Why do we give IVIG to children with Kawasaki Disease?

Newburger et al. The treatment of Kawsaki syndrome with intravenous gamma globulin. *N Engl J Med* 1986; 314:341-7.

Take Home Message: High dose intravenous gamma globulin is effective in reducing the prevalence of coronary-artery abnormalities in children with Kawasaki disease

Highlights: In 1986, Newburger et al. published this multicenter randomized trial[i], establishing that children with Kawasaki disease treated with high-dose intravenous gamma globulin early in the course of their disease, in addition to aspirin, were significantly less likely to have coronary artery abnormalities than those children treated with aspirin alone. The children in the gamma globulin group were one-third as likely to have coronary artery abnormalities as those in the aspirin group at two weeks, and one-fifth as likely at seven weeks. The patients in the gamma globulin group also had a significantly reduced fever and decrease in laboratory values of acute inflammation. This paper changed the standard of care for the treatment of Kawsaki disease.

Four doses of gamma globulin were given in this trial. The same group, again led by Newburger, published another trial in 1991[ii] comparing a single large dose of IVIG (2 grams per kilogram) to four daily doses (400 milligrams per kilogram daily). They found that a single large dose was associated with a more rapid resolution of fever, normalization of laboratory evidence of acute inflammation and lower risk of coronary abnormalities. A single dose of 2 grams/kilogram of intravenous gamma globulin is now the standard of care.

The Nitty-Gritty:

- **Design:**
  - Multicenter, randomized trial
  - N= 168
    - Aspirin group (n=84)
    - Gamma globulin plus aspiring group (n=84)
  - Setting: 6 US university centers
  - Enrollment: 1984-1985
  - Primary outcome: Coronary artery abnormalities
  - Analysis:
- **Population:**
  - **Inclusion Criteria:**
    - have at least five of six signs of Kawasaki Disease (fever, nonexudative conjunctivitis, changes in oropharynx, changes in extremities, rash, cervical adenopathy)
    - no clinical or laboratory evidence of any other disease known to mimic Kawasaki
    - enrolled within 10 days of onset of illness, with day 1 defined as first day of fever

- **Exclusion Criteria:** not specified

- **Baseline Characteristics** from the aspirin group, no significant differences between groups

  - **Age:** 2.3±0.2 years

  - **Day of illness at enrollment:** 6.4±0.2 days

  - **Age-sex group**

    - **Male <1 yr old**: 12%
    - **Female <1 yr old:** 11%
    - **Male≥ 1 yr old:** 48%
    - **Female≥1 yr old:** 30%

  - **Race/ethnic group:**

    - **White**: 43%
    - **Black:** 7%
    - **Asian or Pacific Islander**: 29%
    - **Hispanic:** 5%

- **Mixed:** 17%

§ **Lab data** (means±SE)

- **Temperature:** 38.9±0.1
- **White-cell count** (x10-9/liter): 15.3±0.6
- **Platelet count** (x10-9/liter): 477.8±21.1
- **Alpha1-antitrypsin** (mg/dl)**:** 347.8±10.4
- **IgG** (mg/dl): 640.5±35.1

- **Intervention**:

  o randomized to either aspirin alone or asprin plus gamma globulin. All patients received 100mg/kg/day of asprin until day 14 after which the dose was reduced to 3-5 mg/kg/day. Patients in the gamma globulin group received 400 mg/kg/day of IVIG given on four consecutive days

  o Echocardiograms were obtained at enrollment, at the two-week, and at the seven-week visits. These were interpreted by two blinded pediatric echocardiographers from study centers other than the one at which the patient was enrolled

- **Outcomes:** comparisons are gamma globulin group vs. aspirin alone group

- **Primary outcome:** coronary-artery abnormalities
  - **At two weeks:** 8.0% vs. 23.1% (P=0.01) (when excluding children with coronary artery abnormalities at enrollment: 6.8% vs. 20.0% (P=0.02))
  - **At seven weeks:** 3.8% vs. 17.7% (P=0.005) (when excluding children with coronary artery abnormalities at enrollment: 2.6% vs. 14.7% (P=0.01))
- **Secondary outcomes:**
  - **Fall in temperature between first and second study day:** 1.30±0.16°C vs. 0.42±0.11°C (P=0.001)
  - **Change in laboratory values between day 1 and day 5:**
    - **White-cell count** (x10-9/liter): -4.1±0.7 vs. -0.5±0.7 (P=0.0001)
    - **Platelet count** (x10-9/liter): 191.2±19.0 vs. 237.2±25.5 (P=0.15)
    - **Alpha1-antitrypsin** (mg/dl)**:** -43.7±8.0 vs. -21.6±7.8 (P=0.05)

- **Adverse Events**
  - No serious adverse effects from IVIG
  - Mild congestive heart failure in 4% after first infusion (all tolerated subsequent infusions without difficulty), comparable number of congestive heart failure in the aspirin alone group

- One child with shaking chills and itching that resolved with diphenhydramine and did not recur with subsequent infusions

- One child with sepsis after an intravenous line was inserted for infusion

[i] Newburger et al. The treatment of Kawsaki syndrome with intravenous gamma globulin. *N Engl J Med* 1986; 314:341-7.

[ii] Newburger et al. A single intravenous infusion of gamma globulin as compared with four infusions in the treatment of acute Kawassaki syndrome. *N Engl J Med* 1991; 324:1633-9.