Treatment of Kawasaki Disease: Analysis of 27 US Pediatric Hospitals From 2001 to 2006

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KEY WORDS
Kawasaki disease, coronary artery aneurysm, infliximab

ABBREVIATIONS
CAA—coronary artery aneurysm
ICD-9—International Classification of Diseases Ninth Revision
IVIG—intravenously administered immunoglobulin
KD—Kawasaki disease
PHIS—Pediatric Health Information System
TNF—tumor necrosis factor

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WHAT'S KNOWN ON THIS SUBJECT: Analyses of trends in admissions and use of therapeutic regimens for KD have been handicapped by limitations in existing databases. The PHIS database permits tracking of medications in and across multiple admissions within a center.

WHAT THIS STUDY ADDS: Our report provides the first large, multicenter description of agents used for the treatment of IVIG-resistant KD in the United States. We show that infliximab emerged as an increasingly used treatment for IVIG-resistant KD during the period of 2001–2006.

abstract

OBJECTIVES: We sought to analyze trends in admissions and to describe therapies used for acute Kawasaki disease over a 6-year period.

METHODS: The Pediatric Health Information System provides patient data including demographic variables, International Classification of Diseases, Ninth Revision codes, and services billed to patients. Patient identifiers enable tracking of medication use in and across multiple admissions within a center. We analyzed data for patients with (1) a diagnosis code for Kawasaki disease, (2) intravenously administered immunoglobulin treatment during hospitalization, and (3) discharge between January 1, 2001, and December 30, 2006, from 27 hospitals contributing complete data over the study period.

RESULTS: During the study period, 5197 Kawasaki disease admissions were identified for 4811 patients; numbers increased 32.6% from 2001 (n = 678) to 2006 (*n* = 899). Retreatment with intravenous immunoglobulin was administered to 712 patients (14.8%) over the study period. Other antiinflammatory therapies included intravenously administered methylprednisolone (5.8%), orally administered prednisone (2.8%), and infliximab (1%). Use of infliximab steadily increased from 0.0% (0 of 678 patients) in 2001 to 2.3% (21 of 899 patients) in 2006. Coronary artery aneurysms were coded for 3.3% of patients. Male patients, patients <1 year of age, and Hispanic patients were significantly more likely to have coding for coronary artery aneurysms.

CONCLUSIONS: Our report provides the first large multicenter description of agents used in the treatment of intravenously administered immunoglobulin-resistant Kawasaki disease in the United States. Trends include increased numbers of admissions attributable to Kawasaki disease and increased usage of infliximab. *Pediatrics* 2009;124:1–8

Since its initial description in Japan in 1967,[1] Kawasaki disease (KD) has been reported throughout the world, in children of all races and ethnicities.[2] Melish et al[3] reported the first US case in 1976. Subsequent reports documented cases of KD in many locations and populations across the United States,[4–17] often by using statewide hospital discharge data to generate incidence rates and to identify patient sociodemographic characteristics. US national databases have been used to describe the epidemiological features of KD more thoroughly. In 2002, the Nationwide Inpatient Sample, a database derived from the Healthcare Cost and Utilization Project, was used by Chang[6,7] to evaluate the epidemiological pattern of KD over a 10-year period. Holman et al[14] used the Kids' Inpatient Database to describe hospitalizations attributable to KD in the United States in 1997 and 2000. By using the Centers for Disease Control and Prevention passive surveillance system for KD, Belay et al[4] identified risk factors for coronary artery abnormalities.

Consistent findings in those studies included a median age at admission of 2 to 3 years, a majority of admissions for children <5 years of age, a male/female ratio of ~1.5:1, and higher hospitalization rates during the winter months. Each of those studies was limited by properties inherent to its respective database. Specifically, data on coronary artery abnormalities and intravenously administered immunoglobulin (IVIG) therapy were not available through the Nationwide Inpatient Sample. The Kids' Inpatient Database does not allow for tracking of patients; therefore, data on readmission and retreatment were not analyzed. Lastly, the passive surveillance system accounts for only 10% of admissions attributable to KD in the United States.

More than 40 freestanding, noncompeting, pediatric hospitals in the United States contribute patient information to the Pediatric Health Information System (PHIS). Anonymous patient identifiers allow identification of medications used for individual patients during hospitalization and enable tracking of patients and medication use across multiple admissions within a center. We used the PHIS database to analyze data for patients admitted with a diagnosis of KD between January 1, 2001, and December 30, 2006. Our goals were to describe the therapeutic regimens used during initial admissions and readmissions attributable to acute KD and to analyze secular trends over the 6-year period.

METHODS

Data Source

The PHIS was created by the Child Health Corporation of America and contains patient data for all admissions from 43 freestanding children's hospitals in North America (www.chca.com/owner_hospitals/index.html). Institutions are labeled within the database but cannot be identified in public reporting. Individual patient medical record numbers, billing numbers, and zip codes are encrypted. Data submitted by institutions are monitored for coding consistency and completeness. The database is updated quarterly by the Child Health Corporation of America.

Level 1 data in the PHIS database include demographic information as well as diagnoses and procedures coded with International Classification of Diseases, Ninth Revision (ICD-9) codes. A subset of the PHIS hospitals also contribute level 2 data with detailed pharmacy information including medications prescribed for each patient, as identified with Clinical Transaction Classification codes. Medication usage for individual patients can be determined across admissions and readmissions in the same center.

Identification of Study Group

We identified 27 US hospitals that contributed level 1 and level 2 data to the PHIS during each of the 6 years between January 1, 2001, and December 30, 2006. We extracted information from the database for all admissions, including readmissions, with a discharge diagnosis of KD during the study period in the identified hospitals. We defined readmissions as hospitalizations that occurred within 6 weeks after the first admission. We included only patients who received ≥1 treatment with IVIG during their first admission, to exclude patients who were evaluated for KD and did not receive the diagnosis, as well as patients who were admitted late after illness onset because of cardiac events and/or procedures.

Definition of IVIG Retreatment

IVIG is usually administered to patients with KD over 8 to 12 hours, and multiple bags of IVIG may constitute a single dose. Consequently, administration of IVIG may be recorded over 2 calendar days and pharmacy logs in the PHIS may have >1 entry for IVIG. To evaluate whether patients required >1 dose of IVIG (referred to as "retreatment" with IVIG), doses were considered retreatment if there were ≥2 calendar days between entries for IVIG. Patients with ≥3 IVIG entries were considered to have received retreatment if there were ≥2 days between the first and last entries for IVIG.

Data Analyses

Changes in the distribution of length of stay over the 6-year study period were examined by using the Kruskal-Wallis test. Differences in proportions over time (eg, the proportions of patients

requiring readmission) were evaluated by using the χ^2 test. Relationships between patient characteristics and both readmission and the presence of coronary artery aneurysms (CAAs) also were assessed by using the χ^2 test. The χ^2 goodness-of-fit test was used to determine whether the numbers of admissions attributable to KD changed over the study period.

RESULTS

Demographic characteristics of patients are summarized in Table 1. A total of 5197 admissions were identified for 4811 patients from 27 hospitals. According to US census guidelines, the geographic distribution of the participating hospitals included 6 hospitals in the West, 11 hospitals in the South, 9 hospitals in the Midwest, and 1 hospital in the Northeast. The median age at first admission was 3.4 years (range: 1 month to 21.3 years), and the majority of patients (60.1%) were 1 to 4 years of age. Male patients represented 60.4% of patients. Asian patients were over-represented in the KD population ($P <$ .001, χ^2 test), constituting 6.9% of patients admitted with a diagnosis of KD, compared with 1.6% of patients overall in the PHIS. The median length of stay for admission was 3 days (range: 1–222 days [interquartile range: 2–4 days]), and values did not change significantly during the 6-year study period.

TABLE 1 Demographic Characteristics of Patients ($N = 4811$)

Male, *n* (%)	2896 (60.4)
Age at first admission	
Median (interquartile range), y	3.4 (1.4–4.6)
<1 y, *n* (%)	875 (18.2)
1–4 y, *n* (%)	2893 (60.1)
5–9 y, *n* (%)	890 (18.5)
10–17 y, *n* (%)	150 (3.1)
≥18 y, *n* (%)	3 (0.1)
Insurance type, *n* (%)	
Governmental support[a]	1645 (34.2)
Private insurance	1798 (37.4)
Self-pay	182 (3.8)
Other	1097 (22.8)
No charge	6 (0.1)
Unknown	83 (1.7)
Race/ethnicity	
White, non-Hispanic	1934 (40.2)
Hispanic	798 (16.6)
Black[b]	1121 (23.3)
Asian	334 (6.9)
American Indian	7 (0.1)
Other	382 (7.9)
Unknown	235 (4.9)

[a] Governmental support included Medicare, Medicaid, and other governmental funding.
[b] Hispanic ethnicity was reported for 1 black subject.

Between 2001 and 2006, the number of first admissions attributable to KD increased by 32.6%, from 678 to 899 admissions (Fig 1). The number of admissions attributable to KD increased significantly in 2005–2006, compared with 2001–2004 ($P <$ .001). A total of 351 patients (7.3%) were readmitted at least once within a 6-week period. Two or more readmissions occurred for 31 patients (8.8% of patients who required readmission and 0.6% of all patients), and 1 patient required 4 readmissions. The proportions of patients who required readmission did not change significantly over the study period. Age of <1 year, compared with older age, was associated with a greater likelihood of readmission (9.6% vs 6.8%; $P = .005$); however, readmission rates were not associated with gender, race, or insurance type. For the 27 hospitals studied, there was no relationship between the median length of stay at first admission and the proportion of patients subsequently readmitted (Spearman rank correlation $r_s = -0.06$; $P = .75$).

We analyzed IVIG retreatment during initial admissions and readmissions. Retreatment with ≥1 infusion of IVIG was administered to 712 patients (14.8%) during the 6-year period. Retreatment with IVIG was administered to 531 patients (11.0%) during their first admission. Among 351 patients who were readmitted, 213 (60.7%) received IVIG retreatment during readmission. Thirty-two patients were retreated with IVIG during both initial and subsequent admissions. One hundred thirty-eight patients were readmitted and did not receive IVIG (39.3%). Of those 138 patients, 36 (43.4%) underwent echocardiography, 18 (21.7%) received intravenously administered methylprednisolone, orally administered prednisone, or infliximab, and 29 (34.9%) underwent echocardiography and also received intravenously administered methylprednisolone, orally administered prednisone, or infliximab during readmission. The remaining 55 patients (15.7% of those readmitted) neither received any of those medications nor underwent echocardiography during readmission.

We evaluated the use of medications other than IVIG during admissions and readmissions during the study period (Table 2). Intravenously administered methylprednisolone was given to 278 patients (5.8%) and orally administered prednisone to 133 patients (2.8%). The use of intravenously administered methylprednisolone and orally administered prednisone did not change significantly over time (Fig 2). Forty-eight patients (1.0%) received infliximab. The proportion of patients treated with infliximab increased significantly, from none of 678 patients in 2001 to 21 (2.3%) of 899 patients in 2006 ($P <$ .001). More than one half of the 27 participating hospitals ($n = 14$ [51.9%]) administered infliximab during the study period. Three of the 14 centers participated in a multicenter trial evaluating the safety, tolerability, and pharmacokinetics of infliximab, in comparison with a second dose of IVIG, for patients with IVIG resistance (J. C. Burns, MD, written communication, 2008). Those 3 centers administered infliximab to 12 (25%) of the 48 patients in our analysis.

Antithrombotic therapy was prescribed in a variety of forms. More than 92% of patients ($n = 4429$) received aspirin. Unfractionated heparin

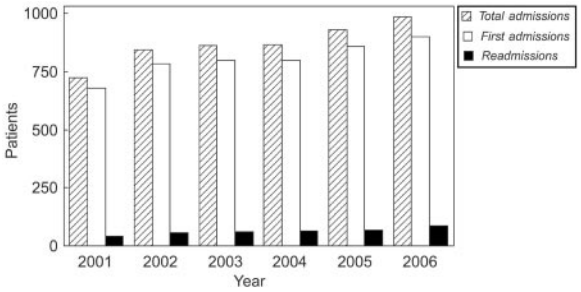

FIGURE 1
Admissions attributable to KD. Between 2001 and 2006, the number of patients admitted with KD increased by 32.6%, from 678 to 899 patients. For 351 patients (7.3%), ≥1 readmission occurred within a 6-week period. The number of readmissions did not change significantly over the study period.

was dispensed to 2004 patients (41.7%), but we could not distinguish between its use for maintenance of intravenous access and its use for therapeutic anticoagulation. Warfarin was prescribed for 54 patients (1.1%). The use of other antithrombotic therapies is described in Table 2. Thirteen patients (0.3%) received propranolol.

CAAs were coded for 127 patients (2.6%) during their first admission and for 157 patients (3.3%) overall. Although there was no linear trend in CAA coding between 2001 and 2006, patients admitted in 2005–2006, compared with 2001–2004, had a significantly greater likelihood of having a CAA code (4.4% vs 2.6%; $P = .001$). Male patients were more likely than female patients to have discharge diagnosis codes for CAAs (3.8% vs 2.4%; $P = .006$). Coding for CAAs occurred more often for children <1 year of age, compared with older children (8.0% vs 2.2%; $P < .001$).

TABLE 2 Use of Non-IVIG Therapy for 4811 Patients With KD

	n (%)
Antiinflammatory therapy	
Methylprednisolone	278 (5.8)
Orally administered prednisone and prednisolone	133 (2.8)
Infliximab	48 (1.0)
Antithrombotic therapy	
Aspirin	4429 (92.1)
Heparin	2004 (41.7)
Warfarin	54 (1.1)
Enoxaparin	49 (1.0)
Tissue plasminogen activator	33 (0.7)
Clopidogrel	16 (0.3)
Abciximab	10 (0.2)

Race and ethnicity were significantly correlated with the prevalence of CAA coding in our study population ($P < .001$) (Fig 3). The highest rates of CAAs were observed for American Indian patients, but the total number of patients was small and the results were not statistically meaningful. The second highest rates were reported for patients of Hispanic ethnicity (5.9%), with the lowest rates for black, Asian, and other groups (1.8% for each group). The rate of coding of CAAs for Hispanic patients was significantly higher than the rates for other racial and ethnic groups ($P < .001$). Data on race were missing for 235 patients, 10 (4.3%) of whom had CAA codes. No relationship was found between the type of insurance and coding for CAAs.

Other cardiac complications of KD during the study period were also identified on the basis of ICD-9 coding (Table 3). Sixty-one patients (1.3%) had codes for mitral regurgitation and 40 patients (0.8%) had codes for myocarditis, cardiomyopathy, or left ventricular dysfunction. Six patients (0.1%) had codes for myocardial infarction. Coronary artery aneurysm without myocardial infarction was coded for 5 patients (0.1%). Cardiac arrest was coded for 4 patients (0.1%); 1 of those patients also had the code for acute myocardial infarction.

Six patients died during hospitalization over the 6-year period, yielding a mortality rate of 0.12%. The age of the deceased patients ranged from 5 months to 11 years (median: 29 months). Four patients died during the first admission, and 2 patients died during a subsequent admission. Patients who died had a longer length of stay (ie, total days in the hospital across admissions) than did those who survived (median: 24.5 days [range: 1–82 days] vs 3 days [range: 1–222 days]; $P = .01$). The time from the first admission to death ranged from 1 to 102 days (mean: 44.2 days; median: 38 days). All 6 patients received ≥1 dose of IVIG, aspirin, and heparin. Therapeutic regimens, time from admission to death, and pertinent diagnoses for each patient are presented in Table 4.

DISCUSSION

To our knowledge, our report provides the first large, multicenter description of agents used for the treatment of IVIG-resistant KD in the United States. Therapy for IVIG-resistant KD often is administered on the basis of limited data, with considerable practice variation. Delineation of temporal trends in the treatment of KD in the United States is thus important but has been hindered by the inability of national databases to track an individual patient's clinical information across his or her hospital admissions. By using the PHIS database, which tracks medication usage for individual patients across multiple admissions within a center, we found that nearly 15% of patients who were admitted because of KD received retreatment with IVIG during the first or subsequent admissions, consistent with previous reports.[18–20] Administration of antiinflammatory medicines other than IVIG (eg, inflix-

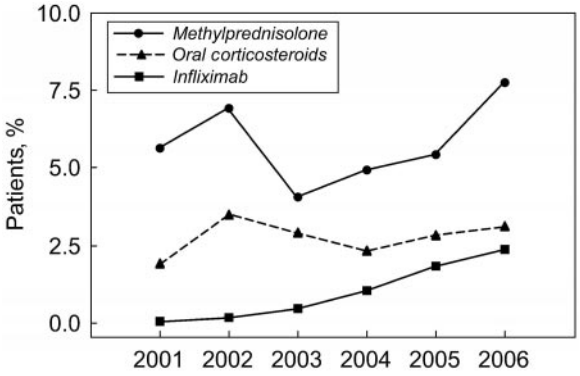

FIGURE 2
Use of antiinflammatory therapies other than IVIG during all admissions. Intravenously administered methylprednisolone was given to 5.8% of the study population, orally administered corticosteroids to 2.8% of the study population, and infliximab to 1% of the study population. Use of infliximab increased exponentially over the study period.

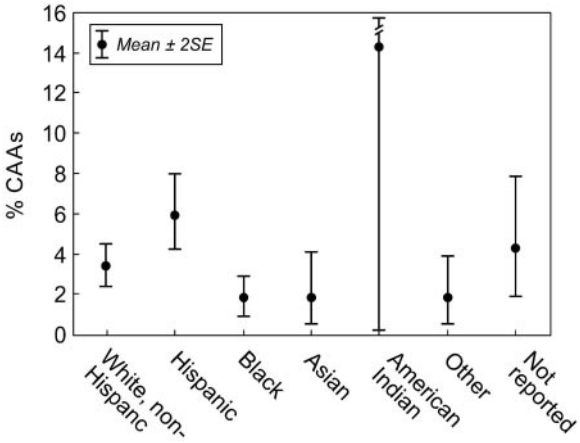

FIGURE 3
Race and ethnicity in relation to the prevalence of CAA coding. American Indian patients had the largest proportion of CAAs, but the population was small. A total of 5.9% of Hispanic patients had codes for CAAs, compared with 3.4% of white patients and 1.8% each of black and Asian patients ($P < .001$).

imab or corticosteroids) occurred for 9.5% of our study population. One percent of all patients received ≥1 dose of infliximab during the study period, with its use increasing from 0% to 2.3% of patients admitted between 2001 and 2006.

Despite the absence of controlled, prospective, clinical trials with adequate power to assess the efficacy and safety of infliximab in KD, treatment of refractory KD with infliximab increased exponentially over the study period. Infliximab is a chimeric monoclonal antibody to tumor necrosis factor (TNF) α, a pivotal cytokine in the acute inflammatory response.[21] Infliximab binds to TNF-α and blocks attachment to TNF-α receptors on T cells, ameliorating the inflammatory response. Elevated levels of TNF-α have been found in patients with KD, particularly those with coronary artery abnormalities.[22] Given the inflammatory and thrombotic properties of TNF-α, blockade at the level of TNF-α may be a logical approach for patients who have experienced failure of conventional therapy for KD. Previous descriptions of infliximab use in KD include case reports on 22 patients, the first of which was published in 2004.[23–27] Infliximab has been approved by the US Food and Drug Administration for use in pediatric Crohn disease and has proven to be efficacious[28,29] but not without complications.[30] Because infliximab is administered only once (or at most twice) for patients with KD, its administration may cause fewer complications in the KD population than in populations with other diseases for which it is administered repetitively. Further investigation of the safety and efficacy of infliximab administration for KD is warranted.

We found that both admissions attributable to KD and coding for CAAs increased significantly in 2005–2006, compared with 2001–2004. In 2004, the American Heart Association and the American Academy of Pediatrics released recommendations regarding the diagnosis and treatment of KD.[31] The recommendations liberalized criteria for IVIG treatment by providing an algorithm for the evaluation and treatment of patients with suspected incomplete KD by using supportive laboratory and echocardiographic data. Furthermore, IVIG retreatment was recommended for patients who failed to respond to initial therapy. Finally, a graph was provided for assessment of coronary artery *z* scores (ie, coronary artery dimensions adjusted for body surface area). The American Heart Association/American Academy of Pediatrics recommendations were disseminated widely in late 2004, and their release might have played a role in the observed trends. However, it would be unusual for recommendations from an expert body to be adopted so rapidly. Furthermore, neither symptoms of KD nor detailed data on coronary artery size are coded reliably in the PHIS database. Therefore, we cannot determine the extent to which the observed secular changes are related to changing KD epidemiological features, better case ascertainment through educa-

TABLE 3 Cardiac Complications Among 4811 Patients With KD, According to ICD-9 Codes

Diagnosis	ICD-9 Code	*n* (%)
Coronary Artery Aneurysm	414.11	157 (3.3)
Mitral valve disorder	424.0	61 (1.3)
Myocarditis	429.0	38 (0.8)
Left ventricular dysfunction	428.1	1 (<0.1)
Cardiomyopathy in other diseases	425.8	1 (<0.1)
Myocardial infarction	410.9	2 (<0.1)
Coronary artery occlusion without myocardial infarction	411.81	5 (0.1)
Acute myocardial infarction, unspecified site, initial episode	410.91	4 (0.1)
Cardiac arrest	427.5	4 (0.1)

tion of medical personnel, increased referral of KD cases to children's hospitals, or broader criteria for the treatment of KD or the diagnosis of coronary artery abnormalities.

Similar to the findings of Belay et al,[4] we found that the risk for developing coronary artery abnormalities was higher for male patients, children <1 year of age, and patients of Hispanic ethnicity. In contrast to the report by Belay et al,[4] however, we did not find an increased risk of CAAs among Asian patients. Our methods for identifying patients with CAAs differed from those used by Belay et al[4] in important ways. The patient population described by Belay et al[4] was assembled through voluntary reporting to the Centers for Disease Control and Prevention and represented a small proportion of actual KD cases in the nation. As noted in that study, selective reporting of more classic and more severe cases of KD might have influenced the identification of risk factors. Furthermore, we used ICD-9 codes to identify diagnoses and complications in the PHIS database, whereas Belay et al[4] collected information from case report forms. We do not know whether hospitals contributing to the PHIS used coronary artery *z* scores or Japanese Ministry of Health guidelines for coding cases with CAAs. Hospitals contributing to the PHIS might have used the CAA code for cases of mild dilation of the coronary vessels, which would have led to overestimation of the number of patients with CAAs because the ICD-9 code refers to aneurysms only.

Our findings should be viewed in light of additional limitations. Diagnoses or medication uses might have been omitted or incompletely captured because of errors in data entry or coding. Patients might have been more likely to leave the hospital with a CAA code if a cardiologist was involved in their care. Patients with unreported race/ethnicity had a high rate of CAAs of 4.3%, which potentially influenced our analyses of CAAs according to race/ethnicity. Our data sample was drawn from 27 freestanding pediatric hospitals in the United States, and our findings may not be applicable to KD admissions in pediatric wards within general hospitals. Nearly 16% of children readmitted during the study period did not receive IVIG, corticosteroids, or infliximab and did not have an echocardiogram performed during readmission; possible explanations for these readmissions include observation because of fever or more-invasive procedures such as cardiac catheterization. We were unable to report doses of medications with the PHIS, because children's weights were not available. Although the PHIS tracks patients across admissions at the same hospital, some patients might have been transferred to a different hospi-

TABLE 4 Characteristics of Deceased Patients With KD

Patient	Age	No. of IVIG Doses	Methylprednisolone	Prednisolone	Warfarin	Enoxaparin	No. of Tissue Plasminogen Activator Doses	Time From First Admission to Death, d	Other Pertinent Diagnoses
1	3 y	1	Yes	Yes	Yes	Yes	3	47	Cardiac arrest; mitral valve disorder
2	11 y	3	Yes	No	No	Yes	0	82	Other shock without mention of trauma
3	5 mo	2	Yes	No	No	No	2	4	CAA; coronary artery occlusion without myocardial infarction
4	5 y	1	No	No	No	No	0	1	Cardiac arrest; coronary artery occlusion without myocardial infarction; mitral valve disorder
5	1.7 y	2	Yes	Yes	No	No	0	29	Cardiac arrest; CAA
6	1.5 y	3	Yes	No	No	No	1	102	Myocarditis; acute myocardial infarction, unspecified site, initial episode of care

tal after initial treatment, which would cause underestimation of the frequency of IVIG retreatment and other therapies in KD. For example, a patient transferred to a PHIS hospital after initial treatment elsewhere would not have been classified as being retreated if he or she received only a single dose of IVIG at the PHIS center. Our definition of IVIG retreatment required 2 entries separated by ≥2 calendar days, because information regarding the time of day at which medications were administered is not available through the PHIS. Therefore, some patients who received IVIG retreatment ≤36 hours after the initial treatment might have been missed. Rates of IVIG retreatment and other treatments in our study thus represent lower limits.

CONCLUSIONS

By using a large, pediatric, inpatient database that tracks patients across admissions, we found that the number of admissions attributable to KD increased in the 5 years from 2001 to 2006. Although the proportions of patients who received IVIG retreatment and corticosteroids remained stable, infliximab administration emerged as an increasingly used treatment for IVIG-resistant KD during this period. Future prospective studies should evaluate the impact on patient outcomes of changes in the rates and types of treatment and retreatment for KD.

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