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Delayed Diagnosis of Kawasaki Disease: What Are the Risk Factors?

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ABSTRACT

OBJECTIVE. Because late diagnosis of Kawasaki disease increases the risk for coronary artery abnormalities, we explored the prevalence of and possible risk factors for delayed diagnosis by using the database of the Pediatric Heart Network trial of corticosteroid treatment for Kawasaki disease.

METHODS. We collected sociodemographic and clinical data at presentation for all patients who were treated for presumed Kawasaki disease at 8 centers (7 in the United States, 1 in Canada). Delayed diagnosis was evaluated by total number of illness days to diagnosis and by the percentage of patients who were treated after day 10 of illness. Independent predictors of delayed diagnosis were identified by using multivariate linear and logistic regression.

RESULTS. Of the 589 patients who received intravenous immunoglobulin, 27 were treated before screening for the trial and excluded; 562 patients formed the cohort for analysis. Kawasaki disease was diagnosed at 7.9 ± 3.9 days, 92 (16%) cases after day 10. Centers were similar with respect to patient age and gender. Centers differed in the patient percentage with incomplete Kawasaki disease; clinical criteria of cervical adenopathy, oral changes, and conjunctivitis; and distance of residence from the center. Independent predictors of greater number of illness days at diagnosis included center, age of <6 months, incomplete Kawasaki disease, and greater distance from the center. Independent predictors of diagnosis after day 10 were age of <6 months, incomplete Kawasaki disease, and greater distance). Socioeconomic variables had no association with delayed diagnosis.

CONCLUSIONS. Even after adjustment for patient factors, illness duration at diagnosis varies by center. These findings underscore the need to maintain a high index of suspicion of Kawasaki disease in the infant who is younger than 6 months and has prolonged fever even with incomplete criteria. Outreach educational programs may be useful in promoting earlier recognition and treatment of Kawasaki disease.

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Key Words

Kawasaki disease, delayed diagnosis, Pediatric Heart Network

Abbreviations

KD—Kawasaki disease
IVIg—intravenous immunoglobulin
PHN—Pediatric Heart Network
OR—odds ratio

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KAWASAKI DISEASE (KD) is an acute febrile vasculitis that is associated with coronary artery aneurysms in ~20% of untreated children.^{1,2} Treatment with intravenous immunoglobulin (IVIg), if administered during the first 10 days of illness, reduces the prevalence of coronary aneurysms approximately fivefold.^{3,4} When treatment is delayed beyond day 10 of illness, the incidence of coronary artery aneurysms increases nearly threefold over earlier treatment.⁵ Indeed, treatment on or before day 7 of illness is ideal.^{6,7}

Timely diagnosis of KD is often a challenge. Despite almost 4 decades of research, the cause of KD remains unknown, so the diagnosis depends on nonspecific clinical signs rather than a definitive laboratory test. The epidemiologic case definition includes fever and at least 4 of 5 principal clinical criteria: changes in the extremities, polymorphous exanthema, bilateral conjunctival injection, changes in the lips and oral cavity, and cervical adenopathy.^{1,7} These findings may be transient, and the constellation of principal clinical criteria that are present on physical examination may vary over time. Furthermore, coronary artery aneurysms have been documented in incomplete cases with <4 principal clinical criteria.⁸

The purposes of this study were to describe the prevalence of and risk factors for delayed diagnosis of KD. Our study population comprised all children who were treated with IVIg during a 2-year period at clinical centers that participate in the National Heart, Lung, and Blood Institute Pediatric Heart Network (PHN) corticosteroid trial for KD treatment.⁹

METHODS

Patients

From December 2002 through December 2004, the PHN conducted a multicenter, randomized, double-blind, placebo-controlled trial to evaluate the efficacy of corticosteroids for the primary treatment of KD at 8 clinical centers in North America (7 in the United States and 1 in Canada). For determination of eligibility and for provision of descriptive statistics for the population from which patients were enrolled in the randomized trial, screening data were obtained for all patients who were treated with IVIg for a presumed diagnosis of KD. These screened patients form the cohort for this report.

Patient data were deidentified by using study identification numbers, and the study protocol and screening forms for the trial were reviewed and approved by the institutional review board at each of the 8 clinical centers and the data-coordinating center. An independent data and safety monitoring board monitored the conduct of the trial.

Data Collection and Definitions

Demographic data that were collected on the screening form included age at presentation, gender, race and eth-

nicity, and zip or postal code. Clinical data included number of illness days from onset of fever to diagnosis of KD, previous treatment with IVIg, and the principal clinical criteria that had been or were present by the time of KD diagnosis.

We assessed delay in diagnosis of KD in 2 ways: (1) total number of illness days from onset of fever to diagnosis of KD; and (2) the proportion of patients whose illness was diagnosed after day 10. By convention, the first day of fever was considered day 1 of illness.

The distance from the patient's residence to the center was derived from zip or postal code. Socioeconomic status was estimated by using 2000 census data (www.census.gov/Press-Release/www/2002/sumfile3.html) and was available by US zip code (thus not calculated for Canadian patients). Three measures of socioeconomic status were analyzed: the percentage of the population with a high school degree or higher, median family income, and the percentage of households under the poverty level. Each US patient was assigned the socioeconomic status that corresponded to his or her zip code.

Statistical Analyses

The primary outcome measures for this study were the number of days from the onset of fever to diagnosis of KD as a continuous variable and whether diagnosis occurred after day 10 of illness. We compared center differences in outcomes and proportion with incomplete KD using analysis of variance and Fisher's exact test, respectively. Univariate associations between number of fever days and potential predictors were identified using linear regression. Univariate associations between the proportions of patients whose illness was diagnosed after day 10 were identified using logistic regression. The Tukey multiple-comparisons method was used to compare mean number of illness days between pairs of racial subgroups. Generalized additive modeling was used to examine nonlinearities in age and distance with respect to outcome and to suggest appropriate transformations. Univariate predictors significant at the $P < .20$ level were then evaluated in multivariate modeling. Multivariate linear and logistic regressions were used to identify independent predictors of the number of illness days until diagnosis and the proportion diagnosed after day 10 of illness, respectively. Least-squares means \pm SEs are used to report covariate-adjusted number of illness days. Analyses were conducted by using SAS 9.1 (SAS Institute, Inc, Cary, NC).

RESULTS

During the 2-year study period, 589 patients received IVIg for the treatment of KD. Of these, 27 patients had received at least 1 dose of IVIg before screening at the PHN center and were excluded; the remaining 562 patients were included in the analysis; they had a median age of 2.9 years (range: 11 days to 18.9 years), and 60%

TABLE 1 Patient and Disease Characteristics of Patients Who Were Screened for the PHN KD Trial (Overall and According to Number of Illness Days)

Characteristic	Total	Diagnosis on or Before Day 10	Diagnosis After Day 10	P
<i>n</i>	562	470	92	
Age \pm SD (median), y	3.6 \pm 2.9 (2.9)	3.6 \pm 2.8 (2.9)	3.6 \pm 3.5 (2.7)	.85
Age < 6 mo, %	7	5	16	<.001
Male, %	60	60	64	.42
Race/ethnicity, %				.04
White	55	53	70	
Black/African American	17	18	13	
Asian	20	22	12	
Other	7	7	4	
Hispanic	16	16	14	.69
Distance from center \pm SD, mi	15.9 \pm 16.9	15.2 \pm 16.7	19.3 \pm 17.8	.04
No. of days from fever onset to diagnosis \pm SD (median)	7.9 \pm 3.9 (7.0)	6.6 \pm 1.7 (6.0)	14.8 \pm 4.8 (13.0)	<.001
Clinical criteria, %				
Incomplete KD	28	24	49	<.001
Extremity changes	77	78	71	.17
Rash	86	88	79	.04
Bilateral conjunctival injection	88	92	71	<.001
Oral changes	88	89	72	<.001
Cervical lymphadenopathy	44	46	32	.01

were male (Table 1). The most common racial groups were white (55%) and Asian (20%). The number of illness days at the time of diagnosis of KD was 7.9 ± 3.9 (median: 7.0); 92 (16%) cases were diagnosed after day 10 of illness.

Univariate Analyses

We explored whether delays in diagnosis were related to the presence of fewer clinical criteria. Children who had < 4 criteria (incomplete KD) received the diagnosis significantly later than those with ≥ 4 criteria (9.5 ± 4.7 vs 7.3 ± 3.3 days, respectively; $P < .001$). Similarly, a higher percentage of patients with incomplete KD received the diagnosis after day 10 of illness (29% vs 12%; $P < .001$).

The total number of illness days to diagnosis was associated with the presence versus absence of individual clinical criteria: extremity change (7.7 ± 3.8 vs 8.6 ± 4.0 days; $P = .02$), rash (7.8 ± 3.8 vs 9.0 ± 4.4 days; $P = .01$), bilateral conjunctival injection (7.6 ± 3.4 vs 10.7 ± 5.8 days; $P < .001$), oral change (7.6 ± 3.4 vs 10.2 ± 5.7 days; $P < .001$), and cervical lymphadenopathy (7.5 ± 3.4 vs 8.3 ± 4.2 days; $P = .02$). Similarly, diagnosis after day 10 of illness was more common when specific clinical criteria were absent (Table 1).

Younger age was also significantly associated with delayed diagnosis; nonparametric modeling demonstrated that diagnosis was most likely to be delayed in infants who were younger than 6 months. Infants who were younger than 6 months ($n = 37$), compared with older children ($n = 525$), received the diagnosis after a significantly greater number of illness days (10.0 ± 5.4

vs 7.8 ± 3.7 days; $P < .001$). Similarly, a significantly greater proportion of infants who were younger than 6 months received the diagnosis after day 10 of illness (41% vs 15%; $P < .001$). Age had a curvilinear relationship with diagnosis after day 10 (Fig 1), with adolescents also at risk for delayed diagnosis; however, statistical power was limited in this age range, and a term for additional risk in this age group was not retained in modeling.

We hypothesized that residence at a greater distance from the clinical center would be a risk factor for delayed diagnosis. Greater distance was positively correlated

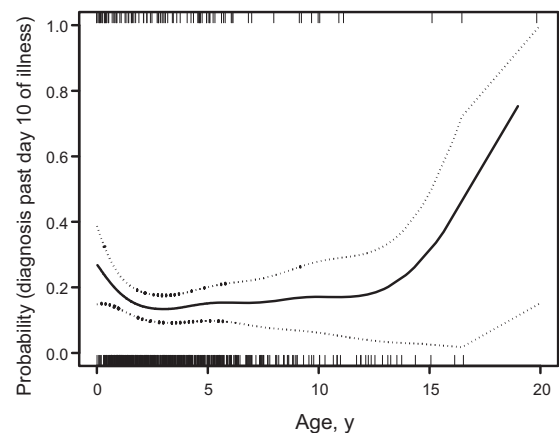


FIGURE 1 Estimated probability of diagnosis after day 10 based on a generalized additive model fit for age. The P value for nonlinearity is .01, primarily because of the increased likelihood of diagnosis after day 10 in younger children. The fringes represent the ages of patients who received the diagnosis after day 10 (upper) and on or before day 10 (lower).

TABLE 2 Multivariate Risk Factors for Illness Days to KD Diagnosis

Parameter	Covariate-Adjusted No. of Illness Days, Mean ± SE ^a	P
Site		.03
1	8.89 ± 0.42	
2	8.70 ± 0.42	
3	9.38 ± 0.57	
4	9.56 ± 0.49	
5	10.31 ± 0.75	
6	8.07 ± 0.82	
7	9.70 ± 0.55	
8	7.54 ± 0.72	
Age		
<6 mo	9.82 ± 0.62	.01
≥6 mo	8.22 ± 0.21	
Distance, mi	0.02 ± 0.01 ^b	.03
Incomplete KD		
Yes (principal criteria < 4)	9.97 ± 0.40	<.001
No (principal criteria ≥ 4)	8.07 ± 0.37	

Linear regression model: $R^2 = 0.12$.

^a The covariate-adjusted mean number of illness days is the mean number of illness days assuming that the mean values of, or prevalences of, each other variable in the model are the same for the subgroups of interest (eg, similar across centers, similar for patients <6 vs ≥6 months); therefore, the estimated subgroup differences in the mean number of illness days cannot be attributed to variation in the other factors included in the model.

^b Covariate-adjusted mean increase in number of illness days per 1-mi increase in distance.

with greater number of illness days ($P < .01$), and mean distance from center was greater in patients who received the diagnosis after day 10 of illness ($P = .04$; Table 1).

In univariate analysis, race was significantly associated with the total number of illness days to diagnosis ($P = .04$) because white patients had a longer time to diagnosis compared with Asian patients (mean: 8.3 vs 7.1 day, pairwise adjusted $P = .01$). The trend was similar for the proportion of patients who received the diagnosis after day 10 of illness, with 20% of white patients having late diagnosis and 10%, 12%, and 11% of Asian, black/African American, and “other” patients, respectively, having a late diagnosis ($P = .04$). Gender had no association with either the total number of illness days to diagnosis ($P = .58$) or the percentage of patients who received the diagnosis after day 10 of illness ($P = .42$).

Among US cases, socioeconomic status was not related to either of the outcome measures used to define delayed diagnosis. The mean for median family income of the patients who received a diagnosis early (on or before day 10) versus late (after day 10) of illness was \$59 700 ± \$27 200 vs \$58 200 ± \$21 500, respectively ($P = .66$). The mean percentage of families who were estimated to be below poverty level was 10 ± 10% vs 9 ± 10% for the patients who received the diagnosis early versus late ($P = .41$). The mean percentage of families who were estimated to have a high school degree or higher was 80 ± 15% vs 82 ± 14% for the patients who received the diagnosis early versus late ($P = .50$).

TABLE 3 Multivariate Risk Factors for KD Diagnosis After Day 10 of Illness

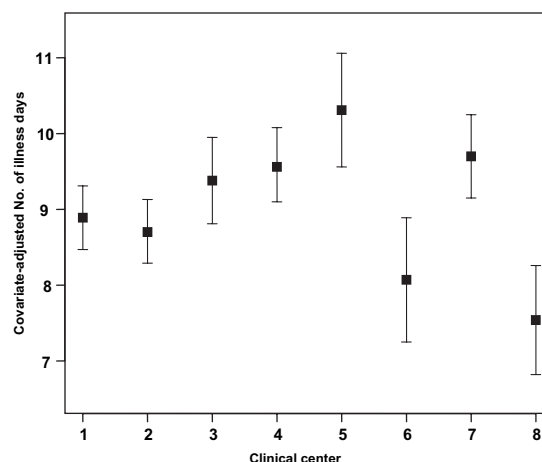
Parameter	OR	95% CI	P
Age, <6 vs ≥6 mo	3.03	1.47–6.27	.003
Incomplete KD vs ≥ 4 principal criteria	2.84	1.77–4.56	<.001
Distance, mi	1.01	1.00–1.02	.04

Logistic regression model: $R^2 = 0.061$. CI indicates confidence interval.

We considered whether center differences were related to the likelihood of delayed diagnosis. Both the total number of days from onset of fever to diagnosis (center mean number of illness days range: 6.4–9.7 days; $P < .01$) and the proportion of total patients who received the diagnosis after day 10 of illness (range: 4% to 30%; $P = .02$) varied significantly by center. Centers also varied significantly in the proportion of treated patients who had <4 principal clinical criteria (range: 13% to 47%; $P = .004$).

Multivariate Analyses

The results of multivariate regression analyses are summarized in Tables 2 and 3. Centers differed in their proportion of patients with incomplete KD and with specific principal clinical criteria; however, clinical center remained an independent risk factor for an increased number of illness days from onset of fever to diagnosis of KD even when adjusting for these factors (Fig 2). Specifically, in models that adjusted for the presence versus absence of incomplete KD (ie, <4 vs ≥4 principal criteria), independent risk factors for greater number of illness days until diagnosis included age < 6 months ($P = .01$), distance from center ($P < .03$), < 4 principal criteria ($P < .001$), and clinical center ($P = .03$). When the multivariable model included individual principal criteria rather than an indicator variable for incomplete KD,

**FIGURE 2**

Covariate-adjusted mean number of illness days according to center. Bars represent ± 1 SE. The number of illness days differs significantly according to center (7 degrees of freedom; $P = .03$), even after adjustment for age (<6 vs ≥6 months), distance from center, and diagnosis of incomplete versus complete KD.

independent predictors included age < 6 months ($P < .01$), clinical center ($P < .05$), absence of bilateral conjunctival injection ($P < .001$), and absence of oral changes ($P < .001$). Greater distance from center was marginally associated with delays in diagnosis in this model ($P = .06$). We assessed whether the impact of distance and incomplete KD on number of illness days depended on age (<6 vs ≥ 6 months) and found no interaction.

We also identified independent predictors of the dichotomous outcome of diagnosis on or before day 10 versus after day 10 of illness using multivariate logistic regression (Table 3). Adjusting for incomplete KD, independent predictors of diagnosis after day 10 included age < 6 months (odds ratio [OR]: 3.03; $P < .01$) <4 principal criteria (OR: 2.84; $P < .001$), and distance from center in miles (OR: 1.01; $P = .04$). Clinical center did not achieve statistical significance in this multivariate model ($P = .11$). Adjusting for individual principal clinical criteria, independent predictors for diagnosis after day 10 of illness included age < 6 months (OR: 3.54; $P < .001$), absence of bilateral conjunctival injection (OR: 0.28; $P < .001$), and absence of oral changes (OR: 0.48; $P < .02$).

DISCUSSION

KD is an acute childhood vasculitis of unknown cause with morbidity and mortality deriving primarily from coronary artery aneurysms.^{1,2} The leading cause of acquired heart disease in children in North America today,¹⁰ KD cannot be diagnosed by any specific test or pathognomonic clinical feature. Rather, the clinician must maintain a high index of suspicion for KD in the febrile patient with a constellation of clinical findings, including fever, bilateral conjunctival injection, erythema of the lips and oral mucosa, changes in the extremities, rash, and cervical lymphadenopathy.

We used 2 outcomes to assess delays in the diagnosis of KD: the number of days from onset of illness to diagnosis (illness days) and diagnosis on or before day 10 versus after day 10 of illness. We found that predictors of delayed diagnosis included age < 6 months, fulfilling <4 principal clinical criteria (ie, incomplete KD), greater distance of residence from the clinical center, and specific clinical center (illness days only). The presence of conjunctival injection or of oral changes was protective against a late diagnosis of KD.

Previous studies have explored the consequences and predictors of delayed diagnosis of KD. A retrospective chart review of patients who had KD and were treated during a 6-year period in Denver revealed that patients who were treated after day 10 of illness were 2.8 times more likely to have coronary artery aneurysms than those who were treated earlier.⁵ Indeed, because vascular injury is evident as early as 1 week after the onset of fever,⁶ the most recent American Heart Association/American Academy of Pediatrics guidelines for KD rec-

ommend treatment by day 7 if possible.⁷ Treatment within this period depends on both timely medical consultation by the parents and early recognition of KD by the clinician who is evaluating the child.

A variety of factors may have a negative impact on the timely diagnosis of KD. Anderson et al⁵ retrospectively explored the reasons for diagnosis after day 10 of illness during an outbreak in Colorado. In contrast to our prospective study in which 16% of children received the diagnosis after day 10 of illness, they found that 24% of their KD patients received the diagnosis after day 10. In their study, late diagnosis was not related to age, gender, time to the first medical visit, number of medical visits, physician specialty, number of antibiotics received, white blood count, or sedimentation rate but was related to dispersion of symptoms over a longer period. In fact, patients in their study eventually exhibited the typical features of KD. Delays in diagnosis were also associated with significantly more days of fever, rash, conjunctival injection, or oral changes in their study. Because data were obtained only at 1 point in time (screening), we were unable to assess whether the incomplete cases in our study eventually fulfilled the recommended American Heart Association/American Academy of Pediatrics criteria for KD. Their latter finding was not supported by our study, however, in which the presence of conjunctival injection and oral changes actually lessened the likelihood of delayed diagnosis.

Incomplete cases have also been implicated as a major factor in late diagnosis. A review¹¹⁻¹³ reported that children with fewer than the recommended 4 criteria account for 15% to 20% of patients who are treated for KD. The percentage of incomplete cases was higher in this study (28%) and may represent the referral pattern for KD at the participating centers.

Younger age was previously reported^{5,14-16} as a risk factor for late diagnosis and coronary abnormalities. A recent study from Taiwan¹⁵ reported that infants who were < 6 months received the diagnosis an average of 2 days later than older children, and 50% received the diagnosis after day 10 compared with 22% of children who were ≥ 6 months. Despite these reports, many physicians continue to have a low index of suspicion for KD in the febrile infant. In a 2004 survey, 57% of 132 pediatricians and 26% of 345 pediatric infectious disease physicians reported that they did not consider the diagnosis of KD for a child who was younger than 6 months or older than 8 years.¹⁷ The failure even to consider KD may account for our finding that infants in this age group received the diagnosis after significantly more illness days and had 3.5 times the odds for receiving the diagnosis after day 10 of illness. Our data suggest a U-shaped relationship with age and support previous reports of delayed diagnosis in older children as well,^{18,19} but because of the small number of patients in the older

age group, there was insufficient power to show significance.

Practice variation among centers may also account for delays in diagnosis. Clinical centers differed significantly in the proportion of incomplete cases that were treated with IVIg as well as in the number of illness days to diagnosis and the proportion of patients who were treated after day 10. We found that the specific clinical center at which a child was treated was an independent predictor of greater illness days at diagnosis even after adjusting for age < 6 months, clinical presentation, and distance. In contrast, center differences for diagnosis after day 10 of illness were explained at least in part by differences in the specific principal criteria (eg, absence of conjunctival injection or extremity changes) met at the centers.

This study should be viewed in light of its limitations. First, because there is no diagnostic laboratory test for KD, the child may be treated even without diagnostic certainty, especially for incomplete cases. The design of this study did not permit us to determine the criteria used for diagnosis or to explore the extent to which time to diagnosis of KD was affected by differing thresholds among physicians and centers for treatment of incomplete KD. Second, the patient's zip code was used as a proxy for socioeconomic status. Although it is a common practice for health researchers to use this approach, the use of such aggregate proxy can introduce statistical bias.²⁰ Third, the data set did not allow us to determine the particular characteristics of each center that were associated with a higher percentage of patients with delayed diagnosis. Specific factors that were evaluated in previous studies, such as the medical specialty of the provider, number of antibiotics received, number of follow-up visits, and access-to-care issues, were not collected from our screened cohort. Finally, in patients who were screened but not enrolled in the randomized trial, data were not collected on coronary artery abnormalities or laboratory test results, further limiting our ability to explore risk factors for and consequences of delayed diagnosis.

CONCLUSIONS

Independent risk factors for a greater number of illness days to diagnosis and a higher percentage of patients who received the diagnosis of KD after day 10 of illness include patient factors as well as disease and center characteristics. Our findings underscore the need to maintain a high index of suspicion of KD when prolonged fever occurs in the infant who is younger than 6 months, even with incomplete principal clinical criteria. It seems likely that outreach education for both clinicians and parents would heighten awareness of KD and lessen delays in its diagnosis and treatment. Future research should explore the center-specific factors that are responsible for practice variations to facilitate the design

of effective strategies for improving the quality of care for children with KD.

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REFERENCES

1. Dajani AS, Taubert KA, Takahashi M, et al. Guidelines for long-term management of patients with Kawasaki disease: report from the Committee on Rheumatic Fever, Endocarditis, and Kawasaki Disease, Council on Cardiovascular Disease in the Young, American Heart Association. *Circulation*. 1994;89:916-922
2. Kato H, Sugimura T, Akagi T, et al. Long-term consequences of

- Kawasaki disease: a 10- to 21-year follow-up study of 594 patients. *Circulation*. 1996;94:1379–1385
3. Furusho K, Kamiya T, Nakano H, et al. High-dose intravenous gammaglobulin for Kawasaki disease. *Lancet*. 1984;2(8411):1055–1058
 4. Newburger JW, Takahashi M, Burns JC, et al. The treatment of Kawasaki syndrome with intravenous gamma globulin. *N Engl J Med*. 1986;315:341–347
 5. Anderson MS, Todd JK, Glode MP. Delayed diagnosis of Kawasaki syndrome: an analysis of the problem. *Pediatrics*. 2005;115(4). Available at: www.pediatrics.org/cgi/content/full/115/4/e428
 6. Kobayashi T, Inoue Y, Takeuchi K, et al. Prediction of intravenous immunoglobulin unresponsiveness in patients with Kawasaki disease. *Circulation*. 2006;113:2606–2612
 7. Newburger JW, Takahashi M, Gerber MA, et al. Diagnosis, treatment, and long-term management of Kawasaki disease: a statement for health professionals from the Committee on Rheumatic Fever, Endocarditis and Kawasaki Disease, Council on Cardiovascular Disease in the Young, American Heart Association. *Circulation*. 2004;110:2747–2771
 8. Rowley AH, Gonzalez-Crussi F, Gidding SS, Duffy CE, Shulman ST. Incomplete Kawasaki disease with coronary artery involvement. *J Pediatr*. 1987;110:409–413
 9. Newburger JW, Sleeper LA, McCrindle BW, et al. Randomized trial for pulse corticosteroid therapy for primary treatment of Kawasaki disease. *N Engl J Med*. 2007;356:663–675
 10. Taubert KA, Rowley AH, Shulman ST. Nationwide survey of Kawasaki disease and acute rheumatic fever. *J Pediatr*. 1991;119:279–282
 11. Burns JC, Glode MP. Kawasaki syndrome. *Lancet*. 2004;364:533–544
 12. Yanagawa H, Nakamura Y, Yashiro M, et al. Results of the nationwide epidemiologic survey of Kawasaki disease in 1995 and 1996 in Japan. *Pediatrics*. 1998;102(6). Available at: www.pediatrics.org/cgi/content/full/102/6/e65
 13. Yanagawa H, Nakamura Y, Yashiro M, et al. Incidence survey of Kawasaki disease in 1997 and 1998 in Japan. *Pediatrics*. 2001;107(3). Available at: www.pediatrics.org/cgi/content/full/107/3/e33
 14. Burns JC, Wiggins JW Jr, Toews WH, et al. Clinical spectrum of Kawasaki disease in infants younger than 6 months of age. *J Pediatr*. 1986;109:759–763
 15. Chang FY, Hwang B, Chen SJ, Lee PC, Meng CC, Lu JH. Characteristics of Kawasaki disease in infants younger than six months of age. *Pediatr Infect Dis J*. 2006;25:241–244
 16. Rosenfeld EA, Corydon KE, Shulman ST. Kawasaki disease in infants less than one year of age. *J Pediatr*. 1995;126:524–529
 17. Pannaraj PS, Turner CL, Bastian JF, Burns JC. Failure to diagnose Kawasaki disease at the extremes of the pediatric age range. *Pediatr Infect Dis J*. 2004;23:789–791
 18. Momenah T, Sanatani S, Potts J, Sandor GG, Human DG, Patterson MW. Kawasaki disease in the older child. *Pediatrics*. 1998;102(1). Available at: www.pediatrics.org/cgi/content/full/102/1/e7
 19. Muta H, Ishii M, Sakaue T, et al. Older age is a risk factor for the development of cardiovascular sequelae in Kawasaki disease. *Pediatrics*. 2004;114:751–754
 20. Geronimus AT BJ, Neidert LF. On the validity of using census geocode characteristics to proxy individual socioeconomic characteristics. *J Am Stat Assoc*. 1996;91:529–537

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