# TRIAL OF PULSE STEROID THERAPY IN KAWASAKI DISEASE
# PUBLIC USE DATASET

Pediatric Heart Network (PHN)

## ABOUT THE STUDY

The NHLBI Kawasaki Disease (KD) Study was conducted by the Pediatric Heart Network (PHN) at 8 centers in North America from December 2002 to December 2004. Eligible patients were between days 4 and 10 of illness, with day 1 defined as the first day of fever. Patients were randomly assigned to receive either intravenous methylprednisolone (30 mg per kilogram of body weight over 2 to 3 hours) or placebo infusion, within strata according to age (<1 year or ≥1 year) and sex. All patients also received conventional treatment with high-dose intravenous gamma globulin (IVIG) plus aspirin.

During the 2-year study period, 589 children were treated for Kawasaki disease. Of the 313 eligible children, 199 (64%) had parental consent for enrollment in the study. Of these, 101 were randomly assigned to receive intravenous methylprednisolone, and 98 were randomly assigned to receive placebo. Echocardiograms and laboratory data were obtained at baseline and at 1 and 5 weeks after randomization.

The aims of the study were:

Primary aim:

- To compare the effect of IVMP plus IVIG to IVIG alone on coronary artery outcomes.
- Primary outcome:
    - the larger of the body surface area (BSA)-adjusted dimensions (z-scores) of the proximal right coronary artery (RCA) or proximal left anterior descending (LAD) artery, measured five weeks after randomization.
- Secondary outcomes:
    - occurrence of coronary artery aneurysms by Japanese Ministry of Health criteria;
    - individual z-scores of the left main coronary artery (LMCA), proximal RCA, and proximal LAD coronary artery at one and five weeks;
    - changes in absolute coronary dimensions for all coronary artery segments (LMCA, proximal and distal LAD, proximal and distal RCA, posterior descending coronary artery, circumflex artery) from baseline to one and five weeks after randomization

Secondary aim 1:

- To compare the effect of IVMP plus IVIG to IVIG alone on severity and duration of systemic inflammation.
- Primary outcomes:
    - total number of days of fever after completion of the initial IVIG infusion;
    - C-reactive protein measured one week after randomization.
- Secondary outcomes:

- total days of hospitalization;
- requirement for IVIG retreatment as indicated by persistent or recrudescent fever of at least 38.3°C more than 36 hours after completion of the first IVIG treatment;
- laboratory markers of inflammation including C-reactive protein five weeks after randomization and white blood cell count, hemoglobin, and albumin levels measured one and five weeks after randomization.

Secondary aim 2:

- To compare adverse reactions occurring with IVMP plus IVIG to those occurring with IVIG alone.
- Primary outcomes:
  - incidence of one or more adverse side effects;
- Secondary outcomes:
  - incidence of individual adverse reactions believed to be possibly or probably attributable to IVMP and to IVIG.

The study design has been described in great detail in Newburger et al. (*NEJM* 2007; 356:663-675) and in the study protocol (available to users with approved logins). Table 1 provides key subject characteristics. Additional information can be found in the published articles on specialized topics (see posted Bibliography at http://pediatricheartnetwork.com/ResourcesPublications/Publications.aspx#73555-kawasaki-disease-study-medication).

## Table 1. Key KD Study Analytic Cohort (N=199) Characteristics

**Table 1. Demographic, Laboratory, and Echocardiographic Characteristics at Randomization.***

| Characteristic | Intravenous Methylprednisolone | Placebo |
|---|---|---|
| Age at enrollment (199 patients) | | |
| Median (yr) | 2.9 | 2.9 |
| IQR (yr) | 1.3–5.0 | 1.6–4.4 |
| Age <1 yr (%) | 16 | 17 |
| Male sex (%) (199 patients) | 62 | 62 |
| Race or ethnic group (199 patients)† | | |
| White (%) | 63 | 52 |
| Black (%) | 17 | 20 |
| Asian (%) | 14 | 14 |
| American Indian or Alaskan Native (%) | 1 | 2 |
| Native Hawaiian or other Pacific Islander (%) | 1 | 0 |
| More than one (%) | 4 | 10 |
| Other or unknown (%) | 0 | 1 |
| Hispanic (%) | 17 | 17 |
| Days of illness at enrollment (199 patients) | | |
| Median | 6.0 | 6.0 |
| IQR | 6.0–8.0 | 5.0–7.0 |
| Hemoglobin (g/dl) (198 patients) | 11.0±1.1 | 10.9±1.2 |
| White-cell count (198 patients) | | |
| Median ($\times 10^{-3}$/mm$^3$) | 13.5 | 12.9 |
| IQR ($\times 10^{-3}$/mm$^3$) | 10.4–16.6 | 10.0–17.1 |
| Platelet count ($\times 10^{-3}$/mm$^3$) (198 patients) | 394±138 | 393±147 |
| Erythrocyte sedimentation rate (187 patients) | | |
| Median (mm/hr) | 65.5 | 67.0 |
| IQR (mm/hr) | 45.0–90.0 | 40.0–93.0 |
| C-reactive protein (138 patients) | | |
| Median (mg/dl) | 7.2 | 6.8 |
| IQR (mg/dl) | 3.3–14.0 | 3.7–18.4 |
| Albumin (g/dl) (182 patients) | 3.3±0.6 | 3.3±0.6 |
| IgA (158 patients) | | |
| Median (mg/dl) | 79 | 95 |
| IQR (mg/dl) | 50–112 | 55–147 |
| IgG (158 patients) | | |
| Median (mg/dl) | 668 | 731 |
| IQR (mg/dl) | 519–833 | 512–915 |
| IgM (157 patients) | | |
| Median (mg/dl) | 109 | 110 |
| IQR (mg/dl) | 78–146 | 65–140 |
| Body-surface area–adjusted coronary-artery dimensions | | |
| Maximum z score (195 patients)‡ | 1.70±1.45 | 1.60±1.52 |
| Proximal LAD z score (193 patients) | 1.05±1.58 | 1.14±1.49 |
| Proximal RCA z score (190 patients) | 1.19±1.23 | 1.17±1.52 |
| LMCA z score (194 patients) | 0.84±1.04 | 0.93±1.19 |
| Aortic root z score (162 patients) | 0.77±0.85 | 0.84±0.85 |
| No. of patients with coronary-artery abnormalities/no. with echocardiogram (%) (195 patients)§ | 26/99 (26) | 27/96 (28) |

* Plus–minus values indicate means ±SD. No between-group comparisons were significant (all P values >0.10). IQR denotes interquartile range, LAD left anterior descending coronary artery, RCA right coronary artery, and LMCA left main coronary artery.
† Race or ethnic group was assigned by the parent or physician. Percentages exceed 100 because patients could be assigned both to a racial group and to the Hispanic ethnic group.
‡ Maximum z score was defined as the larger of the proximal LAD and the proximal RCA z scores.
§ Patients with coronary-artery abnormalities had a proximal LAD or proximal RCA z score of 2.5 or more or at least one coronary artery that met the criteria of the Japanese Ministry of Health for aneurysms.[14]

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## DATA AND DOCUMENTATION

The following datasets and descriptor files are available for download. A login and password (request access via http://www.pediatricheartnetwork.org) are required for download capability. The lock date used for creation of the public dataset was July 7, 2009. Privacy protection of these data is described in Appendix A.

1. Study data collection forms

2. SAS version 9.4 datasets

3. Excel datasets (with variable formats applied) – These data have a .csv extension, which means that the file may also be opened either in Excel, OR in a text editor, appearing as a comma-delimited file.

4. Codebooks for each dataset – These contain variable names, labels, and descriptive statistics for each variable on the data collection forms. Key created variables are included as well.

5. The file *kdformats.sas7bcat* – Include this file in your program using:
   ```
   options fmtsearch = (fmtlib.kdformats);
   ```
   where fmtlib is specified using a libname statement as the path name.

6. Code lists D and E for form k04a

## STUDY RESOURCES

Resources posted on the pediatricheartnetwork.org website include:

- KD Study bibliography (see http://pediatricheartnetwork.com/ResourcesPublications/Publications.aspx#73555-kawasaki-disease-study-medication)

- KD Study protocol (with login access)

## DATA USE POLICY

- REQUIRED ACKNOWLEDGEMENTS: All presentations and publications using these data must include the following statement: *"The NIH/NHLBI Pediatric Heart Network Kawasaki Disease dataset was used in preparation of this work. Data were downloaded from http://pediatricheartnetwork.org/ForResearchers/PHNPublicUseDatasets.aspx on mm/dd/yyyy"."*
- PAPER, ABSTRACT, and PRESENTATION TITLES: Titles may, at the authors' discretion, mention the PHN database but should not imply that the work is from the PHN. An example of an acceptable phrase would be, "an analysis of the Pediatric Heart Network public database." Whether or not the title makes mention of the PHN, acknowledgement should be made as described in bullet 1.

- All users are requested to send a copy of published abstracts and articles to the PHN Data Coordinating Center at New England Research Institutes (PHNpubs@neriscience.com) within one month of publication. This will allow the PHN and the NHLBI to document the continued impact of this study on the field.

- The login and password provided to each user are valid for 6 months. If a user decides to complete analyses leading to more than one presentation or publication in that time period, it is requested that they notify the PHN Data Coordinating Center at New England Research Institutes of their additional analysis topics, solely for the purposes of tracking.

- The login and password to access the public dataset is provided to a single user. If a colleague would like to access the public dataset for a different analysis topic, a separate request for login and password should be submitted via the www.pediatricheartnetwork.org website.

- As an approved user, you agree that you will not attempt to establish the identities of research participants through use of this dataset.

- As an approved user, you agree to not place these data in other public locations.

## TIPS ON USING THESE DATA

1. Identification numbers for study subjects and study sites have been re-assigned for privacy protection.
    - *subject_id*: Subject ID ranging from 10001 to 10589
    - *site_blind_id*: Site ID ranging from 1 to 8 [only available for randomized subjects]

2. Prior to analysis, original variables must have any special values (typically negative numbers, see Appendix B) set to missing. Created variables (labelled as <created> in the codebooks) already contain a SAS missing value if the measurement is unavailable.

3. The study data are contained in multiple individual forms. These forms may be used jointly by merging on *subject_id,* in combination with VISIT (1=baseline; 2=week 1; 3=week 5).

4. Form k001 contains 589 screening records. The rest of the forms contain records from only the 199 randomized subjects.

5. The kdzscore dataset contains z-scores created from raw echo measures.

6. The lablist dataset contains additional baseline laboratory data, not associated with a form.

## ADDITIONAL ASSISTANCE

If you have questions about the study dataset that this documentation and the above resources (protocol, articles) have not answered, please email the PHN Mailbox at PHNmailbox@neriscience.com.

## APPENDIX A

### Implementation of Privacy Protection Rules for Public Use of the PHN KD Study Dataset

Variables that could lead to subject identification were eliminated in the public dataset. Steps included:

1. Removal of original study ID number (replaced with *subject_id*, a random consecutive numbering ranging from 10001 to 10589), and removal of zip code, acrostic, and name of person completing the forms. Of note, no names, addresses, or medical record numbers were ever contained in the original study dataset.

2. All dates in the original datasets were removed, and replaced with subject age on that date, in years with one decimal place.

3. To assist with interpretation of events and treatments that occurred in rapid succession, all time variables have also been converted to time from start of study drug (in minutes). For events/treatments that typically took place before the start of study drug, this was calculated as [date/time of study drug] – [date/time of event/treatment]. For events/treatments that typically took place after the start of study drug, this was calculated as [date/time of event/treatment] – [date/time of study drug]. Thus, the vast majority of these times are positive numbers, though negative numbers are sometimes present, depending on the event type.

4. Free (write-in) text variables were removed from the public datasets.

5. Race categories with small sample size were recoded into an “other” category.

## APPENDIX B

## Special Value Codes

-9 = missing

-8 = don’t know/indeterminate

-7 = refused to answer

-6 = not recorded

-5 = measurement could not be reliably recorded or is not interpretable (study technically inadequate)

-4 = illegible

-2 = programmed skipped field based on results of or response to a previous question

-1 = not applicable/structure not present