Prediction of Intravenous Immunoglobulin Unresponsiveness in Patients With Kawasaki Disease

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Background—In the present study, we developed models to predict unresponsiveness to intravenous immunoglobulin (IVIG) in Kawasaki disease (KD).

Methods and Results—We reviewed clinical records of 546 consecutive KD patients (development dataset) and 204 subsequent KD patients (validation dataset). All received IVIG for treatment of KD. IVIG nonresponders were defined by fever persisting beyond 24 hours or recrudescent fever associated with KD symptoms after an afebrile period. A 7-variable logistic model was constructed, including day of illness at initial treatment, age in months, percentage of white blood cells representing neutrophils, platelet count, and serum aspartate aminotransferase, sodium, and C-reactive protein, which generated an area under the receiver-operating-characteristics curve of 0.84 and 0.90 for the development and validation datasets, respectively. Using both datasets, the 7 variables were used to generate a simple scoring model that gave an area under the receiver-operating-characteristics curve of 0.85. For a cutoff of 0.15 or more in the logistic regression model and 4 points or more in the simple scoring model, sensitivity and specificity were 86% and 67% in the logistic model and 86% and 68% in the simple scoring model. The kappa statistic is 0.67, indicating good agreement between the logistic and simple scoring models.

Conclusions—Our predictive models showed high sensitivity and specificity in identifying IVIG nonresponders among KD patients. (Circulation. 2006;113:2606-2612.)

Key Words intravenous immunoglobulin ■ nonresponder ■ prediction ■ Kawasaki disease ■ risk factor

Kawasaki disease (KD) is an acute febrile illness of childhood characterized by clinical laboratory and histopathological features of systemic vasculitis. Immunologic abnormalities detectable during the acute phase of KD reflect marked activation of the immune system leading to increased cytokine production by activated effector cells. High-dose intravenous immunoglobulin (IVIG) therapy, given together with aspirin, is effective in resolving inflammation from KD and reducing occurrence of coronary artery abnormalities (CAA). However, 10% to 20% of KD patients have persistent or recurrent fever after IVIG treatment; furthermore, many studies have shown that these patients are at increased risk of developing CAA.

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Pathologically, an affected coronary artery shows influx of neutrophils in the early stage (7 to 9 days after onset) followed by a rapid transition to large mononuclear cells together with lymphocytes (predominantly CD8+ T cells) and IgA plasma cells. Destruction of the internal elastic lamina and eventually fibroblastic proliferation occur at this stage. Finally a coronary aneurysm is formed. This sequence underscores the critical importance of attenuating inflammation and vasculitis as soon as possible, before pathological change can be seen. Early identification of likely IVIG nonresponders who will require additional therapy might reduce risk of coronary artery injury. However, a method for predicting unresponsiveness to an initial course of IVIG has not been established.

Our aim in this study was to predict who among patients with KD will be IVIG nonresponders, on the basis of clinical profiles and laboratory findings before initial treatment.

Methods

Study Population

We retrospectively reviewed clinical records of consecutive KD patients treated from September 2000 to August 2004 at 13 medical institutions in Gunma and Saitama prefectures in Japan. These data (development dataset) were used to develop our predictive model. From September 2004 to January 2006, an additional 204 patients were treated and studied prospectively to test accuracy of prediction; these data represented the validation dataset.
Our criteria for a diagnosis of KD included fever (temperature exceeding 38°C) accompanied by the presence of at least 4 of the following 5 findings: bilateral conjunctival injection, changes in the lips and oral cavity, nonpuntunent cervical lymphadenopathy, polymorphous exanthema, and changes in the extremities. These diagnostic criteria are compliant with the Diagnostic Guidelines for Kawasaki Disease (5th revision). The first day of the illness was defined as the first day of fever. Patients were excluded when clinical or laboratory evidence suggested any other disease known to mimic KD (such as adenovirus infection, Epstein-Barr virus infection, scarlet fever, or bacterial cervical lymphadenitis) or atypical KD. Patients who presented with CAA before initial treatment also were excluded from study. This study was approved by the institutional review board of Gunma University Graduate School of Medicine and was performed with the informed consent from the parents of each patient.

### Treatment

In all institutions involved in the present study, IVIG was given as 1 g/kg per day over 12 hours for 2 consecutive days, as S-sulfonated human immunoglobulin (Kenketsu Venilone I; Teijin Pharma, Tokyo, Japan). Patients also received aspirin (30 mg/kg) and dipyridamole (2 mg/kg per day). The dose of aspirin was decreased to 5 mg/kg per day after normalization of C-reactive protein (CRP). A patient was considered afebrile when body temperature remained below 37.5°C for more than 24 hours. Additional rescue therapy was given when patients had persistent fever that lasted more than 24 hours or recrudescence fever associated with KD symptoms after an afebrile period. These patients were defined as IVIG nonresponders. Coronary arteries were assessed by 2-dimensional echocardiography performed before initial treatment and repeated between 6 to 8, 12 to 16, and 25 to 30 days after the initial treatment. CAA was diagnosed when any of these examinations showed an internal lumen diameter ≥3 mm in a child <5 years old or ≥4 mm in a child ≥5 years old; if the internal diameter of a segment was at least 1.5 times as large as that of an adjacent segment; or if the lumen appeared irregular.

### Data Analysis

All analyses were carried out by means of an SPSS statistical software package, version 13.0J (SPSS Japan, Tokyo). Data are presented as the mean ± SD for continuous variables or as a percentage for categorical variables. For all analyses a 2-sided probability value below 0.05 was considered to indicate statistical significance.

Univariable analysis using an unpaired t test was performed to determine whether white blood cell count, percentage of white blood cells representing neutrophils (% neutrophils), hematocrit, and platelet count; or serum concentrations of total bilirubin, aspartate aminotransferase (AST), alanine aminotransferase (ALT), sodium, potassium, chloride, total protein, albumin, and CRP discriminated between IVIG nonresponders and IVIG responders. If a laboratory test was performed twice or more before initial IVIG, the highest value was chosen for analysis in the case of white blood cell count, % neutrophils, serum total bilirubin, AST, ALT, and CRP; or the lowest value in the case of platelet count, hematocrit, serum sodium, potassium, chloride, total protein, and albumin. To identify independent predictors of IVIG unresponsiveness, multivariable logistic regression models were constructed using demographic variables (age in months, gender, and days of illness at initial treatment) plus laboratory variables that had been selected by univariable analysis. Multivariable logistic regression analysis was performed using stepwise logistic regression with forward selection and backward elimination. A probability value of P<0.05 was considered to indicate lack of deviation between the model and observed event rate. Patients with missing values were excluded from the multivariable regression analysis.

### Results

#### Characteristics and Clinical Outcomes of Patients

During the study period, 756 consecutive KD patients were treated with IVIG. Six patients were excluded: Four patients had a CAA before initial treatment, whereas 2 others did not complete IVIG treatment because of treatment-associated hypotension. Thus, 750 KD patients were analyzed in this study (development dataset, n=546; validation dataset, n=204). Table 1 shows baseline characteristics and clinical outcomes of patients in both development and validation datasets. No significant differences were demonstrated between development and validation datasets except for serum albumin and CRP (serum albumin 4.0±0.4 versus 3.9±0.5, P=0.001; CRP 8.9±5.3 versus 7.8±4.8, P=0.007). CAA developed significantly more often in IVIG nonresponders than in responders (acute-phase CAA, 32% versus 0.8%, P<0.001; CAA at 4 weeks, 15% versus 0.2%, P<0.001 by Fisher exact test).

### Predictive Model for IVIG Unresponsiveness

In the development dataset, univariable analysis identified 10 laboratory variables (% neutrophils, platelet count, total bilirubin, AST, ALT, sodium, chloride, total protein, albumin, and CRP) as significant predictors of IVIG unresponsiveness (Table 2). These 10 laboratory variables plus 3 demographic variables (male gender, age in months, and days of illness at initial treatment) were selected as variables for the regression model. Multivariable logistic regression analysis was performed using an odds ratio with a 95% confidence interval (CI). The discrimination of the multivariable predictors of being an IVIG nonresponder, we created a logistical prediction rule by assigning point scores for the presence of each covariate. The sum of all points was calculated for each patient. For the final risk score, 2 risk strata (low- and high-risk group) were defined according to the model that we established. The k statistic was used to determine concordance between the logistical regression and simple scoring models; k values above 0.4, 0.6, and 0.8 indicate fair, good, and excellent agreement.

### Table 1. Baseline Characteristics and Clinical Outcomes

<table>
<thead>
<tr>
<th></th>
<th>Development Dataset (n=546)</th>
<th>Validation Dataset (n=204)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age in months</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean±SD</td>
<td>29.1±22.1</td>
<td>28.4±20.5</td>
<td>0.71</td>
</tr>
<tr>
<td>Range</td>
<td>1–119</td>
<td>2–88</td>
<td></td>
</tr>
<tr>
<td>Male gender, n (%)</td>
<td>315 (58)</td>
<td>102 (50)</td>
<td>0.07</td>
</tr>
<tr>
<td>Days of illness at initial treatment</td>
<td>4.9±1.5</td>
<td>4.8±1.3</td>
<td>0.72</td>
</tr>
<tr>
<td>Range</td>
<td>1–13</td>
<td>2–9</td>
<td></td>
</tr>
<tr>
<td>IVIG nonresponders, n (%)</td>
<td>112 (21)</td>
<td>42 (21)</td>
<td>1.00</td>
</tr>
<tr>
<td>Coronary artery abnormalities, n (%)</td>
<td>43 (8)</td>
<td>11 (5)</td>
<td>0.27</td>
</tr>
</tbody>
</table>

To increase the usefulness of this risk stratification in clinical practice, we approximated it with a simple scoring model where integer score points were assigned to each variable. Values beyond cutoff points for individual variables were defined approximately as those in the upper quartile (AST, % neutrophils, and CRP) or the lower quartile (sodium, days of illness at initial treatment, age in months, and platelet count), and multivariable logistic regression analysis was performed. On the basis of logistic coefficients for each of the multivariable predictors of being an IVIG nonresponder, we created a logistical prediction rule by assigning point scores for the presence of each covariate. The sum of all points was calculated for each patient. For the final risk score, 2 risk strata (low- and high-risk group) were defined according to the model that we established. The k statistic was used to determine concordance between the logistical regression and simple scoring models; k values above 0.4, 0.6, and 0.8 indicate fair, good, and excellent agreement.

The authors had full access to the data and take full responsibility for its integrity. All authors have read and agree to the manuscript as written.
of illness at initial treatment) were included in the stepwise forward logistic regression analysis. Sodium, % neutrophils, days of illness at initial treatment, AST, age in months, platelet count, and CRP proved to be independent predictors of IVIG nonresponse (IVIG responders, \(n=380\); IVIG nonresponders, \(n=108\); Table 3). The area under the ROC curve was 0.86 (95% CI, 0.83 to 0.89) for the logistic regression model and 0.85 (95% CI, 0.81 to 0.88) for the risk-scoring model, representing excellent discrimination by either model. The Hosmer-Lemeshow statistic was not significant (probability value of 0.17 and 0.82 for the logistic model and the risk-scoring model, respectively; Figure 1). After identifying the prevalence of IVIG nonresponders and overall numbers of patients for individual scores, a risk score was developed on the basis of the sum of points present in each case. For simplicity, 2 risk strata were identified: low risk, with scores of 0 to 3, encompassing 56% of patients; and high risk, with scores of 4 or more, 44% of patients. Sensitivity and specificity were 86% and 67% in the logistic model and 86% and 68% in the simple scoring model. The \(\kappa\) statistic was 0.67, which indicated good agreement between the logistic model and the simple scoring model. Observed rates of IVIG unresponsiveness and CAA occurrence according to this simple scoring model are shown in Figures 2 and 3. In the high-risk group (scores \(\geq 4\)), the occurrence of IVIG unresponsiveness was 43%, whereas it was only 5% in the low-risk group (scores 0 to 3). Similarly, the occurrence of CAA was 16% in the high-risk group, whereas it was only 1% in the low-risk one. Especially in patients with very high scores (score \(\geq 7\)), the occurrence of IVIG unresponsiveness and CAA was extremely high (75% and 36%, respectively).

**TABLE 3. Multivariable Logistic Regression Analyses for Prediction of IVIG Nonresponse in the Development Dataset**

<table>
<thead>
<tr>
<th></th>
<th>IVIG Responders</th>
<th>IVIG Nonresponders</th>
<th>(P)</th>
</tr>
</thead>
<tbody>
<tr>
<td>White blood cell count, (\times 10^{9}/\text{mm}^3) &amp; 14.6±4.7         &amp; 15.2±5.7           &amp; 0.30</td>
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<td></td>
<td></td>
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<tr>
<td>% Neutrophils          &amp; 67.1±14.2       &amp; 77.0±10.6          &amp; &lt;0.001</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Hematocrit, %          &amp; 33.7±2.8        &amp; 33.6±2.8           &amp; 0.88</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Platelet count, (\times 10^{12}/\text{mm}^3) &amp; 36.3±20.0        &amp; 34.1±18.0          &amp; 0.22</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total bilirubin, mg/dL &amp; 0.7±0.7         &amp; 1.4±1.2            &amp; &lt;0.001</td>
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<td></td>
</tr>
<tr>
<td>AST, IU/L              &amp; 78±132          &amp; 209±277            &amp; &lt;0.001</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ALT, IU/L              &amp; 70±112          &amp; 117±183            &amp; &lt;0.001</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sodium, mmol/L         &amp; 134.9±2.7       &amp; 132.9±2.1          &amp; &lt;0.001</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Potassium, mmol/L      &amp; 4.3±0.4         &amp; 4.3±0.4            &amp; 0.30</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Chloride, mmol/L       &amp; 99.1±3.4        &amp; 97.8±3.3           &amp; &lt;0.001</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total protein, g/dL    &amp; 6.6±0.6         &amp; 6.4±0.6            &amp; 0.001</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Albumin, g/dL          &amp; 4.0±0.4         &amp; 3.9±0.4            &amp; 0.005</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CRP, mg/dL             &amp; 8.5±5.1         &amp; 10.7±5.7           &amp; &lt;0.001</td>
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</table>

**Discussion**

Principal findings of the present study to develop and validate new prediction models were (1) that IVIG nonresponders could be identified accurately in advance using 7 laboratory and demographic variables available before initial treatment; (2) that the prediction models could be used to define 2 risk...
strata in patients with KD indicating high or low risk for IVIG unresponsiveness; and (3) that a simple scoring model could be constructed that would show good agreement with the logistic regression model.

Several scoring models for predicting development of CAA have been developed previously. The first of these, reported by Asai in 1983, was useful in determining indications for cardiac catheterization at a time before 2-dimensional echocardiography was widely used in Japan for routine monitoring of all KD patients. Scoring models for predicting CAA devised by Nakano et al and by Iwasa et al have not been verified using multicenter data; they also require repeated laboratory tests over several days before treatment. Beiser et al also reported a predictive instrument of CAA based on a large multicenter trial. Because their sequential classification for predicting CAA requires data concerning fever on the day after infusion of IVIG, one cannot use it to assess risk before initiation of IVIG treatment. The Harada score is used by many Japanese physicians to decide whether IVIG therapy should be given. However, the influence of the Harada score has been fading in Japan because IVIG now is given to almost KD patients. Fukunishi et al reported that KD patients with CRP \( \geq 10 \) mg/dL, lactate dehydrogenase \( \geq 590 \) IU/L, and/or hemoglobin \( \leq 10 \) g/dL before initial treatment were likely to be IVIG nonresponders. Although predictive values were encouraging (sensitivity of 84.6% and specificity of 87.0%), the sample size was too small to be reliable (n=82, including only 13 IVIG nonresponders).

Our large multicenter study showed that high AST, CRP, and % neutrophils; low age in months, sodium, and platelet count; and administration of IVIG early in the course of illness were independent risk factors for IVIG unresponsiveness. Each of the variables included in our scoring model also has been reported to be a risk factor for CAA, which appears reasonable because most KD patients with CAA are unresponsive to IVIG. In our present study, CAA during the acute phase developed significantly more often in IVIG nonresponders than in IVIG responders. Day of illness at initial treatment was confirmed to be a risk factor for IVIG unresponsiveness. As all patients in our trial received IVIG as an initial treatment, the results are consistent with some previous reports showing early administration of IVIG to be a strong predictor of IVIG unresponsiveness or development of CAA. On the other hand, delay in diagnosis and initiation of treatment has been suggested to result in increased risk of CAA formation. An important question thus arises as to why patients with early diagnosis and treatment had increased risk for IVIG unresponsiveness and CAA. We therefore calculated separate mean scores in groups defined by timing of treatment using all variables in the simple scoring model except for day of illness at initial treatment. These mean scores still were higher in patients beginning treatment after 4 days of illness than in patients beginning treatment after 5 days of illness (2.9 ± 2.5 versus 2.1 ± 2.0, \( P < 0.001 \), unpaired \( t \) test). Accordingly, we speculate that some patients diagnosed and treated earlier in their illness may have had a more severe form of KD that would increase incidence of IVIG nonresponse and CAA.

In the present study, low serum sodium concentration and high serum AST both strongly predicted IVIG unresponsiveness. In previous reports about the relationship between serum sodium concentration and outcome of KD, Nakamura...

### Table 4. Multivariable Predictors of IVIG Unresponsiveness in a Simple Scoring Model

<table>
<thead>
<tr>
<th></th>
<th>Logistic Coefficient (β)</th>
<th>SE</th>
<th>Odds Ratio</th>
<th>Lower</th>
<th>Upper</th>
<th>Score Points</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sodium ≤133 mmol/L</td>
<td>1.47</td>
<td>0.23</td>
<td>4.34</td>
<td>2.75</td>
<td>6.87</td>
<td>2</td>
</tr>
<tr>
<td>Days of illness at initial treatment ≤4</td>
<td>1.31</td>
<td>0.25</td>
<td>3.70</td>
<td>2.29</td>
<td>6.00</td>
<td>2</td>
</tr>
<tr>
<td>AST ≥100 IU/L</td>
<td>1.27</td>
<td>0.25</td>
<td>3.57</td>
<td>2.21</td>
<td>5.77</td>
<td>2</td>
</tr>
<tr>
<td>Neutrophil ≤80%</td>
<td>1.21</td>
<td>0.27</td>
<td>3.34</td>
<td>1.99</td>
<td>5.62</td>
<td>2</td>
</tr>
<tr>
<td>CRP ≥10 mg/dL</td>
<td>0.81</td>
<td>0.24</td>
<td>2.25</td>
<td>1.39</td>
<td>3.63</td>
<td>1</td>
</tr>
<tr>
<td>Age ≤12 mo</td>
<td>0.79</td>
<td>0.28</td>
<td>2.20</td>
<td>1.26</td>
<td>3.83</td>
<td>1</td>
</tr>
<tr>
<td>Platelet count ≤3.0 × 10^11 mm^3</td>
<td>0.72</td>
<td>0.23</td>
<td>2.06</td>
<td>1.31</td>
<td>3.25</td>
<td>1</td>
</tr>
</tbody>
</table>

**Figure 1.** Calibration plot of predicted-actual rates of IVIG unresponsiveness. X-axes refer to decile of predicted risk based on the logistic regression model (A) and simple scoring model (B).
et al.\textsuperscript{20,21} noted that serum sodium might be the most useful predictor of giant coronary aneurysms caused by KD; our results are compatible with theirs. The relationship between hypotension and severity of KD might involve permeability of the endothelium and/or dehydration; further studies are needed to clarify mechanisms. KD patients frequently show moderate hepatic impairment. Because cytokine-activated natural killer cells accumulate at inflammatory lesions in the acute phase of KD, these activated natural killer cells might accumulate in vascular endothelium and along liver sinusoids,\textsuperscript{25} where they would be likely to participate in hepatic injury as well as vascular endothelial cell injury in KD.

The relationship between IVIG unresponsiveness and CAA according to the defined risk score had a nonlinear nature in our study. This might be anticipated, considering that nonresponse may reflect only severity of ongoing inflammation, whereas development of CAA might be affected by both ongoing inflammation and hemodynamics after initiation of treatment. For example, tachycardia was confirmed to be a powerful predictor of CAA.\textsuperscript{26} This report supports the importance of hemodynamics in KD-associated CAA.

Our predictive algorithm for prognosis in patients with KD may be used to help guide clinicians in the initial decision about the site of therapy. Because KD patients with high scores are at high risk for IVIG unresponsiveness and CAA, careful follow-up such as more frequent echocardiography should be considered in such patients. However, a question remains as to the appropriate therapy in patients whose scores predict high risk for IVIG unresponsiveness. Because KD patients with IVIG unresponsiveness are thought to have severe inflammation and vasculitis, a more aggressive initial anti-inflammatory treatment subsequent to early identification of likely IVIG nonresponders might reduce the occurrence of IVIG unresponsiveness and CAA. Recent reports suggest that corticosteroid therapy combined with IVIG as the initial treatment may promote the more rapid resolution of inflammation\textsuperscript{27–29} and lower the occurrence of CAA.\textsuperscript{30,31} Treatment with tumor necrosis factor-\(\alpha\) blockers might also be a initial therapy for high-risk patients; especially given that a pilot study has shown that treatment with infliximab in IVIG nonresponders abolished fever and decreased serum CRP without infusion reactions or complications.\textsuperscript{32} No firm conclusions can be reached at this time about the usefulness of each treatment in KD; therefore, prospective clinical trials are warranted to determine the role of these therapies in patients at high risk for IVIG nonresponse.
This study has several limitations. The first is the possibility of selection bias, because the initial phase of the study was retrospective. Second, late data from subsequent prospectively enrolled patients were used to validate performance of the logistic model developed on the basis of the early data. A more stringent external validation would involve completely new data from other institutions to further assess generalizability of the proposed scoring model. Caution in applying the model is warranted until this is carried out. Third, the IVIG dosage used in this study, one of the standard regimens in Japan, differs from the regimen recommended in the United States and elsewhere (2 g/kg as a single infusion). Finally, we adopted Japanese Ministry of Health criteria as the definition of CAA, because they are simple and easy to use in clinical settings. One should note, however, that De Zorzi et al have reported that the use of Japanese Ministry of Health criteria might underestimate the true incidence of CAA in patients with KD.

In conclusion, our predictive models based on demographic and laboratory variables accurately predicted IVIG nonresponse in initial treatment of patients with KD. These models should prove valuable for making decisions about initial treatment in patients with KD and should facilitate and encourage exploration of alternative treatments for patients at high risk for IVIG unresponsiveness and CAA.

Acknowledgments
We thank all investigators and their staff for their contributions to this study at the following institutions: Department of Pediatrics, Kiryu Kosei General Hospital; Department of Pediatrics, Tatebayashi Kosei Hospital; Department of Pediatrics, Takasaki National Hospital; Department of Pediatrics, Fujioka General Hospital; Department of Pediatrics, Iesaki Municipal Hospital; Department of Pediatrics, Gunma Central General Hospital; Department of Pediatrics, Suiseikai Maebashi Hospital; Department of Pediatrics, Haramachi Red Cross Hospital; Department of Pediatrics, Fukaya Red Cross Hospital; Department of Pediatrics, Tone Central Hospital; Department of Pediatrics, Maebashi Red Cross Hospital; Department of Cardiology, Gunma Children’s Medical Center; and Department of Pediatrics, Gunma University Graduate School of Medicine.

Disclosures
None.

References
CLINICAL PERSPECTIVE

Intravenous immunoglobulin (IVIG) therapy for Kawasaki disease (KD), administered together with aspirin, improves vasculitis and reduces the occurrence of coronary artery abnormalities. However, 10% to 20% of KD patients have persistent or recurrent fever after IVIG; many studies have demonstrated that this subgroup of children is at an increased risk of developing coronary artery abnormalities. We propose new models to predict persistent fever after IVIG using commonly assessed demographic and laboratory variables, including day of illness at initial treatment, age in months, percentage of neutrophils in the white blood count, platelet count, and serum aspartate aminotransferase, sodium, and C-reactive protein. Our predictive models may prove valuable in stratification and decision-making with respect to the initial treatment for KD patients.
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_Circulation_. 2006;113:2606-2612; originally published online May 30, 2006; doi: 10.1161/CIRCULATIONAHA.105.592865

_Circulation_ is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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Print ISSN: 0009-7322. Online ISSN: 1524-4539

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