IVIG therapy alone, and to determine the overall efficacy and safety of IVIG plus corticosteroid therapy for initial treatment of Kawasaki disease

**Design**
Meta-analysis

**Studies**
Inclusion criteria
- Diagnosis of KD
- Studies that compared the efficacy of IVIG + CS versus IVIG alone
- Two-dimensional echocardiography, or coronary artery catheterization, was performed to detect the presence of coronary artery abnormality during study follow-up

**Outcomes**
- Primary: incidence of patients with coronary artery abnormality at follow-up
- Secondary: adverse events

**Methods**
- Published studies up until March 31, 2012
- Medline, The Cochrane Library, the Clinical Trials, and Embase Database
- Subgroup analysis for coronary abnormalities performed

**Results**
- Nine clinical studies included (n=1011)

<table>
<thead>
<tr>
<th>Meta-analysis category</th>
<th>Odds ratio (OR)*</th>
<th>95% Confidence interval (CI)</th>
</tr>
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<tbody>
<tr>
<td>Coronary abnormality</td>
<td>0.30</td>
<td>0.20 – 0.46</td>
</tr>
<tr>
<td>Subgroup analysis for coronary abnormality</td>
<td></td>
<td></td>
</tr>
<tr>
<td>- Randomized control trials</td>
<td>0.30</td>
<td>0.18 – 0.50</td>
</tr>
<tr>
<td>- Studies using blinded-endpoint manner</td>
<td>0.32</td>
<td>0.19 – 0.55</td>
</tr>
<tr>
<td>- Studies using non-blinded-endpoint manner</td>
<td>0.27</td>
<td>0.14 – 0.52</td>
</tr>
<tr>
<td>- Patients with high risk for IVIG resistance</td>
<td>0.20</td>
<td>0.10 – 0.36</td>
</tr>
<tr>
<td>- Studies whose patients received PSL</td>
<td>0.12</td>
<td>0.05 – 0.26</td>
</tr>
<tr>
<td>- Studies whose patients received IVMP</td>
<td>0.48</td>
<td>0.28 – 0.81</td>
</tr>
<tr>
<td>- Studies with follow-up of 4 weeks or more</td>
<td>0.27</td>
<td>0.17 – 0.44</td>
</tr>
<tr>
<td>Adverse events</td>
<td>1.24</td>
<td>0.33 – 4.67</td>
</tr>
</tbody>
</table>

* IVIG + CS compared to IVIG monotherapy

**Conclusions**
IVIG + CS as initial treatment reduced the risk of coronary abnormalities in patients with KD

**Strengths**
- Large sample size
- Well-developed study methods
- Performance of a sub-group analysis for RCTs
- All studies initiated primary treatment within the first 10 days

**Limitations**
- Moderate heterogeneity was detected among the trials
  - Disparate study design
  - Different patient enrollments
  - Drug administration
  - Non-blinded endpoint manner
  - Different follow-up duration

**Recap**

I. Outcomes on CAA
   B. No difference: Newburger J, et al.

II. Mini-conclusion:
   A. Available literature suggests improved coronary artery outcomes in patients with KD treated initially with CS + IVIG
Study of Corticosteroids as Primary Treatment in Select Kawasaki Disease Patients


| Purpose | To examine the clinical efficacy and safety of intravenous methylprednisolone-pulse plus intravenous immunoglobulin combination therapy (IVMP+IVIG) for the initial treatment of patients predicted to have refractory KD |
| Design | Prospective, randomized trial |
| Patients | • Inclusion criteria: 5 of the 6 clinical criteria  
• Exclusion criteria  
  o Previous diagnosis of KD  
  o Presence of CAL before initial treatment  
  o Patients who received steroid therapy before being diagnosed with KD |
| Outcomes | • Efficacy  
  o Primary: afebrile (<37.5°C) at least 36 hours after completion of initial treatment  
  o Secondary  
    ▪ Duration of fever  
    ▪ Laboratory measurements of vasculitic markers  
    ▪ z scores of coronary arteries  
• Safety: adverse events |
| Methods | • April 2007 – November 2010  
• 122 patients with KD  
• Egami score was used to predict refractory KD patients before treatment (See Appendix II)  
• Patients predicted to have refractory KD  
  o IVMP 30 mg/kg for 1 dose over 2 hours + IVIG 2 g/kg for 24 hours  
  o IVIG 2 g/kg for 24 hours alone  
• All patients received ASA 30 mg/kg every 8 hours until afebrile for 36 hours, then decreased to 5 mg/kg/day as a single-dose  
• Treatment resistance: persistent or recrudescent fever (axillary temperature ≥ 37.5°C) at 36 hours after completion of the initial treatment  
• Presence of CAL in the left main trunk coronary artery (LMT), LAD, RCA: de Zorzi method |
| Results | • Seventy-four patients (60.7%) were predicted to be IVIG responder  
• Forty-eight patients (39.3%) were predicted to have refractory KD on the basis of the Egami score  
  o Single-IVIG group (n=26)  
  o IVMP + IVIG group (n=22)  
• Prompt defervescence: 19/22 patients (86.4%) in IVMP + IVIG group compared with 6/26 patients (23.1%) in single-IVIG group  
• Z score ≥ 2.5 significantly more common in single-IVIG group at 1 month: 10/26 patients( 38.5%) vs. 2/22 patients( 9.1%); P = 0.04  
• No serious adverse events were observed in either treatment group |
| Conclusions | IVMP+IVIG therapy is safe and effective for KD patients predicted to be refractory |
| Strengths | • Prospective, randomized trial  
• Baseline characteristics were similar in the patients predicted to have IVIG resistance  
• Appropriate inclusion and exclusion criteria  
• Used IVIG + ASA for primary treatment  
• Echocardiograms read by a blinded reviewer |
| Limitations | • Applicability to other ethnic populations may be limited  
• Japanese treatment dosing used |
Summary & Recommendations

I. Summary
   A. KD continues to be a mystery around the world even 45 years after its first description by Dr. Tomisaku Kawasaki
   B. IVIG + ASA continue to be the mainstay of therapy
      1. A significant number of patients will not respond to initial IVIG-resistant
      2. Approximately 5% of patients develop CAA and 1% develop giant aneurysms even after IVIG therapy
   C. Biologic plausibility for reduction of CAA with CS; however, early literature demonstrated worsening or increased incidence of coronary artery abnormalities
   D. Studies suggesting worse outcomes were of poor quality, small numbers, with multiple limitations
   E. Benefits for CS seen in many studies
      1. Early defervescence
      2. Prevention of vascular remodeling prior to CAA formation
   F. CS are not without adverse events
   G. Multi-variable predictors have been shown to detect IVIG unresponsiveness

II. Recommendations:
   A. CS should be added to primary therapy for all patients in KD
   B. Further studies should evaluate the utility of scoring systems in identifying patients who are IVIG resistant
References


Appendix I


A. Recommendations are evidence based and derived from published data wherever possible

B. Levels of evidence
   1. Level A (highest): multiple randomized clinical trials
   2. Level B (intermediate): limited number of randomized trials, nonrandomized studies, and observational registries
   3. Level C (lowest): expert consensus

Appendix II

### Scoring systems for predicting treatment refractory Kawasaki disease

<table>
<thead>
<tr>
<th></th>
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</tr>
</thead>
<tbody>
<tr>
<td>Number of variables</td>
<td>7</td>
<td>5</td>
<td>4</td>
</tr>
<tr>
<td>Variables (points)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1. Age ≤ 12 months (1)</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>2. Illness day at diagnosis ≤ 4 days (2)</td>
<td></td>
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<tr>
<td>3. Neutrophils ≥ 80 % (2)</td>
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<tr>
<td>4. Platelet count ≤ 30.0 x 10^9/mm^3 (1)</td>
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<tr>
<td>5. AST ≥ 100 IU/L (2)</td>
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<tr>
<td>6. Sodium ≤ 133 mmol/L (2)</td>
<td></td>
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<tr>
<td>7. CRP ≥ 10 mg/dL (1)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>High-risk</td>
<td>≥ 4 points</td>
<td>≥ 3 points</td>
<td>≥ 2 points</td>
</tr>
<tr>
<td>Sensitivity</td>
<td>86%</td>
<td>78%</td>
<td>73.3%</td>
</tr>
<tr>
<td>Specificity</td>
<td>67%</td>
<td>76%</td>
<td>61.9%</td>
</tr>
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</table>