PEDIATRICS®
OFFICIAL JOURNAL OF THE AMERICAN ACADEMY OF PEDIATRICS

Performance of 2004 American Heart Association Recommendations for Treatment of Kawasaki Disease

Elizabeth S. Yellen, Kimberlee Gauvreau, Masato Takahashi, Jane C. Burns, Stanford Shulman, Annette L. Baker, Nancy Innocentini, Chiara Zambetti, Joan M. Pancheri, Adam Ostrow, Jeffrey R. Frazer, Robert P. Sundel, David R. Fulton and Jane W. Newburger

Pediatrics 2010;125;e234-e241; originally published online Jan 25, 2010;
DOI: 10.1542/peds.2009-0606

Performance of 2004 American Heart Association Recommendations for Treatment of Kawasaki Disease

WHAT'S KNOWN ON THIS SUBJECT: Diagnosis of incomplete KD remains challenging but vital, because failure to treat patients expediently with IVIG infusions results in increased CAA formation. No studies have assessed the utility of the 2004 AHA KD initial diagnosis and treatment recommendations.

WHAT THIS STUDY ADDS: This study is the first to assess performance of the 2004 AHA recommendations for children with suspected KD. Our results imply that use of the recommendations would have directed at least 97% of the children at highest risk toward appropriate IVIG therapy.

AUTHORS: Elizabeth S. Yellen, MD,[a] Kimberlee Gauvreau, ScD,[a] Masato Takahashi, MD,[b] Jane C. Burns, MD,[c] Stanford Shulman, MD,[d] Annette L. Baker, MSN, PNP,[a] Nancy Innocentini, RN,[d] Chiara Zambetti, MD,[a] Joan M. Pancheri, RN,[c] Adam Ostrow, MD,[b] Jeffrey R. Frazer, MD,[c] Robert P. Sundel, MD,[a] David R. Fulton, MD,[a] and Jane W. Newburger, MD, MPH[a]

[a]Department of Cardiology, Children's Hospital Boston and Harvard Medical School, Harvard University, Boston, Massachusetts; [b]Department of Cardiology, Children's Hospital of Los Angeles and Keck School of Medicine, University of Southern California, Los Angeles, California; [c]Department of Pediatrics, Rady Children's Hospital San Diego and School of Medicine, University of California, San Diego, California; and [d]Department of Pediatrics, Children's Memorial Hospital and Feinberg School of Medicine, Northwestern University, Chicago, Illinois

KEY WORDS

Kawasaki disease, guidelines, diagnostic recommendations, cardiac disease, coronary aneurysm

ABBREVIATIONS

KD—Kawasaki disease
CAA—coronary artery aneurysm
AHA—American Heart Association
IVIG—intravenous immunoglobulin
CRP—C-reactive protein
ESR—erythrocyte sedimentation rate
ALT—alanine aminotransferase

www.pediatrics.org/cgi/doi/10.1542/peds.2009-0606

doi:10.1542/peds.2009-0606

Accepted for publication Aug 15, 2009

Address correspondence to Elizabeth S. Yellen, MD, Children's Hospital Boston, Department of Cardiology, 300 Longwood Ave, Boston, MA 02115. E-mail: elizabeth.yellen@cardio.chboston.org

PEDIATRICS (ISSN Numbers: Print, 0031-4005; Online, 1098-4275).

FINANCIAL DISCLOSURE: *The authors have indicated they have no financial relationships relevant to this article to disclose.*

abstract

OBJECTIVE: The 2004 American Heart Association (AHA) statement included a clinical case definition and an algorithm for diagnosing and treating suspected incomplete Kawasaki disease (KD). We explored the performance of these recommendations in a multicenter series of US patients with KD with coronary artery aneurysms (CAAs).

METHODS: We reviewed retrospectively records of patients with KD with CAAs at 4 US centers from 1981 to 2006. CAAs were defined on the basis of *z* scores of >3 or Japanese Ministry of Health and Welfare criteria. Our primary outcome was the proportion of patients presenting at illness day ≤21 who would have received intravenous immunoglobulin (IVIG) treatment by following the AHA guidelines at the time of their initial presentation to the clinical center.

RESULTS: Of 195 patients who met entry criteria, 137 (70%) met the case definition and would have received IVIG treatment at presentation. Fifty-three patients (27%) had suspected incomplete KD and were eligible for algorithm application; all would have received IVIG treatment at presentation. Of the remaining 5 patients, 3 were excluded from the algorithm because of fever for <5 days at presentation and 2 because of <2 clinical criteria at >6 months of age. Two of these 5 patients would have entered the algorithm and received IVIG treatment after follow-up monitoring. Overall, application of the AHA algorithm would have referred ≥190 patients (97%) for IVIG treatment.

CONCLUSIONS: Application of the 2004 AHA recommendations, compared with the classic criteria alone, improves the rate of IVIG treatment for patients with KD who develop CAAs. Future multicenter prospective studies are needed to assess the performance characteristics of the AHA algorithm in febrile children with incomplete criterion findings and to refine the algorithm further. *Pediatrics* 2010;125: e234–e241

Kawasaki disease (KD) is a leading cause of acquired heart disease in North American children, producing coronary artery aneurysms (CAAs) in 20% to 25% of children who do not receive intravenous immunoglobulin (IVIG) treatment before the tenth day of illness.[1–3] With unknown cause and no diagnostic test or pathognomonic clinical finding, KD has been diagnosed by using a clinical case definition that requires fever together with ≥4 of 5 principal clinical criteria. However, children with incomplete KD (ie, those who do not meet the complete clinical case definition) seem to have a risk of CAAs at least as great as that of children who fulfill the classic criteria.[4] Timely diagnosis and treatment of children with incomplete KD remain challenging.

In 2004, the American Heart Association (AHA) published a statement on the diagnosis, treatment, and long-term management of KD, which subsequently was endorsed by the American Academy of Pediatrics.[5] The report included an algorithm to aid clinicians in the evaluation of patients with suspected KD who do not meet the complete case definition and thus may not be identified or receive timely referral for IVIG treatment. The AHA algorithm for patients with suspected incomplete KD was based on expert opinion and anecdotal reports, rather than large clinical trials or registries. In a retrospective, multicenter study, we sought to assess the performance of the AHA recommendations for IVIG treatment for children with CAAs attributable to KD.

METHODS

Subjects

We performed a retrospective chart review of data for children with KD and CAAs who were evaluated at 4 US pediatric hospitals. Inclusion criteria included (1) presentation with KD between 1981 and 2006; (2) diagnosis within 21 days after fever onset; (3) CAA defined on the basis of Japanese Ministry of Health and Welfare criteria or *z* score of >3 for the left main, proximal left anterior descending, or proximal right coronary artery; and (4) medical records adequate for determination of whether the patient met the complete case definition and, when the case definition was not met, for application of the AHA algorithm for suspected incomplete KD. Specifically, we required a record of age, date of fever onset, date of diagnosis, and data before treatment, including the presence or absence of each principal clinical criterion, C-reactive protein (CRP) level and/or erythrocyte sedimentation rate (ESR), and ≥4 of the 6 supplemental laboratory criteria enumerated in the AHA guidelines, that is, hemoglobin level, white blood cell count, platelet count if fever was present for ≥7 days, albumin level, alanine aminotransferase (ALT) level, and urinary white blood cell count. The study was reviewed and approved by the institutional review board at each participating institution.

Data Collection and Definitions

Patients who met the complete case definition were defined as having ≥3 fever days and ≥4 classic symptoms (nonspecific rash, nonexudative bilateral conjunctivitis, redness and swelling of the hands and feet, typical oral changes, and cervical lymphadenopathy) at presentation. We used the AHA algorithm for the assessment of suspected incomplete KD for patients at the time of their first presentation to the clinical center (Fig 1). Patients were eligible to enter the algorithm if they either had had fever for ≥5 days and met 2 or 3 clinical criteria or were infants ≤6 months of age with ≥7 days of fever, systemic inflammation without explanation, and <2 criteria.

Charts were reviewed for patient age at fever onset, day of fever at diagnosis, presence or absence of each of the 5 major clinical criteria, and pretreatment laboratory data from the time of presentation (see above). Echocardiographic records for all patients were reviewed by the contributing center, and the maximal dimension in any vessel determined through echocardiography between 1981 and 2006 was recorded. Coronary artery *z* scores were calculated for the left main coronary, right proximal coronary, and proximal left anterior descending coronary arteries by dividing the difference between the actual coronary artery dimension and the predicted coronary dimension for a child of a given body surface area (Haycock method) by the SD.[6,7] For patients with enlargement in the distal right coronary, posterior descending, and circumflex coronary arteries or other coronary artery segments without validated predicted dimensions for body surface area in children, absolute values were used and coronary abnormalities were classified by using Japanese Ministry of Health and Welfare criteria.[8] In those instances, CAAs were defined on the basis of a dimension of >3 mm for patients <5 years of age or >4 mm for children ≥5 years of age.

Statistical Analyses

Continuous variables were summarized as medians and ranges. For comparisons between patients with complete KD and those with incomplete KD who entered the AHA algorithm, as well as between patients ≤6 months of age and those >6 months of age, the Wilcoxon rank sum test was used for continuous variables and Fisher's exact test was used for categorical variables. For comparisons across the 4 centers, the Kruskal-Wallis test was used for continuous variables and Fisher's exact test was used for categorical variables.

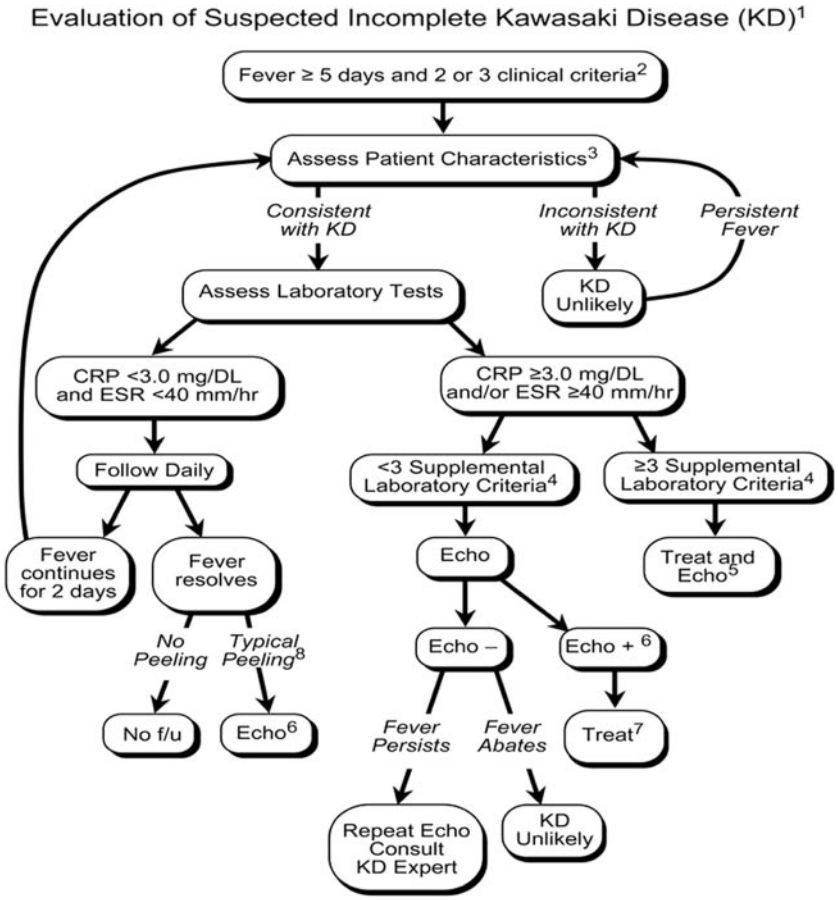

FIGURE 1

Evaluation of suspected incomplete KD. (1) In the absence of a standard method for diagnosis, this algorithm cannot be evidence-based but represents the informed opinion of the expert committee. Consultation with an expert should be sought whenever assistance is needed. (2) Infants <6 months of age on the seventh day of fever without other explanation should undergo laboratory testing and, if evidence of systemic inflammation is found, echocardiography, even if the infants meet no clinical criteria for diagnosis. (3) Characteristics suggesting KD are listed in Table 1. Characteristics suggesting diseases other than KD include exudative conjunctivitis, exudative pharyngitis, discrete intraoral lesions, bullous or vesicular rash, and generalized adenopathy. Alternative diagnoses should be considered (Table 2). (4) Supplemental laboratory criteria include albumin levels of <3.0 g/dL, anemia for age, elevation of ALT level, >450 000 platelets per mm^3 after the seventh day, white blood cell count of >15 000 cells per mm^3, and >10 white blood cells per high-power field in the urine. (5) Treatment can begin before echocardiography is performed. (6) Echocardiograms are considered positive for purposes of this algorithm if any of 3 conditions are met, that is, the *z* score for the anterior interventricular or right coronary artery is >2.5, coronary arteries meet Japanese Ministry of Health and Welfare criteria for aneurysms, or there are >3 other suggestive features, including perivascular brightness, lack of tapering, decreased left ventricular function, mitral regurgitation, pericardial effusion, or *z* scores for the anterior interventricular and right coronary arteries between 2 and 2.5. (7) If the echocardiogram is positive, then treatment should be given to children within 10 days after the onset of fever and to those beyond the 10th day with clinical and laboratory signs of ongoing inflammation. (8) Typical peeling begins under the nail beds of fingers and then toes. Echo indicates echocardiography; f/u, follow-up. (Reproduced with permission from 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(17):1709.)

RESULTS

During the 25-year review period, we identified 263 patients with KD and CAAs. Of those patients, 248 (94%) presented in the first 21 days of illness and 195 (74%) had data adequate for application of the clinical case definition for complete KD and the AHA algorithm for suspected incomplete KD. Of the 195 patients who represent our study subjects (Table 1), 73% were male. The median age at diagnosis was 2.1 years (range: 0.1–19.4 years), and 37 patients (19%) were ≤6 months of age. The median duration of fever at diagnosis was 7 days (range: 3–21 days). We explored the number of principal clinical criteria met by our study population, all of whom had CAAs (Fig 2). All 5 classic clinical criteria were met in 53 cases (27%), 4 criteria in 84 (43%), 3 criteria in 41 (21%), 2 criteria in 14 (7%), and 1 criterion in 3 (2%). Therefore, 30% of children had incomplete KD. At least 1 IVIG infusion was eventually administered to 184 patients (94%), including 56 (97%) of 58 with incomplete KD.

We applied the 2004 AHA recommendations retrospectively to determine how many of our population of children with CAAs attributable to KD would have been treated with IVIG infusions if the guidelines had been applied at presentation (Fig 3). Among the 195 patients, 137 (70%) met the case definition for complete KD and would have been referred for immediate IVIG treatment. Of the remaining 58 patients, 53 (91%) were eligible to enter the AHA algorithm for suspected incomplete KD because they either had fever for ≥5 days and 2 or 3 classic clinical criteria ($n = 52$) or were ≤6 months of age with <2 criteria, systemic inflammation, and ≥7 days of fever without other explanation ($n = 1$). Application of the AHA algorithm for suspected incomplete KD would have referred all 53 eligible patients with incomplete KD for IVIG treatment.

Five (3%) of the 195 patients neither met the complete case definition nor would have been eligible to enter the AHA algorithm for suspected incomplete KD at the time of their first pre-

TABLE 1 Demographic, Clinical, and Laboratory Characteristics of Patients With KD and CAAs at Presentation

	All ($N = 195$)	Complete KD ($N = 137$)	Incomplete KD Eligible for AHA Algorithm ($N = 53$)	P (Complete KD vs Incomplete KD)
Age at symptom onset, median (range), y	2.1 (0.1–19.4)	2.3 (0.1–19.4)	1.9 (0.1–15.3)	.47
≤6 mo of age, %	19	16	28	.067
Male, %	73	73	74	1.0
Fever duration at diagnosis, median (range), d	7 (3–21)	6 (3–17)	9 (5–21)	<.001
Rash, %	94	100	79	<.001
Conjunctival injection, %	94	100	85	<.001
Oral changes, %	88	97	68	<.001
Lymphadenopathy, %	43	53	19	<.001
Extremity changes, %	69	88	21	<.001
CRP level of ≥3.0 mg/dL or ESR of ≥40 mm/h, % (*n*)	100 (195)	100 (137)	100 (53)	
WBC count of ≥15 000 cells per mm^3, % (*n*)	51 (195)	53 (137)	49 (53)	.75
Anemia, % (*n*)	60 (193)	60 (136)	65 (52)	.51
Platelet count of ≥450 × 10^3 cells per mm^3 if ≥7 d of fever at presentation, % (*n*)	61 (108)	62 (65)	66 (41)	.42
Albumin level of ≤3.0 g/dL, % (*n*)	48 (172)	48 (119)	49 (49)	1.0
ALT level elevation, % (*n*)	49 (180)	55 (127)	33 (48)	.011
Urinary WBC count of >10 cells per high-power field, % (*n*)	21 (169)	27 (123)	5 (41)	.002

WBC indicates white blood cell.

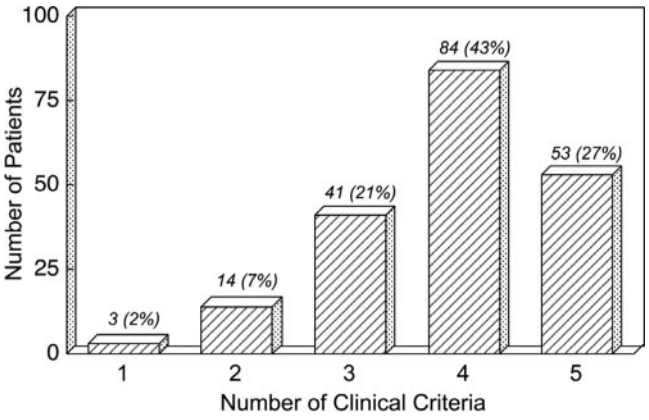

FIGURE 2
Number of clinical criteria present at the time of initial evaluation for 195 patients with KD and CAAs. Clinical criteria included rash, conjunctival injection, oral changes, lymphadenopathy, and extremity changes.

sentation to the clinical center (Table 2). Three would have become eligible later, because their fevers lasted ≥5 days and they had 2 or 3 principal clinical criteria. If those 3 patients had then entered the algorithm, 1 would have satisfied the criteria for immediate IVIG treatment. The other 2 would have been referred for echocardiography, and 1 would have received IVIG treatment, on the basis of abnormal echocardiographic findings, on day 5. The other had negative echocardiographic findings on day 6 and so would not have been referred for IVIG treatment; subsequent echocardiography performed on day 12 of illness showed a CAA. The remaining 2 children, each of whom was >6 months of age with only 1 principal clinical criterion, would not have been eligible to enter the algorithm. Therefore, careful follow-up monitoring in the days after the first presentation to the clinical center would have resulted in successful application of the AHA algorithm and appropriate IVIG treatment for 2 of 5 children. With inclusion of those children, ≥192 (98%) of 195 subjects with KD and CAAs would have been referred appropriately for IVIG treatment, including ≥55 (95%) of 58 patients with incomplete KD at initial presentation.

We compared the characteristics of patients who satisfied the criteria for complete KD with those of patients who had AHA algorithm-eligible incomplete KD. Patients with incomplete KD who were eligible to enter the algorithm had a longer time to KD diagnosis (median: 9 days [range: 5–21 days] vs 6 days [range: 3–17 days]; $P < .001$) and a greater tendency to be ≤6 months of age (28% vs 16%; $P = .067$). The 2 groups had similar laboratory measures (Table 1) with the exception of serum ALT levels, which were more frequently elevated for age in patients with complete KD (55% vs 33%; $P = .011$).

We compared the characteristics of infants ≤6 months of age, who represented 19% of the study population, with those of patients >6 months of age (Table 3). Infants ≤6 months of age tended to be more likely to have incomplete KD (41% vs 27%; $P = .063$) and had more days of fever at presentation (median: 9 vs 7 days; $P = .003$). Only 16% of young infants had cervical lymphadenopathy at the time of presentation, compared with 49% of older children ($P < .001$). Infants ≤6 months of age were more likely to have white blood cell counts of >15 000 ($P = .05$) and anemia for age ($P = .005$) and were less likely to have elevated ALT levels for age ($P < .001$). Other clinical and laboratory findings were similar between the 2 age groups.

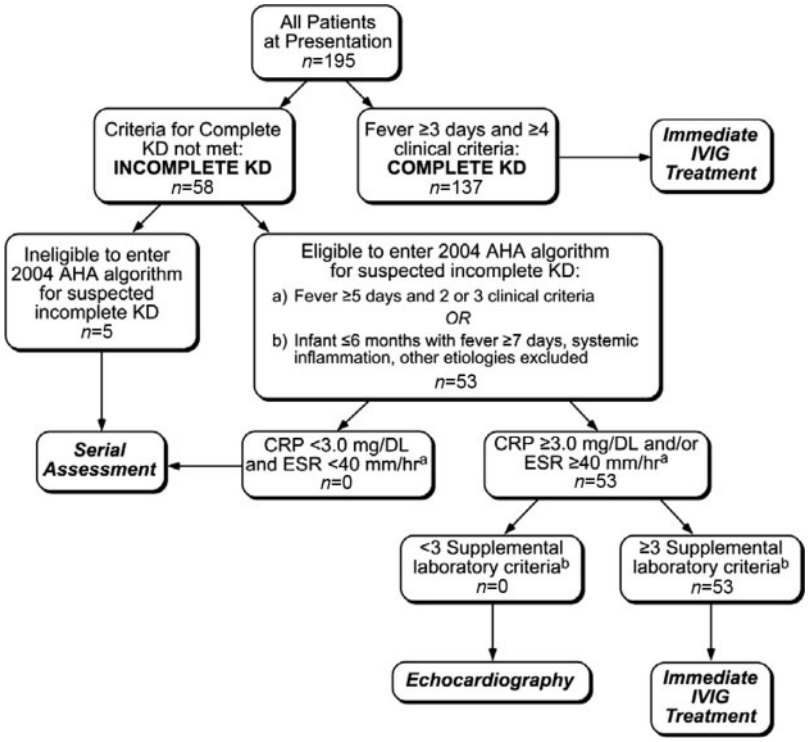

FIGURE 3
Classification and projected treatment on the basis of data obtained at the first evaluation for 195 patients with KD and CAAs with application of the 2004 AHA recommendations for the diagnosis and treatment of KD. [a] When both the ESR and CRP level were recorded, a CRP level of ≥3.0 mg/dL or ESR of ≥40 mm/hour was considered a positive marker of systemic inflammation, regardless of the other value. [b] Positive supplemental criteria included (1) white blood cell count of ≥15 000 cells per mm^3, (2) anemia for age, (3) platelet count of ≥450 × 10^3 cells per mm^3 if fever had been present for ≥7 days at the time of presentation, (4) albumin level of ≤3.0 g/dL, (5) ALT level elevation for age, and (6) urinary white blood cell count of >10 cells per high-power field.

We explored variations in the performance of the AHA recommendations according to clinical center (Table 4). Centers varied according to age at presentation ($P < .001$), proportion of infants ≤6 months of age ($P = .005$), and proportion of infants with elevated ALT levels for age ($P < .001$). Centers were otherwise similar with respect to laboratory data and clinical characteristics, including proportion male, days of fever, and proportion with incomplete presentation. The centers did not differ with respect to performance of the 2004 AHA recommendations in successfully guiding IVIG treatment, with limited statistical power. Similarly, performance of the 2004 AHA recommendations did not differ when we analyzed patients who presented by day 21 ($n = 195$), day 14 ($n = 182$), or day 10 ($n = 154$). However, our statistical power to detect such differences was limited.

DISCUSSION

Timely IVIG treatment is hampered by incomplete clinical signs in at least 15% to 20% of children with KD.[9–11] Indeed, incomplete presentation with KD is a risk factor for delayed diagnosis, failure to treat with IVIG infusions, and development of coronary artery lesions.[12,13] In the absence of a diagnostic test for KD, several groups have published strategies for the evaluation of children with suspected incomplete KD.[14–16] In 2004, the AHA updated scientific statement not only included criteria for classic KD but also proposed a new algorithm for the initial assessment and treatment of children with suspected incomplete KD. This algorithm was based primarily on expert consensus, because of the dearth of evidence-based studies. The present study is the first to examine the performance of the 2004 AHA recommendations in a large population of children meeting the standard for the diagnosis of KD, that is, CAAs.

Our retrospective review suggests that, among North American children with CAAs secondary to KD, application

TABLE 2 Patients With Neither Complete KD Nor AHA Algorithm-Eligible Incomplete KD

Center	Age, y	Duration of Fever at Presentation, d	No. of Clinical Criteria Present	Reason Not Eligible to Enter AHA Algorithm for Suspected Incomplete KD	CRP Level of ≥3.0 mg/dL or ESR of ≥40 mm/h	No. of Positive Supplemental Laboratory Criteria	Findings on First Echocardiogram	Time at IVIG Treatment, d
1	9.1	4	2	<5 d of fever	Yes	1	First echocardiogram negative on day 6; repeat echocardiogram with CAA on day 12	6
4	2.9	4	3	<5 d of fever	Yes	1	CAA on day 5	5
4	1.9	4	3	<5 d of fever	Yes	3	Unknown	5
1	1.3	8	1	<2 clinical criteria	Yes	1	CAA on day 8	8
3	8.3	14	1	<2 clinical criteria	Yes	3	CAA on day 14	14

TABLE 3 Demographic, Clinical, and Laboratory Characteristics of Patients According to Age at Presentation

	≤6 mo ($N = 37$)	>6 mo ($N = 158$)	P
Age at symptom onset, median (range), y	0.29 (0.1–0.5)	2.8 (0.54–19.4)	<.001
Male, %	70	73	.69
Duration of fever at diagnosis, median (range), d	9 (4–21)	7 (3–22)	.003
Rash, %	97	93	.47
Conjunctival injection, %	89	96	.23
Oral changes, %	92	87	.58
Lymphadenopathy, %	16	49	<.001
Extremity changes, %	70	68	1.0
No. of clinical criteria present, median (range)	4 (1–5)	4 (1–5)	.052
CRP level of ≥3.0 mg/dL or ESR of ≥40 mm/h, %	100	100	
WBC count of ≥15 000 cells per mm^3, %	62	49	.15
Anemia for age, % (*n*)	81 (37)	55 (156)	.005
Platelet count of ≥450 × 10^3 cells per mm^3 if ≥7 d of fever at presentation, % (*n*)	69 (26)	59 (82)	.37
Albumin level of ≤3.0 g/dL, % (*n*)	55 (33)	47 (139)	.45
ALT level elevation, % (*n*)	9 (34)	58 (146)	<.001
Urinary WBC count of ≥10 cells per high-power field, % (*n*)	18 (34)	22 (135)	.65
Complete KD, %	59	73	.12
Incomplete KD eligible for AHA algorithm, %	41	24	.063

WBC indicates white blood cell.

TABLE 4 Demographic, Clinical, and Laboratory Characteristics of Patients With KD and CAAs at Presentation According to Center

	Center 1 ($N = 97$)	Center 2 ($N = 27$)	Center 3 ($N = 22$)	Center 4 ($N = 49$)	P
Age at symptom onset, median (range), y	2.1 (0.1–19.4)	0.7 (0.1–14.5)	3.4 (0.2–9.5)	3.0 (0.1–15.3)	<.001
Male, %	75	74	82	63	.35
Age of ≤6 mo, %	21	41	9	8	.005
Duration of fever at diagnosis, median (range), d	6 (3–21)	8 (3–21)	8 (5–16)	7 (4–16)	.086
Rash, %	98	93	86	90	.043
Conjunctival injection, %	95	96	91	94	.84
Oral changes, %	86	96	73	94	.043
Lymphadenopathy, %	51	26	41	37	.10
Extremity changes, %	65	78	77	67	.52
No. of clinical criteria present, median (range)	4 (1–5)	4 (2–5)	4 (1–5)	4 (2–5)	.55
CRP level of ≥3.0 mg/dL or ESR of ≥40 mm/h, %	100	100	100	100	
WBC count of ≥15 000 cells per mm^3, %	47	52	55	57	.73
Anemia for age, % (*n*)	61 (95)	63 (27)	68 (22)	53 (49)	.63
Platelet count of ≥450 × 10^3 cells per mm^3 if ≥7 d of fever at presentation, % (*n*)	69 (48)	45 (20)	62 (13)	59 (27)	.35
Albumin level of ≤3.0 g/dL, % (*n*)	47 (75)	38 (26)	73 (22)	45 (49)	.088
ALT level elevation, % (*n*)	51 (87)	16 (25)	32 (22)	72 (46)	<.001
Urinary WBC count of ≥10 cells per high-power field, % (*n*)	22 (88)	23 (26)	18 (17)	21 (38)	1.0
Complete KD, (%) *n*	(72) 70	(74) 20	(59) 13	(69) 34	.79
Eligible for suspected incomplete KD AHA algorithm, (%) *n*	(26) 25	(26) 7	(36) 8	(27) 13	
Met neither definition, (%) *n*	(2) 2	(0) 0	(5) 1	(4) 2	

WBC indicates white blood cell.

of the 2004 AHA recommendations would have identified the majority for appropriate IVIG treatment at the time of presentation. Only 70% of our subjects would have been treated with IVIG infusions if clinicians had relied on fulfillment of the complete case definition, whereas ≥97% of subjects would have been treated through use of the 2004 AHA recommendations. We infer that use of the 2004 AHA recommendations by primary care providers may hasten treatment of incomplete KD and thereby reduce the likelihood and severity of CAA formation related to delayed or missed KD diagnosis.

Children ≤6 months of age were overrepresented in our study group with CAAs. Furthermore, a larger proportion of infants tended to present with incomplete KD, compared with the older group. Several previous studies found that infants were at increased risk for both incomplete presentation[17–19] and coronary abnormalities.[20–26] Delayed diagnosis, which is common in the infant KD population,[12] also was demonstrated to be a risk factor for the development of coronary abnormalities.[25] Other investigators found that pediatricians are less likely to consider a diagnosis of KD for infants even when they present with complete KD.[27] These findings underscore the need for increased clinical suspicion for incomplete KD in infants with an unknown cause of fever. The new AHA algorithm for patients with suspected KD seems to be of particular benefit when used for the assessment of infants; all infants would have been referred for IVIG treatment at presentation (Fig 4).

We explored the reasons why the AHA algorithm would not have directed some children in the series to IVIG treatment. Two patients had only a single principal clinical criterion in addition to fever. Children with fever and a single principal criterion do not enter the AHA algorithm unless they are ≤6 months of age and hence would not be explicitly addressed by the 2004 AHA recommendations. We cannot exclude the possibility that other symptoms of KD were transient in these 2 children

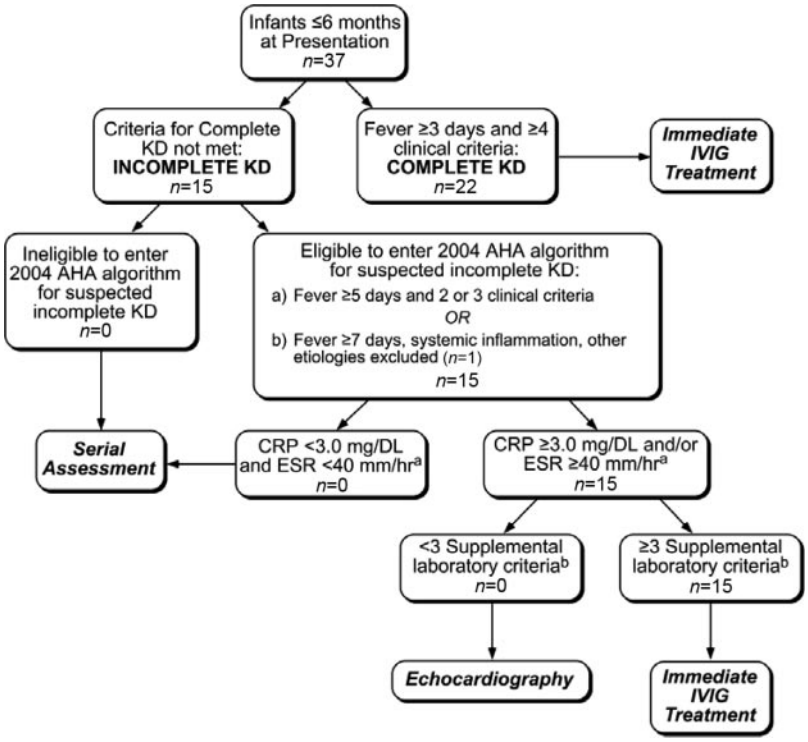

FIGURE 4

Classification and projected treatment on the basis of data obtained at the first evaluation for 37 infants ≤6 months of age with KD and CAAs with application of the 2004 AHA recommendations for the diagnosis and treatment of KD. [a] When both the ESR and CRP level were recorded, a CRP level of ≥3.0 mg/dL or ESR of ≥40 mm/hour was considered a positive marker of systemic inflammation, regardless of the other value. [b] Positive supplemental criteria included (1) white blood cell count of ≥15 000 cells per mm^3, (2) anemia for age, (3) platelet count of ≥450 × 10^3 cells per mm^3 if fever had been present for ≥7 days at the time of presentation, (4) albumin level of ≤3.0 g/dL, (5) ALT level elevation for age, and (6) urinary white blood cell count of >10 cells per high-power field.

and were missed by parents and care providers. It is worth noting that 1 child was 8 years of age, outside the typical KD age range. Older age itself has been shown to be a risk factor for delayed diagnosis, development of CAAs, complications, and persistence of CAAs over time.[24,28] One other child had incomplete criterion findings, with normal echocardiographic findings on day 6 of illness; a second echocardiogram was not performed until day 12 of illness, when coronary changes were seen. Although the AHA algorithm suggests repeating echocardiography when fever persists in children with elevated CRP levels and/or ESRs and <3 supplemental laboratory criteria, the appropriate interval for retesting is not given. Future iterations of the algorithm might specify that repeat echocardiography be performed sooner, particularly if the first echocardiogram is obtained early in the course of illness. However, changes in the algorithm that improve sensitivity must be balanced against worsening specificity, with widespread overuse of echocardiography and IVIG treatment.

Our retrospective study should be viewed in light of its limitations. We assessed patient characteristics at presentation, and it is possible that some patients with incomplete presentations might have satisfied the criteria completely with longer follow-up monitoring. CAAs were determined on the basis of echocardiographic interpretation at each participating clinical center, rather than in a core laboratory. Because we included only patients with KD with CAAs, laboratory results for our study population are likely to be skewed toward greater systemic inflammation, compared with average children with KD.[29] Our study design did not permit us to assess the specificity of the algorithm for suspected KD, and we could not evaluate the number of unnecessary laboratory tests, echocardiograms, or IVIG infusions. The retrospective nature of the study also precluded us from determining whether application of the 2004 AHA guidelines improved patient outcomes. Of note, the most important aim of IVIG treatment for patients with KD is to prevent CAAs. By restricting the study population to children who developed coronary artery sequelae of KD, we were able to demonstrate that the 2004 AHA guidelines successfully guided children at highest risk toward IVIG treatment.

CONCLUSIONS

Our study is the first to assess the performance of the 2004 AHA recommendations in facilitating the diagnosis and treatment of KD in children with CAAs. Fewer than three fourths of children with CAAs met the complete case definition at presentation. Incorporation of the AHA algorithm for suspected incomplete KD in the initial assessment would have referred the great majority of this high-risk KD population for immediate IVIG treatment. Future multicenter prospective studies are needed for assessment of the performance characteristics of the AHA algorithm among febrile children with incomplete criterion findings and further refinement of the algorithm.

ACKNOWLEDGMENTS

The Ciaranello Family Fund is a philanthropic fund used to support clinical research in cardiology at Children's Hospital Boston. A grant from

the National Heart, Lung, and Blood Institute (grant K24 HL074864) provides a portion of Dr Burns' salary.

We thank Oswaldo Salgado, BA, and Elizabeth Crawford, BA, for their assistance in digitizing echocardiograms, David Brown, MD, who reviewed selected echocardiograms, and Kathy Alexander, who provided administrative support.

REFERENCES

1. 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(6):1379–1385
2. Furusho K, Kamiya T, Nakano H, et al. High-dose intravenous gammaglobulin for Kawasaki disease. *Lancet*. 1984;2(8411):1055–1058
3. Newburger JW, Takahashi M, Burns JC, et al. The treatment of Kawasaki syndrome with intravenous gamma globulin. *N Engl J Med*. 1986;315(6):341–347
4. Sonobe T, Kiyosawa N, Tsuchiya K, et al. Prevalence of coronary artery abnormality in incomplete Kawasaki disease. *Pediatr Int*. 2007;49(4):421–426
5. 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(17):2747–2771
6. McCrindle BW, Li JS, Minich LL, et al. Coronary artery involvement in children with Kawasaki disease: risk factors from analysis of serial normalized measurements. *Circulation*. 2007;116(2):174–179
7. de Zorzi A, Colan SD, Gauvreau K, Baker AL, Sundel RP, Newburger JW. Coronary artery dimensions may be misclassified as normal in Kawasaki disease. *J Pediatr*. 1998;133(2):254–258
8. Ministry of Health and Welfare, Research Committee on Kawasaki Disease. *Report of the Subcommittee on Standardization of Diagnostic Criteria and Reporting of Coronary Artery Lesions in Kawasaki Disease*. Tokyo, Japan: Ministry of Health and Welfare; 1984
9. 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
10. 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
11. Burns JC, Glode MP. Kawasaki syndrome. *Lancet*. 2004;364(9433):533–544
12. Minich LL, Sleeper LA, Atz AM, et al. Delayed diagnosis of Kawasaki disease: what are the risk factors? *Pediatrics*. 2007;120(6). Available at: www.pediatrics.org/cgi/content/full/120/6/e1434
13. Wilder MS, Palinkas LA, Kao AS, Bastian JF, Turner CL, Burns JC. Delayed diagnosis by physicians contributes to the development of coronary artery aneurysms in children with Kawasaki syndrome. *Pediatr Infect Dis J*. 2007;26(3):256–260
14. Asai T. Diagnosis and prognosis of coronary artery lesions in Kawasaki disease: coronary angiography and the conditions for its application (a score chart) [in Japanese]. *Nippon Rinsho*. 1983;41(9):2080–2085
15. Harada K. Intravenous gamma-globulin treatment in Kawasaki disease. *Acta Paediatr Jpn*. 1991;33(6):805–810
16. Beiser AS, Takahashi M, Baker AL, Sundel RP, Newburger JW. A predictive instrument for coronary artery aneurysms in Kawasaki disease. *Am J Cardiol*. 1998;81(9):1116–1120
17. Joffe A, Kabani A, Jadavji T. Atypical and complicated Kawasaki disease in infants: do we need criteria? *West J Med*. 1995;162(4):322–327
18. Tseng CF, Fu YC, Fu LS, Betau H, Chi CS. Clinical spectrum of Kawasaki disease in infants. *Zhonghua Yi Xue Za Zhi (Taipei)*. 2001;64(3):168–173
19. 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(5):759–763
20. Genizi J, Miron D, Spiegel R, Fink D, Horowitz Y. Kawasaki disease in very young infants: high prevalence of atypical presentation and coronary arteritis. *Clin Pediatr (Phila)*. 2003;42(3):263–267
21. Honkanen VE, McCrindle BW, Laxer RM, Feldman BM, Schneider R, Silverman ED. Clinical relevance of the risk factors for coronary artery inflammation in Kawasaki disease. *Pediatr Cardiol*. 2003;24(2):122–126
22. Witt MT, Minich LL, Bohnsack JF, Young PC. Kawasaki disease: more patients are being diagnosed who do not meet American Heart Association criteria. *Pediatrics*. 1999;104(1). Available at: www.pediatrics.org/cgi/content/full/104/1/e10
23. 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(3):241–244
24. 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
25. 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
26. Rosenfeld EA, Corydon KE, Shulman ST. Kawasaki disease in infants less than one year of age. *J Pediatr*. 1995;126(4):524–529
27. 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(8):789–791
28. 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(3):751–754
29. Kim T, Choi W, Woo C, et al. Predictive risk factors for coronary artery abnormalities in Kawasaki disease. *Eur J Pediatr*. 2007;166(5):421–425

Performance of 2004 American Heart Association Recommendations for Treatment of Kawasaki Disease

Elizabeth S. Yellen, Kimberlee Gauvreau, Masato Takahashi, Jane C. Burns, Stanford Shulman, Annette L. Baker, Nancy Innocentini, Chiara Zambetti, Joan M. Pancheri, Adam Ostrow, Jeffrey R. Frazer, Robert P. Sundel, David R. Fulton and Jane W. Newburger

Pediatrics 2010;125;e234-e241; originally published online Jan 25, 2010;
DOI: 10.1542/peds.2009-0606