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Pediatrics 2009;123;e783
DOI: 10.1542/peds.2008-1871

ARTICLE

Recognition of a Kawasaki Disease Shock Syndrome

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The authors have indicated they have no financial relationships relevant to this article to disclose.

What's Known on This Subject

Although the cardiac complications of KD are well known, hemodynamic instability is unusual in the acute phase of illness, except as a complication of intravenous IVIG administration.

What This Study Adds

We have observed shock and hypotension with increasing frequency in newly diagnosed KD. Compared with hemodynamically normal KD, KDSS is associated with increased inflammation, platelet consumption, IVIG resistance, coronary artery abnormalities, mitral regurgitation, and myocardial dysfunction.

ABSTRACT

OBJECTIVE. We sought to define the characteristics that distinguish Kawasaki disease shock syndrome from hemodynamically normal Kawasaki disease.

METHODS. We collected data prospectively for all patients with Kawasaki disease who were treated at a single institution during a 4-year period. We defined Kawasaki disease shock syndrome on the basis of systolic hypotension for age, a sustained decrease in systolic blood pressure from baseline of ≥20%, or clinical signs of poor perfusion. We compared clinical and laboratory features, coronary artery measurements, and responses to therapy and analyzed indices of ventricular systolic and diastolic function during acute and convalescent Kawasaki disease.

RESULTS. Of 187 consecutive patients with Kawasaki disease, 13 (7%) met the definition for Kawasaki disease shock syndrome. All received fluid resuscitation, and 7 (54%) required vasoactive infusions. Compared with patients without shock, patients with Kawasaki disease shock syndrome were more often female and had larger proportions of bands, higher C-reactive protein concentrations, and lower hemoglobin concentrations and platelet counts. Evidence of consumptive coagulopathy was common in the Kawasaki disease shock syndrome group. Patients with Kawasaki disease shock syndrome more often had impaired left ventricular systolic function (ejection fraction of <54%: 4 of 13 patients [31%] vs 2 of 86 patients [4%]), mitral regurgitation (5 of 13 patients [39%] vs 2 of 83 patients [2%]), coronary artery abnormalities (8 of 13 patients [62%] vs 20 of 86 patients [23%]), and intravenous immunoglobulin resistance (6 of 13 patients [46%] vs 32 of 174 patients [18%]). Impairment of ventricular relaxation and compliance persisted among patients with Kawasaki disease shock syndrome after the resolution of other hemodynamic disturbances.

CONCLUSIONS. Kawasaki disease shock syndrome is associated with more-severe laboratory markers of inflammation and greater risk of coronary artery abnormalities, mitral regurgitation, and prolonged myocardial dysfunction. These patients may be resistant to immunoglobulin therapy and require additional antiinflammatory treatment. *Pediatrics* 2009;123:e783–e789

www.pediatrics.org/cgi/doi/10.1542/peds.2008-1871

doi:10.1542/peds.2008-1871

Key Words
Kawasaki disease (mucocutaneous lymph node syndrome), shock, echocardiography, ventricular function

Abbreviations
KD—Kawasaki disease
IVIG—intravenous immunoglobulin
KDSS—Kawasaki disease shock syndrome

Accepted for publication Jan 12, 2009

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KAWASAKI disease (KD) is the most common cause of acquired heart disease in the pediatric age group and results in permanent damage to the coronary arteries in up to 25% of untreated children.[1] However, hemodynamic instability during the acute phase of the illness, not related to the infusion of intravenous immunoglobulin (IVIG), is uncommon. In 2006–2007, we treated an increased number of children with KD who required hemodynamic support in the critical care setting. This prompted us to define this complication of KD and to compare the clinical characteristics and outcomes of patients with KD shock syndrome (KDSS) with those of patients with hemodynamically normal KD.

METHODS

Since January 2001, the KD Research Center at Rady Children's Hospital San Diego has maintained a prospective database on patients treated for KD. From this database, we identified all patients with acute KD who had been admitted to this freestanding children's hospital, which serves as the principal pediatric inpatient facility for a population base of ~3 million. We included all patients treated during the 4-year period from May 2003 through

April 2007 who had fever for ≥3 days but ≤10 days and who fulfilled ≥4 of 5 diagnostic criteria (rash, conjunctival injection, cervical lymphadenopathy, changes in the oral mucosa, and changes in the extremities) or 3 criteria plus coronary artery abnormalities documented through echocardiography.[2] Patients with KD were divided into a group with shock (KDSS group) and a group in hemodynamically normal condition before infusion of IVIG. We defined hypotension and shock according to previously published guidelines, and we made the diagnosis of KDSS if the sustained presence of any of the following conditions caused the treating clinicians to initiate volume expansion, infusion of vasoactive agents, or transfer to an intensive care setting: systolic hypotension for age (infants 0–28 days of age, <60 mm Hg; infants 1–12 months of age, <70 mm Hg; children 1–10 years of age, <70 + [2 × age] mm Hg; youths >10 years of age, ≤90 mm Hg[3,4]), a decrease in systolic blood pressure from baseline of ≥20%, or clinical signs of poor perfusion (tachycardia, prolonged capillary filling time, cool extremities, diminished pulses, oliguria, or mental status changes not accounted for by other conditions such as fever or ambient temperature) regardless of measured blood pressure.[3,5] Patients with KD who were admitted during the same period and did not meet the criteria for the definition of shock formed the comparison group with hemodynamically normal KD.

Although no patients with KD presented with shock in the prospective database before 2003, we postulated that earlier cases might have been misdiagnosed and therefore never included in our database. To identify patients with KD who were treated for shock but were misclassified with other diagnoses, we conducted a computerized search, on the basis of International Classification of Diseases, Ninth Revision codes, for patients discharged from the critical care unit between January 1, 2001, and August 31, 2006, with diagnoses of toxic shock syndrome ($n = 6$), systemic inflammatory response syndrome with ($n = 160$) or without ($n = 109$) organ dysfunction, septicemia ($n = 28$), shock (unspecified) ($n = 66$), or viremia ($n = 4$). We reviewed the patients' hospital records to identify clinical features of KD.

For all patients with KD, we accessed the following prospectively collected data: demographic data (age, gender, ethnicity, and number of days of fever at presentation); laboratory values obtained before the administration of IVIG (white blood cell and differential counts, platelet count, erythrocyte sedimentation rate, and concentrations of hemoglobin, C-reactive protein, alanine transaminase, and γ-glutamyl transpeptidase); laboratory evaluations of coagulation function within 72 hours before or after IVIG administration; response to IVIG; and echocardiographic data. We converted neutrophil and band counts reported as percentages to absolute neutrophil and band counts and hemoglobin levels to age-adjusted z scores.[6] We defined IVIG resistance as persistent or recrudescent fever (temperature of ≥38.0°C, measured rectally or orally) ≥36 hours after completion of the IVIG infusion (2 g/kg).[2]

We compared echocardiographic measurements between the KDSS group and the subset of the hemodynamically normal KD group for which complete echocardiographic data were available ($n = 86$). Echocardiography (Sequoia; Siemens Medical Systems, Malvern, PA) was performed with standard techniques during the acute (echocardiogram 1; 0–10 days after disease onset), subacute (echocardiogram 2; 11–21 days), convalescent (echocardiogram 3; 22–90 days), and chronic (echocardiogram 4; 91–365 days) phases. We measured the internal diameters of the proximal right coronary artery and left anterior descending coronary artery, as well as the aortic root at 4 locations (annulus, sinus, sinotubular junction, and ascending aorta). The coronary arteries were classified as normal (luminal internal diameters of the right coronary artery and left anterior descending coronary artery measured with echocardiography were <2.5 SD units from the mean normalized for body surface area; z score of <2.5), dilated ($2.5 \leq z$ score < 4.0), or aneurysmal (saccular or fusiform dilation of a coronary artery segment with a z score of ≥4.0).[7] We defined the lower limit of the reference range for the ejection fraction as 54%, and we defined abnormal valvular insufficiency as retrograde flow of ≥1+.[8]

Parameters of ventricular diastolic function included mitral inflow velocities during early diastolic filling (E wave velocity) and atrial contraction (A wave velocity), deceleration time (time, in milliseconds, from the peak of the E wave to baseline), and Doppler measurement of tissue velocity at the lateral mitral annulus during early diastolic filling (E′ velocity). Data calculated from the diastolic measurements included the mitral E wave velocity/A wave velocity ratio and the E wave velocity/E′ velocity ratio. Diastolic parameters were compared with published normal values[9–11] and, when regression equations were available, z scores were generated.

We performed bivariate comparisons by using the Mann-Whitney U test for medians and the χ^2 test or Fisher's exact test for dichotomous or ordinal variables, as appropriate. For laboratory values that were outside the dynamic range of the test (eg, erythrocyte sedimentation rate of >140 mm/hour), the maximal or minimal value detected in the assay was used, as appropriate. We performed statistical analyses with SPSS 11.5 for Windows (SPSS, Chicago, IL).

RESULTS

Each of the 373 patients discharged from the critical care unit with shock syndromes between January 2001 and August 2006 either had an unequivocal alternate diagnosis with supporting test results or did not meet the diagnostic criteria for KD. Therefore, we identified no reasonably likely cases of missed KDSS. Between May 2003 and April 2007, 13 patients with KDSS among 187 patients with KD were treated in a critical care unit ($n = 12$) or closely monitored setting ($n = 1$) for shock (Table 1 and Fig 1). All received volume resuscitation (median: 53 mL/kg) and 7 (54%) received infusions of vasoactive agents for 3 to 135 hours (median: 68 hours). The following agents were used singly or in combination: dobutamine, dopamine, epinephrine, milrinone, and norepinephrine. Compared with patients with hemodynamically normal KD, patients with KDSS were more often female and had greater proportions

TABLE 1 Hemodynamic and Coagulation Abnormalities in Patients With KDSS

Patient No.	Age	Gender	Ethnicity	Lowest Blood Pressure, mm Hg	Critical Care Time, d	Prothrombin Time, s	Partial Thromboplastin Time, s	Fibrinogen Level, mg/dL	D-Dimer Titer	Platelet Count Before IVIG Treatment, $\times 10^9$ Cells per L	Lowest Platelet Count, $\times 10^9$ Cells per L
1	1.6 mo	F	Hispanic	74/33[a]	0 (17 in step-down unit)	13.0[b]	46[b]	134	1:2	63[c]	7
2	4 mo	M	Mixed	45/22	1	13.7	31	281	Positive undiluted	346	313
3	2.0 y	M	White	82/40[a]	2	11.6	29	NA	NA	148	19
4	2.4 y	M	Mixed	70/56	2	NA	NA	NA	NA	NA	NA
5	2.4 y	F	White	73/26	2	16.9[b]	48[b]	242	Positive undiluted	106	85
6	2.8 y	M	Hispanic	60/40	5	15.6[b]	45[b]	287	NA	132	77
7	2.8 y	F	Hispanic	74/36[a]	3	15.2[b]	38[b]	363	Positive undiluted	275	245
8	3.8 y	F	Mixed	69/42	2	NA	NA	NA	NA	NA	NA
9	4.0 y	F	Hispanic	61/37	5	18.4[b]	35	663	NA	235	235
10	4.9 y	F	Hispanic	57/40	5	17.3[b]	35	559	NA	446	273
11	6.9 y	F	Hispanic	64/30	8	12.7	64[b]	304	1:2	35	35
12	7.1 y	F	Hispanic	70/30	6	13.7	39[b]	512	1:2	104	68
13	9.0 y	F	Mixed	70/33	2	12.9	39[b]	411	1:2	89	89

Coagulation data were obtained within 72 hours after IVIG treatment. F indicates female; M, male; NA, not available.

[a] Shock according to clinical criteria and/or decrease in systolic blood pressure of ≥20%.

[b] Prolonged, on the basis of age-adjusted normal values.

[c] Value obtained after platelet transfusion.

of bands, lower platelet counts, lower age-adjusted hemoglobin *z* scores, and higher C-reactive protein concentrations (Table 2). Age, ethnicity, illness duration, and other laboratory characteristics did not differ between the groups. Although the difference was not statistically significant, patients reporting Hispanic ethnicity were nearly twice as common in the KDSS group and Asian patients were not represented. Of the 11 patients who underwent a coagulation evaluation, 5 patients (45%) had evidence of consumptive coagulopathy, with low platelet counts ($<150 \times 10^9$ cells per L), positive D-dimer results, and prolonged partial thromboplastin times for age (Table 1). The remaining 6 all demonstrated ≥1 abnormality in their coagulation evaluations. IVIG resistance was more common in KDSS, affecting 6 patients (46%) (Table 2), who required additional IVIG or infliximab to control their inflammation.

The KDSS group had more-severe abnormalities in numerous echocardiographic measures of coronary artery anatomic features and ventricular function (Table 3). The maximal left anterior descending coronary artery and right coronary artery *z* scores were higher in the KDSS group, but aortic root *z* scores were not. Abnormally low ejection fractions and mitral regurgitation occurred more frequently in the KDSS group; however, both parameters were normal by the subacute phase (echocardiogram 2). None of the echocardiograms performed in the acute phase of KDSS revealed aortic regurgitation or pericardial effusions. All patients with KDSS underwent echocardiography during the subacute period, and 6 had convalescent echocardiograms. None had residual mitral regurgitation, and coronary artery diameters were normal in 5 of the 6 convalescent studies performed to monitor acute dilation. None of the electrocardiograms or echocardiograms obtained during the acute phase or during the follow-up period revealed evidence of ischemia or infarction.

Striking abnormalities of diastolic function were noted in the KDSS group (Table 4). Fusion of E and A waves in acute-phase echocardiograms limited the assessment of diastolic function for all except 2 patients in the KDSS group. Mitral E wave velocities were abnormal

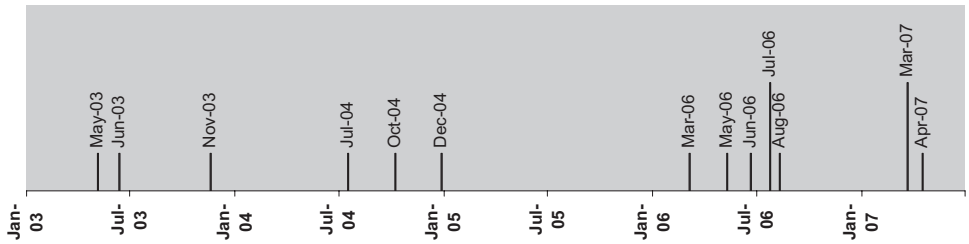

FIGURE 1
Recognition of KDSS over 4 years, according to date of presentation.

TABLE 2 Demographic and Laboratory Characteristics of Patients With KDSS or KD Without Shock

Characteristic	KDSS ($N = 13$)	KD Without Shock ($N = 174$)[a]	P
Age, median (IQR), y	2.8 (2.2–5.9)	2.1 (0.9–3.9)	.15
Male, *n* (%)	4 (31)	104 (60)	.04
Ethnicity, *n* (%)			.19
Hispanic	7 (54)	50 (29)	
White	2 (15)	46 (26)	
Asian	0 (0)	23 (13)	
Other	4 (31)	55 (32)	
Time of diagnosis, median (IQR), d of fever	5 (5–6.5)	5 (4–7)	.8
White blood cell count, median (IQR), $\times 10^9$ cells per L	12.4 (7.1–15.9)	14.3 (11.3–17.6)	.08
Neutrophils, median (IQR), %	0.41 (0.31–0.56)	0.52 (0.38–0.63)	.1
Band forms, median (IQR), %	0.36 (0.18–0.43)	0.16 (0.08–0.25)	.005
Absolute neutrophil count, median (IQR), $\times 10^9$ cells per L	6.7 (5.8–12.2)	9.1 (6.8–12.3)	.2
Absolute band count, median (IQR), $\times 10^9$ cells per L	3.0 (1.52–6.6)	2.2 (1.0–3.8)	.2
Hemoglobin level, age-adjusted *z* score, median (IQR), SD units	−2.1 (−3.5 to −0.9)	−1.2 (−2.2 to −0.1)	.02
Platelet count, median (IQR), $\times 10^9$ cells per L	148 (97–302)	410 (331–491)	<.001
Erythrocyte sedimentation rate, median (IQR), mm/h	40 (19–68)	59 (44–77)	.06
C-reactive protein level, median (IQR), mg/dL	18.4 (8.7–22.1)	8.2 (4.6–14.4)	.003
Alanine transaminase level, median (IQR), U/L	74 (42–126)	41 (22–112)	.2
γ-Glutamyl transpeptidase level, median (IQR), U/L	55 (35–166)	38 (18–140)	.2
IVIG resistance, *n* (%)	6 (46)	32 (18)	.03

IQR indicates interquartile range.

[a] Data availability for the group with KD without shock was as follows: absolute neutrophil count, $n = 173$; band level and absolute band count, $n = 153$; erythrocyte sedimentation rate, $n = 170$; C-reactive protein level, $n = 172$; alanine transaminase level, $n = 162$; γ-glutamyl transpeptidase level, $n = 172$.

on echocardiogram 1 for 5 of 13 patients with KDSS and continued to be abnormally low on echocardiograms 3 and 4 for 3 of 5 patients. On echocardiogram 2, the mitral E wave velocity/A wave velocity ratio was more frequently decreased in KDSS, which suggests impaired ventricular relaxation. Abnormally low E wave velocity/A wave velocity ratios persisted through the convalescent and chronic studies for patients with KDSS. At echocardiogram 2, elevated mitral E wave velocity/E′ velocity ratios for 6 of 7 patients with KDSS suggested persistent elevation of left ventricular end diastolic pressures, and shortened deceleration times for 3 of 12 patients suggested decreased ventricular compliance. E wave velocity/E′ velocity ratios and deceleration times were not available for sufficient numbers of patients for comparison with data for patients without shock in later stages, but deceleration times were shortened for 1 of 3 patients and 2 of 5 patients with KDSS in the convalescent and chronic stages, respectively.

DISCUSSION

We report the occurrence of shock and hypotension unrelated to IVIG administration in 13 of 187 patients with KD over a 4-year period, a phenomenon that we had not observed previously at our center. Compared with patients with hemodynamically normal KD, pa-

TABLE 3 Echocardiographic Data During the Acute Phase of Illness for Patients With KDSS or KD Without Shock

Characteristic	KDSS ($N = 13$)		KD Without Shock ($N = 86$)		P
	n (%) or Median (IQR)	Range	*n* (%) or Median (IQR)	Range	
Coronary artery abnormality	8 (62)		20 (23)		.008
Dilated	6 (46)		15 (17)		
Aneurysm	2 (15)		5 (6)		
Left anterior descending coronary artery maximal *z* score	1.9 (1.2–3.1)	0.4–25.4	1.3 (0.6–2.0)	−0.7 to 15.1	.04
Left anterior descending coronary artery maximal *z* score of ≥2.5	5 (39)		16 (19)		.1
Right coronary artery maximal *z* score	1.9 (1.7–3.6)	0.4–16.4	1.1 (0.5–1.9)	−1.3 to 8.6	.002
Right coronary artery maximal *z* score of ≥2.5	5 (39)		10 (12)		.03
Aortic sinus maximal *z* score	1.2 (0.9–2.6)	0.1–4.0	1.1 (0.6–1.6)	−0.2 to 1.6	.3
Ejection fraction	60.0 (52.0–63.9)	41.7–69.4	66.0 (62.1–70.3)	20.4–79.0	.002
Ejection fraction of <54%	4 (31)		2 (4)		.002
Mitral regurgitation of ≥1+	5 (39)		2 (2)[a]		.0004
Aortic regurgitation of ≥1+	0 (0)		0 (0)[a]		

IQR indicates interquartile range.

[a] Reported for 83 patients without shock.

TABLE 4 Echocardiographic Measures of Diastolic Function in Patients With KDSS or KD Without Shock

Characteristic	No. Abnormal/No. Tested (%)		*P*
	KDSS (*N* = 13)	KD Without Shock (*N* = 86)	
Abnormal E wave velocity in echocardiogram 1	5/12 (42)	27/74 (37)	.8
Abnormal E wave velocity in echocardiogram 2	1/12 (8)	10/43 (23)	.4
Abnormal E wave velocity/A wave velocity ratio in echocardiogram 2	5/12 (42)[a]	10/38 (26)	.5
Abnormal deceleration time in echocardiogram 2	4/12 (33)	7/38 (18)	.4
Abnormally high E wave velocity/E′ velocity ratio in echocardiogram 2	6/7 (86)	2/9 (22)	.04
Abnormal E wave velocity in echocardiogram 3	3/5 (60)[a]	6/41 (15)	.04
Abnormal E wave velocity/A wave velocity ratio in echocardiogram 3	4/5 (80)[a]	5/38 (13)	.005
Abnormal E wave velocity in echocardiogram 4	3/5 (60)[a]	3/15 (20)	.1
Abnormal E wave velocity/A wave velocity ratio in echocardiogram 4	3/5 (60)[a]	4/13 (31)	.3

[a] All abnormal values for these parameters were abnormally low for patients with KDSS ($P < .05$ for all comparisons of proportions with abnormally low values).

tients with KDSS were more likely to be female, to have laboratory findings consistent with greater inflammation, and to have impaired systolic and diastolic function. Patients with KDSS also exhibited resistance to IVIG more often and had higher rates of coronary artery dilation and aneurysm formation.

Although the most-overt cardiovascular disturbances resolved promptly with therapy, evidence of abnormal ventricular diastolic function persisted into the chronic phase of follow-up monitoring. Ventricular relaxation, which is an active process in early diastole, allows normal E wave velocity. Early impairment in relaxation results in a depressed E wave velocity/A wave velocity ratio, as seen in our KDSS population. Decreases in ventricular compliance and elevated filling pressures result in shorted deceleration times and elevated E wave velocity/E′ velocity ratios, both of which were present in the subacute phase of KDSS. The cause of persistent ventricular diastolic dysfunction and its long-term significance remain unknown. However, there may be long-term sequelae of KDSS even after coronary artery abnormalities have resolved. Lack of complete diastolic data for the group with hemodynamically normal KD limited our comparisons.

The cause and factors contributing to the development of KDSS are unknown. Although the number of days of fever at diagnosis did not differ between patients with and without KDSS, laboratory test results before treatment and disease outcomes suggested greater underlying inflammation. The inciting factors are unknown, but the high frequency of low-grade consumptive coagulopathy suggests more-intense vasculitis in KDSS. Coagulopathy and platelet activation have been described in acute KD, although the process usually is self-limited and does not require specific therapy beyond treatment of the underlying inflammation.[12]

The prevalence of KDSS was highest in 2006 and 2007 (Fig 1), and we found no cases consistent with KDSS before 2003, through a retrospective review of other diagnostic categories that included shock, which suggests that KDSS is an increasingly recognized phenomenon in our community. Previous reports described patients with KD without evidence of coronary artery occlusion who experienced shock and hypotension in association with acute respiratory distress syndrome,[13] aortic valvular damage and severe aortic regurgitation,[14] renal failure and relative volume overload,[15] and severe renal failure and myocarditis.[16] Our study, which emphasizes the temporal clustering of cases of shock in KD, and the study of a similar series of patients with KDSS from Denver, Colorado,[17] should alert clinicians to the possible increasing prevalence of this complication of acute KD.

We recognize several limitations to this study. In the absence of a previously accepted definition for KDSS, our inclusion criteria combined hypotension, relative blood pressure changes, and clinical measures of hypoperfusion. Normative values for pediatric hypotension are less well established than those for hypertension. We used lower-limit values for systolic hypotension predicted by a simple, age-based formula.[3,4] Comparable lower-limit values are recommended by other sources, including a consensus definition used for pediatric sepsis[18,19] and the extrapolation of 5th percentile values of systolic blood pressure from better-established 50th and 95th percentile values.[20] We incorporated a relative decrease in blood pressure into our definition of KDSS, which is not part of the traditional definition of shock. However, our criterion (≥20% decrease from baseline values) is consistent with the magnitude of changes deemed clinically significant by other pediatric investigators, including relative decreases of 10% to 30% and absolute decreases of 20 to 30 mm Hg in the context of pediatric sedation,[21,22] anesthetic induction,[23–25] emergency airway management,[26] and anaphylaxis.[27] Our inclusion of purely clinical criteria for shock might allow patients with mild, potentially self-limited, hemodynamic disturbances to meet our definition of KDSS. However, our definition is in keeping with those of the Pediatric Advanced Life Support[3] and Advanced Pediatric Life Support[5] courses, which emphasize early detection and treatment of shock without a requirement for

frank hypotension or laboratory or invasive measures of cardiac output and tissue perfusion.

Despite prospective entry of data into the KD database, the recent recognition of KDSS was unanticipated, and patient characteristics, management practices, and other regional and global phenomena contributing to or predicting KDSS and treatment failure might have been overlooked. Similarly, it is conceivable that brief episodes of hemodynamic instability escaped clinical detection either in the KD population before 2003 or in our comparison group of patients without shock after 2003. However, there have been no changes in the referral patterns to our center, which is the principal pediatric tertiary care center for a 3-county region, or in the maintenance or content of the KD database. Nursing care and documentation standards for patients undergoing evaluation and treatment for KD also have remained standardized. Finally, the retrospective nature of our search for previously misclassified patients with KDSS and our small sample of patients with KDSS limit our ability to describe the full spectrum of this phenomenon and to identify independent risk factors through multivariate analyses.

CONCLUSIONS

We have observed shock and hypotension requiring critical care support with increasing frequency among patients with acute KD. These patients seem to have greater incidences of coronary artery abnormalities and IVIG resistance. Additional research is required to elucidate the pathogenesis of this phenomenon, to identify risk factors and predictors for the development of KDSS, and to characterize more fully the long-term abnormalities of diastolic dysfunction. However, clinicians who treat pediatric patients with shock and those who treat patients with acute KD should maintain a heightened awareness of KDSS and should be prepared to institute hemodynamic support and to administer repeat doses of IVIG or adjunctive antiinflammatory therapies. Awareness of KDSS is particularly important for emergency department personnel, who are likely to represent the first point of medical contact for these very ill patients, and for critical care personnel, who rarely care for patients with KD.

ACKNOWLEDGMENTS

This work was supported in part by grants from the National Heart, Lung, and Blood Institute, National Institutes of Health (grant RO1 HL69413 to Drs Burns and Kanegaye and grant K24-HL074864 to Dr Burns).

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. 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
3. Ralston M, Hazinski MF, Zaritsky AL, Schexnayder SM, Kleinman ME. *Pediatric Advanced Life Support Provider Manual*. Dallas, TX: American Heart Association; 2006
4. Dieckmann RA. Pediatric assessment. In: Gausche-Hill M, Fuchs S, Yamamoto L, eds. *APLS: The Pediatric Emergency Medicine Resource*. 4th ed. Sudbury, MA: Jones and Bartlett; 2007: 20–51
5. Fitzmaurice L, Gerardi MJ. Cardiovascular system. In: Gausche-Hill M, Fuchs S, Yamamoto L, eds. *APLS: The Pediatric Emergency Medicine Resource*. 4th ed. Sudbury, MA: Jones and Bartlett; 2007:106–145
6. Tremoulet AH, Best BM, Song S, et al. Resistance to intravenous immunoglobulin in children with Kawasaki disease. *J Pediatr.* 2008;153(1):117–121
7. 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
8. Kimball TR, Michelfelder EC. Echocardiography. In: Allen HD, Driscoll DJ, Shaddy RE, Feltes TF, eds. *Moss and Adams' Heart Disease in Infants, Children and Adolescents: Including the Fetus and Young Adult*. 7th ed. Philadelphia, PA: Lippincott Williams & Wilkins; 2008:95–163
9. Schmitz L, Xanthopoulos A, Koch H, Lange PE. Doppler flow parameters of left ventricular filling in infants: how long does it take for the maturation of the diastolic function in a normal left ventricle to occur? *Pediatr Cardiol.* 2004;25(5):482–491
10. Eidem BW, McMahon CJ, Cohen RR, et al. Impact of cardiac growth on Doppler tissue imaging velocities: a study in healthy children. *J Am Soc Echocardiogr.* 2004;17(3):212–221
11. Schmitz L, Koch H, Bein G, Brockmeier K. Left ventricular diastolic function in infants, children, and adolescents: reference values and analysis of morphologic and physiologic determinants of echocardiographic Doppler flow signals during growth and maturation. *J Am Coll Cardiol.* 1998;32(5): 1441–1448
12. Burns JC, Glode MP, Clarke SH, Wiggins J, Hathaway WE. Coagulopathy and platelet activation in Kawasaki syndrome: identification of patients at high risk for development of coronary artery aneurysms. *J Pediatr.* 1984;105(2):206–211
13. Palmer AL, Walker T, Smith JC. Acute respiratory distress syndrome in a child with Kawasaki disease. *South Med J.* 2005; 98(10):1031–1033
14. Fuse S, Tomita H, Ohara T, Iida K, Takamuro M. Severely damaged aortic valve and cardiogenic shock in an infant with Kawasaki disease. *Pediatr Int.* 2003;45(1):110–113
15. Senzaki H, Suda M, Noma S, Kawaguchi H, Sakakihara Y, Hishi T. Acute heart failure and acute renal failure in Kawasaki disease. *Acta Paediatr Jpn.* 1994;36(4):443–447
16. Case records of the Massachusetts General Hospital: case 36–1998: an 11-year-old girl with fever, hypotension, and azotemia. *N Engl J Med.* 1998;339(22):1619–1626
17. Dominguez SR, Friedman K, Seewald R, Anderson MS, Willis L, Glodé MP. Kawasaki disease in a pediatric intensive care unit: a case-control study. *Pediatrics.* 2008;122(4). Available at: www.pediatrics.org/cgi/content/full/122/4/e786
18. Goldstein B, Giroir B, Randolph A; Members of the International Consensus Conference on Pediatric Sepsis. International pediatric sepsis consensus conference: definitions for sepsis and organ dysfunction in pediatrics. *Pediatr Crit Care Med.* 2005;6(1):2–8
19. Goldstein B, Giroir B, Randolph A. Values for systolic blood pressure. *Pediatr Crit Care Med.* 2005;6(4):500–501
20. Haque IU, Zaritsky AL. Analysis of the evidence for the lower limit of systolic and mean arterial pressure in children. *Pediatr Crit Care Med.* 2007;8(2):138–144

21. Dickinson R, Singer AJ, Carrion W. Etomidate for pediatric sedation prior to fracture reduction. *Acad Emerg Med.* 2001; 8(1):74–77
22. Sharieff GQ, Trocinski DR, Kanegaye JT, Fisher B, Harley JR. Ketamine-propofol combination sedation for fracture reduction in the pediatric emergency department. *Pediatr Emerg Care.* 2007;23(12):881–884
23. Barbi E, Marchetti F, Gerarduzzi T, et al. Pretreatment with intravenous ketamine reduces propofol injection pain. *Paediatr Anaesth.* 2003;13(9):764–768
24. Kaabachi O, Chettaoui O, Ouezini R, Abdelaziz AB, Cherif R, Kokki H. A ketamine-propofol admixture does not reduce the pain on injection compared with a lidocaine-propofol admixture. *Paediatr Anaesth.* 2007;17(8):734–737
25. Tosun Z, Esmaoglu A, Coruh A. Propofol-ketamine vs propofol-fentanyl combinations for deep sedation and analgesia in pediatric patients undergoing burn dressing changes. *Paediatr Anaesth.* 2008;18(1):43–47
26. Zuckerbraun NS, Pitetti R, Herr SM, Roth KR, Gaines BA, King C. Use of etomidate as an induction agent for rapid sequence intubation in a pediatric emergency department. *Acad Emerg Med.* 2006;13(6):602–609
27. Sampson HA, Munoz-Furlong A, Campbell RL, et al. Second symposium on the definition and management of anaphylaxis: summary report: second National Institute of Allergy and Infectious Disease/Food Allergy and Anaphylaxis Network symposium. *Ann Emerg Med.* 2006;47(4): 373–380

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Pediatrics 2009;123;e783
DOI: 10.1542/peds.2008-1871