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Ryan A. Maddox Date

Kawasaki Syndrome:
An Investigation of Recurrence, Atypical Cases, and Treatment

By

Ryan A. Maddox
Doctor of Philosophy

Epidemiology

John R. Boring, III, Ph.D., M.S.
Advisor

Ermias D. Belay, M.D.
Committee Member

Jodie L. Guest, Ph.D., M.P.H.
Committee Member

Robert C. Holman, M.S.
Committee Member

Godfrey P. Oakley, Jr., M.D., M.S.P.M.
Committee Member

Accepted:

Lisa A. Tedesco, Ph.D.
Dean of the James T. Laney School of Graduate Studies

Date

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By

Ryan A. Maddox
B.S., Auburn University, 1998
M.P.H., Emory University, 2000

Advisor: John R. Boring, III, Ph.D., M.S.

An abstract of
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Abstract

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Kawasaki syndrome (KS), an acute illness of unknown etiology, is the leading cause of acquired heart disease among children. This dissertation, in three studies, addresses the following research questions related to KS patients who may be at increased risk for coronary artery abnormalities (CAAs):

1. Are patients with recurrent KS different from non-recurrent KS patients?
2. Are there characteristics of physician-diagnosed KS patients who do not meet the KS case definition that may allow for early identification and treatment?
3. Can KS patients who will not respond to initial intravenous immunoglobulin (IVIG) treatment be predicted?

The first two studies used the Centers for Disease Control and Prevention (CDC) national KS surveillance database (1984-2008) to evaluate recurrence and patients not meeting the CDC KS case definition, respectively. The first study also applied the CDC case definition to the 17th Japanese nationwide KS survey (2001-2002) to assess recurrence in Japan. In the US, 1.7% of KS patients were recurrent; in Japan, 3.5% were. Although recurrent patients were treated earlier than non-recurrent patients, they were more likely to develop CAAs. In the second study, KS patients not meeting the CDC case definition were significantly younger. Physician-diagnosed KS patients were also more likely to be white and less likely to be black compared to patients meeting the CDC case definition, which may reflect quality of care issues.

For the third study, data abstracted from electronic medical records for KS patients discharged from two pediatric specialty hospitals in Atlanta, Georgia from 2006-2008 were analyzed, with a focus on IVIG treatment response. Of KS patients meeting the CDC KS case definition, 23.6% did not respond to initial treatment. Based on logistic regression results, a scoring system was created that improved upon earlier models in predicting nonresponse to initial treatment in our population, which varied markedly from populations evaluated previously.

The three studies emphasize that, until a confirmatory test for KS is developed, physicians must use their best judgment when diagnosing and treating the illness. For high-risk KS patients, more aggressive treatment may be warranted, and further research is needed to determine the best regimen to apply.

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1. Overview

This dissertation addresses issues pertaining to Kawasaki syndrome (KS), an acute illness of unknown cause that primarily affects young children. The dissertation is divided into the following sections: background, introduction, methods, three studies, and discussion. The background describes the history of KS, reviews previous research, and discusses the current understanding of the illness. Next, the introduction presents questions of interest to be addressed in the three studies. The methods section then provides a brief overview of the main analysis techniques that will be used, and the three studies follow. These studies, 1) Kawasaki syndrome recurrence among children in the United States and Japan, 2) Atypical and physician-diagnosed Kawasaki syndrome cases not meeting a Kawasaki syndrome case definition, United States, 1984-2008, and 3) Kawasaki syndrome treatment response at two pediatric specialty hospitals, Atlanta, Georgia, 2006-2008, are written in an appropriate format for submission to a scientific journal, with each study having its own introduction and discussion as well as detailed methods and results. Finally, the discussion section collates the findings of the three studies and proposes recommendations for additional research.

2. Background

This section provides an overview of Kawasaki syndrome, describing the illness, its history, previous research, and current topics. Some information covered in this section will also appear in the introductions of the three studies.

2.1 History

Dr. Tomisaku Kawasaki encountered his first case of what was to later be known as Kawasaki syndrome (KS) in January 1961 in Japan (Burns et al. 2000; Kawasaki and Yanase 2002). The patient, a 4-year-old boy, had clinical signs including fever, rash, bilateral conjunctival injection, enlarged cervical lymph nodes, strawberry tongue, and reddening of the lips, palms, and soles (Burns et al. 2000; Kawasaki and Yanase 2002). The patient recovered, and it was not until the next year that Dr. Kawasaki saw another patient with a similar presentation (Burns et al. 2000; Kawasaki and Yanase 2002). The course of this patient's illness was comparable to the first, and the patient recovered spontaneously as well (Kawasaki and Yanase 2002). In October 1962, Dr. Kawasaki reported seven cases of this "non-scarlet fever syndrome with desquamation," which he believed to be self-limiting and without sequelae (Burns et al. 2000; Kawasaki and Yanase 2002). Twenty-two such cases were gathered by 1964, which he presented as mucocutaneous ocular syndrome (MCOS) (Burns et al. 2000). In 1965, Dr. Noboru Tanaka performed an autopsy on one of Kawasaki's MCOS patients and identified coronary artery thrombosis, demonstrating that potential serious cardiac complications may be associated with the illness (Burns et al. 2000). Dr. Takajiro Yamamoto and colleagues further described cardiac abnormalities among nonfatal KS cases in 1968 (Burns et al. 2000; Kawasaki and Yanase 2002). In 1967, Dr. Kawasaki published his

landmark article in Japan describing 50 cases of what were now termed “pediatric acute mucocutaneous lymph node syndrome;” these 50 cases were first reported in English in 1974 (Kawasaki et al. 1974).

In the United States, children with clinical signs consistent with Kawasaki’s description, predominantly of Asian descent, began to be identified in Hawaii in the early 1970s (Burns et al. 2000). The illness these children experienced, documented by Drs. Marian Melish and Raquel Hicks of the University of Hawaii, was recognized in 1973 as being the same as the newly described syndrome in Japan (Burns et al. 2000). As in Japan, a link between KS and cardiac complications was soon established; a child who died of coronary artery thrombosis in Hawaii in 1971 was retrospectively diagnosed with KS in 1973 (Burns et al. 2000).

KS has now been identified in children around the world (Nakamura and Yanagawa 2004). The question of when and where KS first appeared is difficult to answer. The description of a Japanese patient in a 1953 report by Dr. Toshio Fujikawa is consistent with a KS diagnosis, as are other cases described during that decade in Japan (Kawasaki and Yanase 2002; Kushner and Abramowsky 2010). In the United States, autopsy records back to 1887 have been found that may identify cases of KS (Kawasaki and Yanase 2002). Kushner and Abramowsky speculate that KS existed in the United States before it was imported to Japan in the 1950s (2010). Nonfatal cases may have been misdiagnosed as Stevens-Johnson syndrome, while pathological findings for cases diagnosed with

infantile polyarteritis nodosa (IPN) are identical to those for fatal cases of KS (Kawasaki and Yanase 2002; Newburger et al. 2004; Kushner and Abramowsky 2010).

2.2 Clinical description and case definitions

KS is an acute febrile vasculitis, which, although it is primarily self-limiting, typically causes significant morbidity and can lead to cardiac and noncardiac complications (Newburger et al. 2004; Belay et al. 2006). Because there is no diagnostic test for KS, diagnosis relies on an assessment of disease characteristics (Levy and Koren 1990; Fukushige et al. 1994; Joffe et al. 1995; Khan et al. 1995; Witt et al. 1999; Stapp et al. 2000; Gibbons et al. 2002; Hsieh et al. 2002; Rowley 2002; Freeman and Shulman 2004; Newburger et al. 2004; Belay et al. 2006; Sonobe et al. 2007; Cimaz and Sundel 2009; Ghelani et al. 2012). Several KS case definitions are in use around the world; the most relevant KS case definitions to this dissertation are those used by the United States Centers for Disease Control and Prevention (CDC) and by Japan. In Japan and many other locations, KS is referred to as Kawasaki *disease* (KD). Because the illness is diagnosed by a collection of clinical signs, is of unknown origin, and may have multiple causes, *syndrome* is technically more appropriate (Bell et al. 1983; Kushner et al. 2003); the term KS will therefore be applied throughout this dissertation, regardless of the country of origin or case definition used.

2.2.1 CDC KS case definition

The CDC KS case definition requires the presence of fever, unresponsive to antibiotics, for five or more days (this criterion is met if fever disappears in response to treatment

prior to the fifth day), and four of the following five criteria: bilateral conjunctival injection, oral mucosal changes (erythema of lips or oropharynx, strawberry tongue, or drying or fissuring of the lips), peripheral extremity changes (edema, erythema, or generalized or periungual desquamation), rash, and cervical lymphadenopathy (at least one node ≥1.5 cm in diameter) (Khan et al. 1995). Patients who do not meet this case definition but have fever and coronary artery abnormalities (CAAs), defined as the presence of coronary artery dilatation or aneurysm, are classified as having atypical KS (Gibbons et al. 2002; Belay et al. 2006).

2.2.2 Japanese KS case definition

The fifth revised Japanese KS guidelines differ from the case definition used by the CDC in that fever is not required, but is considered as one of six criteria along with bilateral conjunctival injection, oral mucosal changes, peripheral extremity changes, rash, and cervical lymphadenopathy (no size requirement); at least five of the six criteria must be met for a case to be classified as definitive KS (KD-A). In addition, cases with four criteria and CAAs are also considered definitive KS (KD-B). Cases that are considered to be KS but do not meet the above criteria are classified as suspected KS (Ayusawa et al. 2005; Sonobe et al. 2007).

For some portions of the dissertation, the third revised Japanese KS guidelines are also referenced. These guidelines do not take CAA into account and simply classify KS cases with five or six criteria as having complete KS and those with four or less criteria as having incomplete KS (Sonobe et al. 2007).

2.2.3 Atypical and physician-diagnosed KS

As noted in the previous descriptions, not all physician-diagnosed KS cases meet criteria to be classified as a case by the KS case definition. While some patients fulfill enough criteria to be considered as having atypical KS, others do not meet any definition. Several studies have found that, compared to patients meeting a KS case definition, patients not meeting a definition are at greater risk for CAAs (Joffe et al. 1995; Tseng et al. 2000; Sonobe et al. 2001; Kushner et al. 2003; Yeo et al. 2008; Arima et al. 2012). Young children in particular have been found to be both less likely to fulfill all KS criteria and to be at higher risk for CAAs (Joffe et al. 1995; Witt et al. 1999; Hsieh et al. 2002; Rowley 2002; Newburger et al. 2004). Because of the risk of CAAs, sensitivity is considered a higher priority than specificity in the development of treatment recommendations (Freeman and Shulman 2004), and physicians may opt to initiate treatment in patients before they meet a KS case definition (Joffe et al. 1995; Witt et al. 1999; Stapp et al. 2000; Hsieh et al. 2001; Rowley 2002).

2.2.4 Other disease characteristics

In addition to the clinical criteria required to meet the KS case definitions, cardiac, noncardiac, and laboratory findings may be seen in KS patients (Kushner et al. 2003; Newburger et al. 2004). CAAs, which may occur in >20% of untreated KS patients, are the most serious complications of the illness (Belay et al. 2006). Arthritis, gastrointestinal problems, and irritability are commonly observed (Newburger et al. 2004). In Japan, erythema and induration around the site of previous Bacille Calmette-Guérin vaccination may also be seen (Newburger et al. 2004). During the acute stage, leukocytosis is typical,

as is elevation of erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) concentration. Thrombocytosis is a characteristic feature that usually appears during the second week of illness (Newburger et al. 2004).

2.3 KS surveillance

2.3.1 US surveillance

Since 1976, the US CDC has conducted passive national surveillance for KS using a standardized case report form (Appendix 1)(Khan et al. 1995; Belay et al. 2006). Since 1984, surveillance information has been entered into an electronic database (Belay et al. 2006). The case report form, which collects information on KS patient demographics, clinical signs, treatment, and complications, has been periodically revised, most recently in 2004 (Centers for Disease Control and Prevention 2012).

2.3.2 Japan surveillance

Since 1970, nationwide surveys for KS have been conducted in Japan every two years (Nakamura et al. 1996, 2008a, 2008b, 2012; Hirata et al. 2001; Yanagawa et al. 2006; Sonobe et al. 2007; Uehara et al. 2008). Pediatricians from all pediatric hospitals and all other general hospitals with a pediatric department and ≥100 beds in Japan are asked to complete a questionnaire for each KS case they diagnose during the specified time period (Hirata et al. 2001; Yanagawa et al. 2006; Sonobe et al. 2007; Uehara et al. 2008; Nakamura et al. 2012). Questionnaires vary from survey to survey, but they typically include questions about demographics, treatment, complications, and recurrence.

2.4 KS epidemiology

2.4.1 KS incidence

While KS has been reported worldwide, Japan reports a higher incidence than other countries, with a reported annual incidence of 239.6 cases per 100,000 children <5 years of age reported for 2010 (Nakamura et al. 2012). The number of KS cases and the incidence rate in Japan are believed to be continuously increasing (Nakamura et al. 2008a, 2008b, 2012). In the US, studies have shown the incidence for children <5 years to range from approximately 9-21 cases per 100,000 (Belay et al. 2000; Gibbons et al. 2002; Holman et al. 2003; Holman et al. 2010a). Unlike in Japan, KS incidence in the US has been relatively stable in recent years (Holman et al. 2010a). There appears to be a genetic predisposition for KS that may interact with environmental factors. A study by Holman et al. found that in Hawaii, KS incidence rates for children <5 years of age per 100,000 for 1996-2006 for various racial groups were as follows: Japanese 210.5, Native Hawaiian 86.9, Chinese 83.2, Filipino 64.5, and white 13.7 (Holman et al. 2010b). For the US as a whole, Asian children have been found to have the highest hospitalization rates, followed by black children (Holman et al. 2003, 2010a).

2.4.2. KS demographics

KS is primarily a disease of young children. In the United States, over one-third of cases are younger than 24 months of age, and almost 80% are younger than 5 years (Belay et al. 2006). Consistently, surveillance studies have found KS to be more common in males. In the United States, approximately 60% of cases are male, for a 1.5:1 ratio (Khan et al. 1995; Gibbons et al. 2002; Belay et al. 2006; Holman et al. 2010a). In Japan, a slightly

lower gender ratio of 1.4:1 has been reported during non-epidemic periods and 1.3:1 during epidemic periods (Yanagawa 2002). KS occurs year-round, but does have peaks during certain months. In the United States, these peaks tend to occur around January–April (Dajani et al. 1993; Belay et al. 2006), although a study in the state of Georgia found a May-June increase as well (Gibbons et al. 2002).

2.4.3 KS Recurrence

Recurrent KS cases (i.e. those KS cases in children previously diagnosed with KS) represent a unique subset of KS cases. Studies in the US and Japan have found KS to be recurrent in ~2-3% of patients (Hirata et al. 2001; Newburger et al. 2004; Belay et al. 2006). Recurrent cases have shown a gender difference in Japan, with 3.4% recurrence reported among males versus 3.0% among females (Yashiro, Nakamura, and Yanagawa 2002). Although only a small percentage of KS cases are recurrent, these cases are of interest for several reasons. In Japan, research has suggested that KS patients with a history of previous KS illness may present with a more serious illness than their initial episode (Nakamura et al. 1998; Nakada et al. 2008). In addition, recurrent KS patients may not fulfill criteria to meet KS case definitions, as described by a study of 20 recurrent KS patients in China (Zou et al. 2008). Finally, recurrent KS patients may be more likely to not respond to initial IVIG treatment compared to other KS patients (Muta et al. 2006; Uehara et al. 2008).

2.5 Etiology and transmission

Despite decades of research, the cause of KS is still unknown. Case-control studies conducted during KS outbreaks in the United States have reported associations such as antecedent respiratory illness and exposure to shampooed or spot-cleaned rugs or carpets; however, no risks for KS have been consistently identified (Bell et al. 1981; Rauch et al. 1991; Treadwell et al. 2002). In 2005, it was reported that a novel human coronavirus had been identified that might be associated with KS (Esper et al. 2005); however, the findings could not be replicated in subsequent studies (Belay et al. 2005; Shimizu et al. 2005). Epidemiological features such as the age distribution of cases, seasonality, and the occurrence of outbreaks suggest a transmissible childhood disease caused by an infectious agent or agents, and laboratory features suggest infection as well (Newburger et al. 2004; Uehara and Belay 2012). One common hypothesis is that KS is caused by an infectious agent that only produces clinically apparent disease in children who are genetically predisposed (Newburger et al. 2004); genetic susceptibility may account for the difference in KS incidence in Japan, Korea, and Taiwan compared to that found in North American and European countries (Uehara and Belay 2012).

2.6 Treatment

Because of its anti-inflammatory properties, high-dose aspirin has been used in treatment for KS for years (Newburger et al. 2004). The results of a multicenter controlled trial in Japan, published in 1984, showed that treatment with high-dose intravenous immunoglobulin (IVIG) in addition to aspirin reduced the frequency of CAAs in KS patients compared to treatment with aspirin alone (Furusho et al. 1984). A multicenter, randomized trial in the United States followed, which provided further evidence that

IVIG, despite an unknown mechanism, was safe and effective in reducing CAA prevalence when administered early during KS illness (Newburger et al. 1986). Further study supported the administration of IVIG in a single large dose rather than as four smaller daily doses (Newburger et al. 1991). This finding contributed to the current recommendation in the US to treat patients with 2g/kg IVIG in a single infusion with high-dose aspirin (Newburger et al. 2004). In Japan, the recommendation to administer IVIG as a single dose was not adopted as quickly. In 2003, the Japanese health insurance system began reimbursing physicians for 2g/kg single infusions, and the proportion of KS patients treated in that manner subsequently increased (Uehara et al. 2008). When possible, IVIG should be administered within the first ten days of illness; after day ten, IVIG is still recommended if the patient has persistent fever lacking other explanation or aneurysms and ongoing systemic inflammation (Newburger et al. 2004). Age <6 months, incomplete KS, and distance from the patient's residence to the medical center were shown in a study by Minich et al. to be independent predictors of diagnosis after the tenth day (2007). Socioeconomic variables were not associated with delays in diagnosis in the study, although an investigation by Wilder et al. did suggest such an association (Minich et al. 2007; Wilder et al. 2007).

Approximately 10-23% of patients do not respond to initial IVIG treatment (Burns et al. 1998; Wallace et al. 2000; Durongpisitkul et al. 2003; Muta et al. 2006; Egami et al. 2006; Kobayashi et al. 2006; Sano et al. 2007; Uehara et al. 2008; Tremoulet et al. 2008; Ashouri et al. 2008; Do et al. 2010); Newburger et al. defined treatment failure as persistent or recrudescent fever ≥36 hours after completion of the initial IVIG infusion

(2004), but subsequent studies have used different definitions for nonresponse (Kobayashi et al. 2006; Egami et al. 2006; Sano et al. 2007; Ashouri et al. 2008; Uehara et al. 2008; Tremoulet et al. 2008; Do et al. 2010). Typically, patients who fail to respond to initial IVIG treatment are retreated with IVIG (Newburger et al. 2004). Patients who fail a second treatment of IVIG may receive a third dose of IVIG, although other treatments, particularly methylprednisolone or infliximab, may be employed (Newburger et al. 2004; Newburger et al. 2007; Burns et al. 2008; Okada et al. 2009). Recent randomized trials have explored combinations of therapies for primary treatment of KS patients, such as a pulsed dose of intravenous methylprednisolone in addition to IVIG (Newburger et al. 2007, Okada et al. 2008).

2.6.1 Prediction of those at risk for CAAs

In an effort to predict those at greater risk of CAAs, researchers have attempted to identify risk factors. Ichida et al. found that fever duration ≥2 weeks, platelet count level, elevated ESR, and age younger than five years were risk factors for KS patients in a population of KS patients treated with high-dose aspirin but not IVIG (1987). Mori et al. reported that patients with an increase in white blood cell count, neutrophil count, and CRP concentration after IVIG therapy were more likely to have formation of coronary artery lesions (2000), while Qiu et al. found cell adhesion molecules E-selectin and P-selectin may be predictors (2004). Belay et al. described Asian/Pacific Islander race, Hispanic ethnicity, and male sex as factors significantly associated with CAA development (2006). Age <1 year and >9 years has also been found to be associated (Belay et al. 2006; McCrindle et al. 2009).

Several attempts have been made to produce scoring systems to select patients at risk of CAAs who may benefit from more aggressive treatment (Nakano et al. 1986; Harada 1991; Beiser et al. 1998; Newburger et al. 2004). The Nakano and Harada scores were originally used in Japan as a means to determine which patients should receive IVIG treatment. The Nakano score used different levels of age at onset, CRP, and platelet count to evaluate disease severity (Nakano et al. 1986); the Harada score identified children at risk of future coronary aneurysms as those who fulfilled four of the following criteria within nine days of illness onset: white blood cell count >12,000/mm^3, platelet count <350,000/mm^3, CRP >3+, hematocrit <35%, albumin <3.5 g/dL, age ≤12 months, and male sex (Harada 1991). In the United States, Beiser et al. developed a predictive instrument for the development of coronary artery lesions among children treated with IVIG within the first ten days of illness (Beiser et al. 1998). The instrument used baseline neutrophil and band counts, hemoglobin concentration, platelet count, and temperature on the day after IVIG infusion (Beiser et al. 1998).

2.6.2 Prediction of those at risk for treatment nonresponse

In addition to efforts to predict patients who will develop CAAs, attempts have also been made to identify patients who will not respond to initial IVIG treatment (Fukunishi et al. 2000; Durongpisitkul et al. 2003; Newburger et al. 2004; Muta et al. 2006; Kobayashi et al. 2006; Egami et al. 2006; Sano et al. 2007; Uehara et al. 2008; Tremoulet et al. 2008; Ashouri et al. 2008; Cha et al. 2008; Do et al. 2010). Many of the same factors that predict CAAs also predict IVIG non-response, which may be due to the fact that more severe cases of KS are more likely to not respond to treatment. Fukinishi et al. reported

that CRP concentration >10 mg/dL, lactate dehydrogenase >590 IU/L, and hemoglobin <10 g/dL were all factors likely associated with IVIG non-response (2000), while Durongpisitkul et al. found low hemoglobin <10 g/dL, high neutrophil count (75%), high band count, and low albumin were associated with retreatment (2003). Egami et al. described low platelet count $\leq 30 \times 10^6$/L, elevated alanine aminotransferase ≥80 IU/L, and CRP ≥8 mg/dL as predictors (2006). Ashouri et al. reported higher band counts, lower albumin levels, and a higher number of abnormal echocardiography results at diagnosis among patients not responding to IVIG (2008). Cha et al. found higher bilirubin, aspartate aminotransferase, polymorphonuclear cells, and lower platelet values to be independent predictors of persistent or recurrent fever in KS patients (Cha et al. 2008). Muta et al. and Uehara et al. reported additional risk factors of male sex, recurrent KS, and IVIG treatment before the fifth day of illness (Muta et al. 2006; Uehara et al. 2008).

As with CAA prediction, several scoring models have been created in an effort to predict patients who are more likely to not respond to initial IVIG treatment. Egami et al. developed a model that specified low platelet count $\leq 30 \times 10^{10}$/L, elevated alanine aminotransferase ≥80 IU/L, and CRP ≥8 mg/dL as predictors (2006), while a model by Sano et al. considered patients with two of three predictors (CRP ≥7 mg/dL, total bilirubin ≥0.9 mg, and aspartate aminotransferase (AST) ≥200 IU/L) to be high risk for nonresponse (2007). Kobayashi et al. created a scoring model that assigned two points each for sodium ≤133 mmol/L, days of illness at initial treatment ≤4, AST ≥100 IU/L, and neutrophil ≥80%, and one point each for CRP ≥10 mg/dL, age ≤12 months, and platelet count $\leq 30.0 \times 10^4/mm^3$ (2006). High-risk patients were defined as those with four

or more points (Kobayashi et al. 2006). The Kobayashi and Sano studies were conducted using an IVIG treatment regimen of 1g/kg per day over two consecutive days; this differs from the current Japanese recommendations, and those in the United States, that specify a single infusion of 2g/kg (Kobayashi et al. 2006; Sano et al. 2007; Newburger et al. 2004; Uehara et al. 2008). In the United States, Tremoulet et al. followed with a scoring system that included illness day at initial treatment ≤4 (1 point), % bands ≥20 (2 points), gamma glutamyl transferase (GGT) ≥60 IU/L (1 point), and age-adjusted hemoglobin ≤-2 (1 point), defining those with ≥2 points as high-risk (2008). Sleeper et al. evaluated the three Japanese scoring systems (Kobayashi, Egami, and Sano) and found low sensitivity and moderate to high specificity; the study concluded that accurate prediction of North American KS patients of mixed ethnicity at high risk for IVIG non-response remains a challenge (Sleeper et al. 2011).

2.7 Current research

While current KS research around the world covers a wide range of topics, two particularly popular avenues of investigation are described below.

2.7.1 Genetics

A genetic role in KS has been strongly suggested for years, underscored by epidemiologic studies such as the one by Holman et al. using the diverse population in Hawaii (Holman et al. 2010b) and treatment studies such as the evaluation by Sleeper et al. that demonstrated that Japanese scoring systems were not as sensitive when applied to KS patients in the United States (Sleeper et al. 2011). Modern advancements in genetics

research has opened up new possibilities and methods for testing hypotheses that until recently would not have been possible.

2.7.2 Alternative treatments

It has been over 20 years since the study by Newburger et al. determined that IVIG administered as a single large dose was preferable compared to four smaller daily doses (1991). While this standard treatment guideline is still effective for most KS patients today, almost a quarter of KS patients may fail to respond to the initial dose (Burns et al. 1998; Wallace et al. 2000; Durongpisitkul et al. 2003; Muta et al. 2006; Kobayashi et al. 2006; Egami et al. 2006; Sano et al. 2007; Uehara et al. 2008; Tremoulet et al. 2008; Ashouri et al. 2008; Do et al. 2010). For patients who do not respond to initial treatment, the general recommendation is for another dose of IVIG to be administered (Newburger et al. 2004). If that fails, a third dose may be is given. Additional treatments such as steroids or infliximab may also be given (Newburger et al. 2004; Newburger et al. 2007; Burns et al. 2008; Okada et al. 2009). Ongoing research is being conducted to evaluate different therapeutic combinations to determine the optimal treatment for IVIG nonresponders.

3. Introduction

Kawasaki syndrome has been a medical mystery for decades. Although Dr. Kawasaki's landmark article was published in 1967, many aspects of the disease remain unknown or not fully understood today (Kawasaki et al. 1974). The significance of these gaps in knowledge is underscored by reports in Japan in recent years that suggest that KS incidence is increasing (Nakamura et al. 2012). As the leading cause of acquired heart disease among children in both the United States and Japan, research that can contribute to early detection of the disease and improved treatment of high-risk patients is essential. This dissertation, in three studies, addresses aspects of KS related to this goal.

3.1 Are patients with recurrent KS different from nonrecurrent KS patients?

A small percentage of KS patients have been reported to be recurrent, having had a previous episode of KS at some point in the past (Hirata et al. 2001; Belay et al. 2006). The objective of Study 1 was to use two data sources, the CDC United States KS surveillance database and the 17th Japanese nationwide survey, to describe recurrent KS in the United States and Japan and to ascertain whether risk factors exist among the recurrent patients that would assist a treating physician in diagnosing, and therefore treating, recurrent KS cases earlier.

3.2 Are there characteristics of physician-diagnosed KS patients who do not meet a KS case definition that may allow for early identification and treatment?

Because there is no confirmatory test for KS, classification of cases is dependent on a case definition or case definitions. Previous studies have determined that ~15% of physician-diagnosed KS cases may fail to meet a case definition (Belay et al. 2006; Sonobe et al. 2007). Because they do not meet the definition, these cases may be treated

later and therefore be at increased risk of CAAs. The objective of Study 2 was to describe KS patients not meeting the KS case definition, compare them to those patients who do, and assess similarities with KS cases reported in Japan. Identification of KS patients who may not present with all the clinical signs of KS could help doctors in developing appropriate treatment strategies.

3.3 Can KS patients who will not respond to initial IVIG treatment be predicted?

While scoring systems have been developed in Japan with some success at predicting KS patients who will not respond to initial IVIG treatment, they have failed to have similar sensitivity in identifying patients in United States cohorts (Egami et al. 2006; Kobayashi et al. 2006; Sano et al. 2007; Tremoulet et al. 2008; Sleeper et al. 2011). A scoring system developed in California was found to have a high sensitivity among the population from which it was derived; however, not all components of the scoring system are routinely collected by United States hospitals (Tremoulet et al. 2008). The main objectives of Study 3 were to evaluate KS patients who do not respond to initial IVIG treatment and to develop a simple system to predict IVIG nonresponse in a diverse population. Such a scoring system would be of great use to researchers in testing alternative treatments that may be more effective in KS patients who fail to respond to initial IVIG.

4. Methods

This section provides an overview of the methods used in the three studies. The methods section of each study contains a more detailed description of the relevant methodology.

4.1 Statistical tests

Three statistical tests were applied for the comparison of variables. Which test was used depended on the type of variable and the number of observations.

4.1.1 Categorical variables

The chi square test was used for assessment of categorical variables. This test compares observed results with expected results, with the null hypothesis being that there is no significant difference between the two. Chi square test outcomes were expressed as p-values, with $p<0.05$ as the significant range. When a particular comparison category of a given variable was small (i.e., <5), Fisher's exact test (two-sided) was applied instead of the chi square test.

4.1.2 Continuous variables

To determine whether one of two samples of independent observations had larger values than the other, the Wilcoxon rank-sum test, a non-parametric statistical hypothesis test, was applied. As with the statistical tests described in 4.1.1, outcomes were expressed as p-values, with $p<0.05$ being significant.

4.2 Measures of association

4.2.1 Risk ratio

The risk ratio (RR) is the ratio of the risk in the exposed divided by the risk in the unexposed. The RR was used in the first study to compare the risk of KS recurrence by race and ethnicity.

4.2.2 Odds ratio

Odds ratios were directly estimated from the logistic models (see below) in the second and third studies. In these studies, the odds ratio was the ratio of the odds of one group (atypical or physician-diagnosed KS patients, IVIG nonresponders) having an independent predictor variable present to the odds of another group (KS cases, IVIG responders) having the variable.

4.3 Logistic regression modeling

In the second and third studies, multivariate logistic regression with backward elimination was used to identify independent predictors of a dichotomous dependent variable. In the second study, the dependent variables that were examined were atypical and physician-diagnosed KS; in the third study, the dependent variable was IVIG nonresponse. A p-value <0.05 was used to determine which variables were retained in the final model in the second study, and a p-value <0.2 was used in the third study.

4.4 Assessment of test performance

To assess the performance of our IVIG nonresponse scoring system, as well as compare the performance of previously developed scoring systems, we applied several statistical measures.

4.4.1 Sensitivity and specificity

Sensitivity described the scoring system's ability to predict IVIG nonresponse cases, and specificity described its ability to predict IVIG responsive cases. Positive predictive value, the probability that a patient with a score denoting high-risk will not respond to initial IVIG treatment, and negative predictive value, the probability that a patient with a low-risk score will respond to IVIG treatment, were two additional measures applied.

4.4.2 ROC curves

Sensitivity and 1 minus specificity can be plotted on a graph to create a receiver operating characteristic (ROC) curve. These curves are useful in determining the optimal balance between sensitivity and specificity and assisted in the determination of appropriate cutpoints for laboratory values.

5. Study 1: Kawasaki syndrome recurrence among children in the United States and in Japan

Preface

This study was conducted in collaboration with colleagues at CDC (Ermias Belay, Laura Callinan, Robert Holman, Lawrence Schonberger), Jichi Medical University (Yosikazu Nakamura, Ritei Uehara, Mayumi Yashiro), and Emory University (John Boring, Jodie Guest, Godfrey Oakley).

5.1 Abstract

Background. A small proportion of Kawasaki syndrome (KS) patients have KS recurrence after their initial KS episode.

Methods. Data from two sources, the Centers for Disease Control and Prevention (CDC) US national KS surveillance database and the 17th Japanese nationwide survey, were analyzed to compare recurrent and non-recurrent KS patients and to identify risk factors for recurrence.

Results. Of 5557 KS patients in the CDC US KS database meeting the CDC KS case definition or atypical KS case definition, 97 (1.7%) had recurrent KS. Among Asian KS patients in the database meeting the CDC KS case definition, 3.3% were recurrent, compared to 3.4% of Japanese KS patients found to be recurrent in the Japanese database. Compared to non-recurrent KS cases, recurrent KS cases were more likely to be older and to have coronary artery abnormalities.

Conclusions. Recurrent KS patients may benefit from earlier diagnosis and more aggressive treatment.

5.2 Introduction

Kawasaki syndrome (KS) is an acute febrile vasculitis of unknown etiology (Belay et al. 2000, 2006; Holman et al. 2003; Newburger et al. 2004; Uehara et al. 2008; Nakamura et al. 2012). It was first described in the 1960s by Dr. Tomisaku Kawasaki in Japan and has since been found to occur worldwide (Newburger et al. 2004; Nakamura and Yanagawa 2004). KS primarily affects young children, with the majority of KS cases being <5 years of age, and it is more common in males and among children of Asian descent (Khan et al. 1995; Belay et al. 2000, 2006; Gibbons et al. 2002; Holman et al. 2003, 2005, 2010a; Newburger et al. 2004; Yanagawa et al. 2006; Nakamura et al. 2008a, 2008b, 2012). Japan has reported the highest incidence of KS, with 239.6 cases per 100,000 children <5 years of age reported for 2010 (Nakamura et al. 2012). In the United States (US), studies have shown incidence and hospitalization rates for that age group to range from approximately 9-21 cases per 100,000 (Belay et al. 2000; Gibbons et al. 2002; Holman et al. 2003, 2010a). In Hawaii, where a large proportion of children are of Asian descent, KS incidence has been reported to be 50.4 per 100,000 children <5 years of age, with an incidence of 210.5 for those of Japanese ancestry (Holman et al. 2010b).

KS causes significant morbidity in most patients and may result in cardiac and non-cardiac complications (Khan et al. 1995; Newburger et al. 2004; Belay et al. 2006; Nakamura et al. 2012). The most serious complications are coronary artery abnormalities (CAA), and KS is the leading cause of acquired heart disease among children in the US and Japan (Belay et al. 2000, 2006; Gibbons et al. 2002; Holman et al. 2003; Newburger et al. 2004). Treatment with intravenous immunoglobulin (IVIG) and aspirin is generally

effective in reducing the occurrence of CAAs, and current recommendations in the US specify that IVIG should be administered as soon as possible after illness onset (Newburger et al. 2004; Belay et al. 2006). Delaying treatment beyond 10 days of KS onset may reduce the effectiveness of IVIG to prevent CAAs (Marasini et al. 1991).

While no specific agent has been identified, features of KS appear to be consistent with an infectious etiology (Nakamura et al. 1994; Belay et al. 2000, 2006; Hirata et al. 2001, Newburger et al. 2004). The lack of a diagnostic test for KS means that diagnosis is dependent upon an assessment of the presence of specific disease criteria using a case definition. Because IVIG therapy is believed to be more effective when administered early, physicians may choose to diagnose a patient with KS and begin treatment even if a KS case definition is not fulfilled (Joffe et al. 1995; Witt et al. 1999).

Previous studies in the US and Japan have determined KS to recur in ~2-4% of patients (Nakamura et al. 1994, 1996, 1998, 2008b, 2012; Hirata et al. 2001; Newburger et al. 2004; Belay et al. 2006). A study of 20 recurrent KS patients in China reported 1.34% of KS patients were recurrent, and children with recurrent KS were more likely to present with incomplete clinical signs (Zou et al. 2008). Japanese studies have suggested that patients with recurrent KS may present with a more serious illness than the initial episode (Nakamura et al. 1998; Nakada 2008). Other Japanese studies have reported that recurrence is more common among children who were <3 years of age at the initial episode (Nakamura et al. 1996; Hirata et al. 2001), and have suggested that KS may be more likely to recur in patients treated with IVIG (Nakamura et al. 1996). In the US,

studies of recurrent KS have typically focused on a small number of cases or have been limited to a single institution (Vargo et al. 1986); no in-depth analyses of KS recurrence have been conducted using Centers for Disease Control and Prevention (CDC) national surveillance data.

The goal of this study was to describe the epidemiology of recurrent KS among children in the United States and Japan and test the hypothesis that KS patients with recurrence differ from non-recurrent KS patients by demographic factors, timing of treatment, and the occurrence of CAAs. Determining risk factors for KS recurrence may assist the treating physician, especially if earlier or more aggressive treatment for these cases is warranted. Because recurrence distinguishes KS from common infectious diseases such as measles and rubella (Hirata et al. 2001), research into cases of recurrent KS, and how these cases differ from non-recurrent KS cases in two different populations, could provide insight into the etiology of this illness.

5.3 Methods

5.3.1 US data

Since 1976, the Centers for Disease Control and Prevention (CDC) has conducted passive national surveillance for KS using a standardized case report form (Khan et al. 1995; Belay et al. 2006). Information from these forms has been entered into an electronic database since 1984. The case report form has been periodically revised, most recently in 2004, and collects information on KS patient demographics, clinical signs, treatment, and complications (Centers for Disease Control and Prevention 2012). In 1991, a separate

question was added to the form to ascertain whether the KS case was recurrent and, if so, the onset date of the previous episode. Earlier versions of the form had included recurrence as a possible response to a question about disease outcome. In both scenarios, the classification of a KS case as recurrent has been dependent on the physician's assessment.

US children <18 years of age meeting the CDC epidemiologic case definition for KS or atypical KS with onset during 1984-2008 were selected for analysis (Khan et al. 1995; Belay et al. 2006). The CDC KS case definition requires that a case has fever for ≥5 days (or fever until IVIG administration if given before the fifth day of fever) and the presence of at least 4 of the following 5 clinical signs: bilateral conjunctival injection, oral mucosal changes, peripheral extremity changes, rash, and cervical lymphadenopathy (at least 1.5 cm in diameter) (Khan et al. 1995; Belay et al. 2006). Cases with fewer than 4 clinical findings, but with fever and CAAs, are classified as having atypical KS (Gibbons et al. 2002; Belay et al. 2006). CAA is defined as the presence of coronary artery dilatation or aneurysm. When available, original hardcopies of report forms for recurrent cases were reviewed to ascertain the presence of KS recurrence. In instances where additional information on the form suggested that the recurrent admission was a continuation of the initial episode and not a true recurrence, the patient information was recoded as non-recurrent. Attempts were made to locate information in the database for the initial KS episode of each recurrent KS case; however, unless stated otherwise, analyses of recurrent KS cases used data obtained from the second KS episode for comparison to non-recurrent KS cases.

5.3.2 Japanese data

In Japan, nationwide surveys for KS have been conducted every two years since 1970 (Hirata et al. 2001; Yanagawa et al. 2006; Sonobe et al. 2007; Nakamura et al. 2008a, 2008b, 2012; Uehara et al. 2008). Pediatricians from all pediatric hospitals and all other general hospitals with a pediatric department and ≥100 beds in Japan are asked to complete a questionnaire for each KS case they diagnose during the specified time period (Hirata et al. 2001; Yanagawa et al. 2006; Sonobe et al. 2007; Nakamura et al. 2008a, 2008b, 2012; Uehara et al. 2008). Questionnaires vary from survey to survey, but they typically include questions about demographics, treatment, complications, and recurrence. Data from the 17th Japanese national KS survey, covering the years 2001-2002, were obtained and translated to English by Dr. Ritei Uehara. This survey is unique among the Japanese KS surveys in that information on KS clinical criteria was collected, allowing for analyses using the CDC KS case definition, which varies slightly from the Japanese KS case definition. The Japanese definition does not require the presence of fever, but includes it as 1 of 6 criteria along with the 5 CDC KS criteria mentioned previously. Cases meeting 5 or 6 criteria are considered complete cases; those with 4 criteria and CAAs are classified as incomplete KS (Sonobe et al. 2007). While the US KS definition specifies a size (≥1.5 cm) for cervical lymphadenopathy, the Japanese definition does not; size information was not available in the Japanese survey, so patients recorded as having cervical lymphadenopathy in the Japanese data were classified as meeting this criterion for the purposes of applying the US CDC KS case definition. KS cases in the Japanese survey are classified as recurrent if there is an interval of at least two months from the onset of the first KS illness to onset of the new episode (Hirata et al.

2001). The 17th Japanese KS survey was sent to 2413 hospitals in Japan, with 68% responding (Sonobe et al. 2007).

The Wilcoxon rank-sum test was used for comparison of continuous variables such as patient age, and the Chi square test and Fisher's exact test (two-sided) were used as appropriate to compare categorical variables including the presence of clinical criteria, treatment with IVIG before the fifth day of illness, and the occurrence of CAAs. Risk ratios (RR) with 95% confidence intervals (CI) were calculated to compare KS recurrence by race and ethnicity. Statistical analyses were performed using SAS version 9.2 (SAS institute, Cary, NC) using a p-value <0.05 as the significance level.

5.4 Results

There were 9636 KS patients <18 years of age reported to the CDC KS surveillance program with onset during 1984-2008, with 6195 (64.3%) having recurrence data available. A majority (97.8%) of these 6195 patients had KS onset after 1990. Of the 6195 patients, 5339 (86.2%) met the CDC KS case definition, 218 (3.5%) met the atypical KS case definition, and 638 (10.3%) did not meet either case definition.

The 5339 patients with recurrence data meeting the CDC KS case definition resided in 48 states and the District of Columbia, with 43.9% of the patients living in California. KS recurrence was indicated for 88 of these patients (1.6%) and the proportion was relatively stable over the 1991-2008 period (Figure 5.1). Although there was a slight difference in the proportion of recurrent cases between male and female KS patients (1.8% and 1.3%,

respectively), this difference was not statistically significant (p=0.161). The 40 recurrent KS patients for which age information was available for the initial KS episode had a median age of 23.5 months (mean 28.6, range 3-68 months), which was significantly younger than non-recurrent KS patients, who had a median age of 32 months (mean 39.5 months, range 0-207 months) (p=0.047). Recurrent KS patients at their recurrent KS episode, with a median age of 45.5 months (mean 48.7 months, range 3-148 months) were significantly older than the non-recurrent KS patients) (p=0.001). Of recurrent KS patients experiencing their recurrent KS episode, 19.3% were <2 years of age, compared to 36.1% for non-recurrent patients (p=.001), and 69.3% were <5 years of age, compared to 79.6% for non-recurrent patients (p=.018). There were no significant differences between the presence of clinical criteria among recurrent and non-recurrent KS patients meeting the KS case definition (Table 5.1). For 40 recurrent KS patients with information available on the time between KS episodes, the median duration was 18.5 months (mean 24.6 months, range 3-140 months). No recurrent KS patients were reported to have died; three deaths (0.06%) were reported among non-recurrent KS patients.

Of the 79 recurrent patients meeting the KS case definition who had CAA information available, 19 (24.1%) had CAAs, which was significantly more than the 14.2% of non-recurrent KS patients with CAAs (p=0.014). All recurrent patients with CAAs with treatment information available received IVIG; 45.5% (5 of 11) received treatment within 5 days. If given IVIG, recurrent KS patients were more likely to receive treatment before the 5th day of illness compared to non-recurrent KS patients (p=0.016).

Among the 218 atypical KS patients in the US with recurrence information available, 9 (4.1%) were recurrent, which was significant compared to recurrence among KS patients meeting the KS definition (p=0.006). The 9 recurrent atypical KS cases, when combined with the 88 recurrent cases meeting the CDC KS case definition, provided an overall recurrence of 1.7% among KS cases meeting either case definition. Eight recurrent atypical KS patients had information on the time between episodes available. The median duration was 9.0 months (mean 12.0 months, range 2-30 months).

Eleven of 638 (1.7%) KS patients in the database not meeting the CDC KS case definition or atypical KS case definition were recurrent. This proportion was not significantly different to the proportion of recurrence among KS patients meeting the CDC KS case definition (p=0.887).

Previous admissions were available for 11 recurrent KS patients regardless of case definition status (Table 5.2). Ten of 11 (90.9%) met the CDC KS case definition on their initial KS episode, and 8 of those 10 (80.0%) met the CDC KS case definition on their recurrent KS episode as well. Three of 10 (30.0%) with CAA information available had CAAs on their initial KS episode.

The proportion of Asian KS patients in the US CDC database that were recurrent was significantly higher compared to that for white KS patients (3.3% and 1.4%, respectively; RR 2.4, 95% CI 1.5, 3.9) (Table 5.3). The difference in the proportion of recurrent KS patients between Asian male and female KS patients (3.8% and 2.7%, respectively) was

not statistically significant (p=0.383). The median age for the Asian recurrent KS patients was 47 months (mean 49.1 months, range 5-141 months), which was significantly older than the median age of 28 months (mean 33.7, range 1-178) for Asian non-recurrent cases (p<0.001); 7.4% of Asian recurrent KS patients were <2 years of age, and 77.8% were <5 years of age. Of the 25 Asian recurrent KS patients with CAA information available, 5 (20.0%) had CAAs. The 5 patients all received IVIG, and all with information reported about the start of treatment (4) received treatment within 5 days. If given IVIG, Asian recurrent KS patients were more likely to receive treatment before the fifth day of illness compared to Asian non-recurrent KS patients (p=0.011). Among the 29 Asian patients with atypical KS, 2 (6.9%) were reported as having recurrent KS, which was not significantly different to the proportion of recurrence among Asian KS patients meeting the CDC KS case definition (p=0.266). In total, there were 29 Asian recurrent KS patients meeting the KS case definition or atypical KS case definition, comprising 3.5% of the Asian KS patients.

In the Japanese 17th nationwide survey, there were 16949 physician-diagnosed KS patients <18 years of age with recurrence data available. Of these, 13240 (78.1%) met the CDC KS case definition, 634 (3.7%) met the atypical KS definition, and 3075 (18.1%) met no definition. Of the 13240 patients meeting the CDC KS case definition, 449 (3.4%) were recorded as having recurrent KS. The difference in the proportion of recurrence between male and female patients was not statistically significant (3.5% and 3.2%, respectively, p=0.417). Fewer recurrent KS patients had rash compared to non-recurrent KS patients, while more recurrent patients had cervical lymphadenopathy (Table 1). The

median age for the recurrent KS patients was 40.4 months (mean 44.6 months, range 3.9-189.3 months), significantly higher than the 24.4 months for non-recurrent patients (mean 30.5 months, range 0.3-212.8 months) ($p<0.0001$). For recurrent patients, 22.7% were <2 years of age, compared to 49.1% for non-recurrent patients ($p<0.0001$), and 75.3% were <5 years of age, compared to 89.1% for non-recurrent patients ($p<0.0001$). Of patients with CAA information available, 86 of 449 (19.2%) had CAAs, significantly more than the 1802 of 12791 (14.1%) non-recurrent patients with CAAs ($p=0.003$). Almost all patients with CAAs had IVIG treatment (85/86, 98.8%). Recurrent KS patients were more likely to receive treatment before the fifth day of illness with borderline significance ($p=0.051$). Among the 634 atypical KS patients, 34 (5.4%) were recurrent, which was significant compared to recurrence among KS patients ($p=0.008$). The 34 recurrent atypical KS cases, when combined with the 449 recurrent cases meeting the CDC KS case definition, provided an overall recurrence of 3.5% among Japanese KS cases meeting either KS case definition.

5.5 Discussion

Recurrence of KS among children in the US was relatively stable during 1991-2008, with recurrence reported for 1.6% of KS cases meeting the CDC KS case definition and 1.7% of KS cases meeting either the CDC KS case definition or atypical KS definition. Recurrent KS cases were significantly more likely to be older, which was expected given that they have already experienced a previous episode of KS. Asian children in the US were at increased risk of KS recurrence compared to white KS patients. Despite the heterogeneity of the Asian race classification in the US data, which includes various

Asian populations as well as Pacific Islanders, recurrence among Asian children with KS in the United States (3.3%) was similar to recurrence among Japanese children with KS in Japan (3.4%), demonstrating external validity of the CDC US surveillance data with regards to the Asian population. Regardless of race, recurrent KS patients were more likely to have CAAs compared to non-recurrent KS patients, despite the fact that recurrent patients were more likely to receive IVIG before the fifth day of illness; earlier treatment of recurrent patients was a reasonable finding in that doctors may be more likely to suspect KS and begin treatment promptly in a patient with a KS history. While only 11 patients were matched in the US CDC database with information on initial and recurrent KS episodes, the findings from these episodes were consistent with previous studies (Nakamura et al. 1998; Hirata et al. 2001): CAAs were more commonly reported among the initial episodes, most patients were <3 years of age at their initial episode, and the majority of patients had recurrence within two years of their initial episode.

A previous Japanese study has suggested that IVIG therapy for the initial episode of KS may induce recurrence (Nakamura et al. 1996), although a subsequent study did not reproduce this finding (Hirata et al. 2001). It was not possible to investigate this using the US CDC data, as almost all KS patients were treated with IVIG. IVIG non-response could also not be investigated for US patients, although this has been previously reported to be more likely among recurrent KS patients in Japan (Uehara et al. 2008). Additionally, data were limited to patients diagnosed by a physician as having KS. For some patients with an initial episode of KS, a recurrent illness may occur that does not

meet KS criteria. Recurrent fever syndromes have been reported in some patients with a KS history (Broderick et al. 2011).

Other limitations of the study included the inability to verify KS recurrence for many reported recurrent KS patients in the US CDC database. It is possible that some patients may have been classified as recurrent when they were actually experiencing a continuation of the initial episode. Dates of the initial KS episode were not available for 53.4% of the US recurrent KS patients. Conversely, some recurrent KS patients may not have been identified as recurrent if the person completing the form was not aware of the previous KS episode. Data on recurrence were limited prior to 1991 in the US CDC database due to the case report form in use at the time, and the CDC KS surveillance system itself is passive, accounting for ~10% of KS cases in the United States. Some states and medical centers do not report or fully report KS cases, and some states, notably California, are over-represented in the database. However, epidemiologic findings from previous studies have suggested that the CDC surveillance data may be generalized to the US population (Belay et al. 2006). In addition, for the Japanese database, it has been reported that the majority of KS patients are identified through the national KS surveys, with an estimated >90% of KS patients treated in surveyed hospitals (Yanagawa et al. 2006).

Further study of well-defined recurrent KS patients, particularly focusing on the initial KS episode and treatment response, is needed to identify means to better understand KS recurrence and to appropriately treat such patients. Despite the finding that patients with

recurrent KS are more likely to be treated before the fifth day of illness, recurrent KS patients remain at increased risk of CAAs compared to non-recurrent cases. This finding indicates that a different treatment strategy, such as the use of prednisolone in conjunction with the initial IVIG treatment, may be warranted in patients showing early signs of KS recurrence. Kobayashi et al. recently reported that this regimen was effective in reducing the occurrence of CAAs among severe KS patients in Japan (2012). In the US, a higher suspicion for KS recurrence is recommended for physicians treating children who had an initial KS episode at <3 years of age, children with CAAs at their initial KS episode, and children of Asian descent; these KS patients may benefit from earlier diagnosis and intensified treatment.

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Figure 5.1. Annual number of Kawasaki syndrome (KS) cases by recurrence status with proportion of recurrent KS cases, United States, 1991-2008

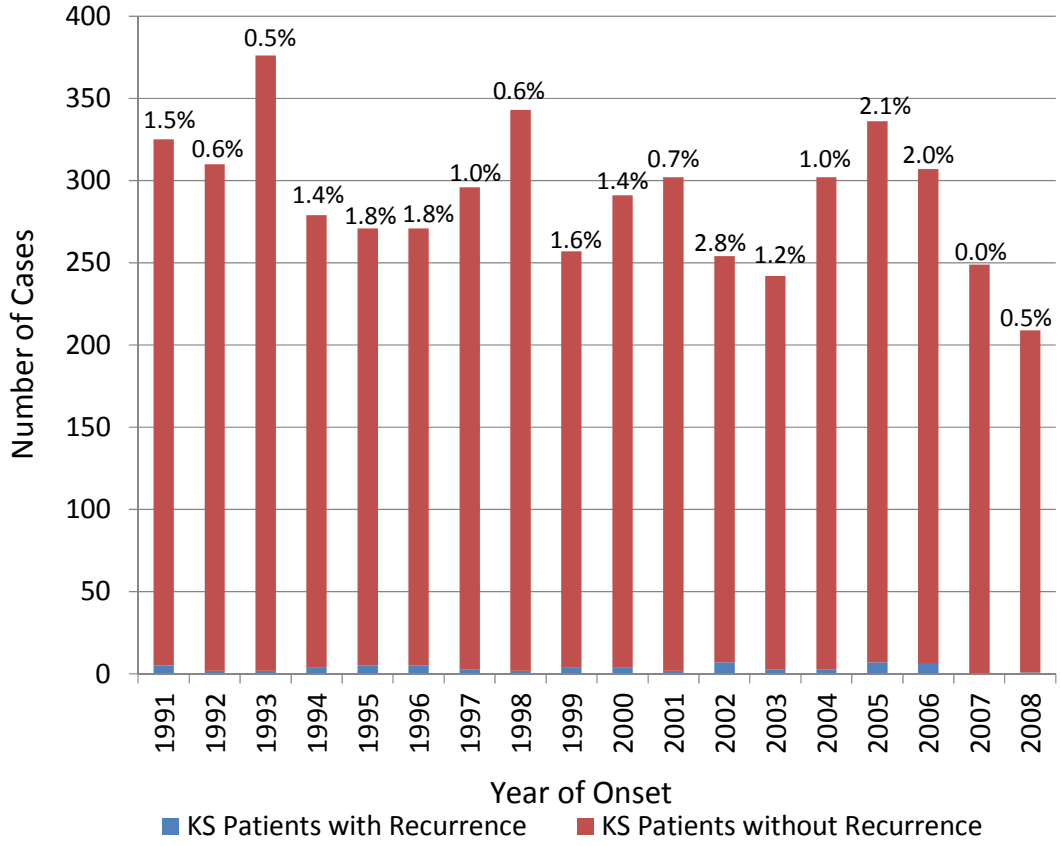

Table 5.1. Recurrent Kawasaki syndrome (KS) and non-recurrent KS by criterion among KS cases meeting the United States CDC KS case definition, United States (1984-2008) and Japan (2001-2002)*

Criterion	Recurrent KS Number (%)		Non-recurrent KS Number (%)		P-value**	
	USA	Japan	USA	Japan	USA	Japan
Bilateral conjunctival injection	86/88 (97.7)	432/449 (96.2)	5067/5203 (97.4)	12391/12791 (96.9)	1.00	0.43
Oral mucosal changes	86/86 (100.0)	429/449 (95.6)	5165/5239 (98.6)	12231/12791 (95.6)	0.63	0.94
Peripheral extremity changes	81/86 (94.2)	398/449 (88.6)	4786/5150 (92.9)	11598/12791 (90.7)	0.65	0.15
Rash	85/88 (96.6)	411/449 (91.5)	5110/5221 (97.9)	12020/12791 (94.0)	0.44	0.03
Cervical lymphadenopathy[§]	52/82 (63.4)	388/449 (86.4)	2920/4787 (61.0)	9525/12791 (74.5)	0.66	<0.001

* US data from Centers for Disease Control and Prevention (CDC) KS surveillance, 1984-2008; Japanese data from 17th nationwide survey, 2001-2002

**Chi square test or Fisher's exact test (two-sided), as appropriate, comparing recurrent KS cases to non-recurrent KS cases

§ Cervical lymphadenopathy ≥1.5 cm in USA, no size requirement in Japan

Table 5.2. Patients' initial and recurrent Kawasaki syndrome (KS) episodes, United States, 1984-2008

Patient demographics	Initial criteria present	CAA	Dx	Recurrent criteria present	CAA	Dx	Time between episodes (months)
27 m, black, non-Hispanic female	5/5	No	KS	5/5	Unk	KS	3
29 m, white, Hispanic male	5/5	No	KS	5/5	No	KS	12
44 m, black, non-Hispanic male	4/5	No	KS	5/5	No	KS	50
40 m, Asian, non-Hispanic female	4/5	No	KS	5/5	No	KS	16
8 m, Asian, non-Hispanic female	4/5	Unk	KS	4/5	Unk	KS	35
32 m, Asian, non-Hispanic male	4/5	Yes	KS	5/5	No	KS	36
63 m, white, non-Hispanic male	4/5	No	KS	4/5	No	KS	16
5 m, white, non-Hispanic male	4/5	No	KS	0/5	Yes	A. KS[§]	18
32 m, white, non-Hispanic male	3/5	No	X	4/5	No	KS	27
27 m, black, non-Hispanic male	4/5	Yes	KS	5/5	Yes	KS	11
21 m, white, Hispanic female	4/5	Yes	KS	3/5	Yes	A. KS[§]	2

m=months
CAA=coronary artery abnormality
Unk=unknown
Dx = Diagnosis
[§]A. KS = Atypical KS
X= Did not meet the Centers for Disease Control and Prevention case definition for KS or atypical KS but was diagnosed as KS by physician

Table 5.3. Recurrent Kawasaki syndrome (KS) by race and by ethnicity, United States, 1984-2008

	Recurrent KS	Non-recurrent KS	Recurrence (%)	RR, 95% CI
Race	**n=82**	**n=4729**		
White	40 (48.8%)	2809 (59.4%)	40/2849 (1.4%)	Reference
Black	12 (14.6%)	885 (18.7%)	12/897 (1.3%)	1.0 (0.5, 1.8)
Asian/Pacific Islander	27 (32.9%)	780 (16.5%)	27/807 (3.3%)	2.4 (1.5, 3.9)
American Indian/ Alaska Native	0 (0.0%)	21 (0.4%)	0/21 (0.0%)	_____
Other	3 (3.7%)	234 (5.0%)	3/237 (1.3%)	0.9 (0.3, 2.9)
Ethnicity	**n=45**	**n=4174**		
Non-Hispanic	34 (75.6%)	3087 (74.0%)	34/3121 (1.1%)	Reference
Hispanic	11 (24.4%)	1087 (26.0%)	11/1098 (1.0%)	0.9 (0.5, 1.8)

RR: Risk ratio
CI: Confidence interval

6. Study 2: Atypical and physician-diagnosed Kawasaki syndrome cases not meeting a Kawasaki syndrome case definition, United States, 1984-2008

Preface

This study was conducted in collaboration with colleagues at CDC (Ermias Belay, Laura Callinan, Robert Holman, Lawrence Schonberger) and Emory University (John Boring, Jodie Guest, Godfrey Oakley).

6.1 Abstract

Background. Because there is no confirmatory test for Kawasaki syndrome (KS), various case definitions based on the presence of clinical criteria are applied to classify cases.

Methods. Data from the Centers for Disease Control and Prevention (CDC) US KS surveillance database were analyzed to compare KS cases meeting a case definition to physician-diagnosed KS cases that did not.

Results. Of KS cases reported to the CDC surveillance system, 13.6% did not meet the CDC KS case definition; the majority of these patients did not meet the case definition because they only lacked one criterion. Physician-diagnosed and atypical KS cases were less likely than KS cases meeting the CDC KS case definition to receive treatment before the fifth day of illness. Physician-diagnosed KS cases were more likely to be white and less likely to be black compared to white and black patients, respectively, meeting the KS case definition.

Conclusions. Until a confirmatory test is available, physicians must maintain a high index of suspicion for KS when assessing patients, particularly among children <1 year of age who are at highest risk of coronary artery abnormalities and not meeting the KS case definition.

6.2 Introduction

Kawasaki syndrome (KS) is an acute febrile vasculitis of unknown etiology that occurs worldwide and primarily affects young children (Levy and Koren 1990; Khan et al. 1995; Belay et al. 2000, 2006; Gibbons et al. 2002; Holman et al. 2003; Cimaz and Sundel 2009; Nakamura et al. 2012). The highest incidence has been reported in Japan, with 239.6 cases per 100,000 children <5 years of age reported for 2010 (Nakamura et al. 2012). In the United States (US), studies have shown incidence and hospitalization rates to range from approximately 9-21 cases per 100,000 children <5 years (Belay et al. 2000; Gibbons et al. 2002; Holman et al. 2003, 2005, 2010a). In Hawaii, however, where a large proportion of children are of Asian descent, KS incidence has been reported to be 50.4 per 100,000 children in this age group, with an incidence of 210.5 for those of Japanese ancestry (Holman et al. 2010b). KS typically causes significant morbidity and may cause long-term effects, and it is the leading cause of acquired heart disease in children in the US and Japan (Khan et al. 1995; Belay et al. 2000, 2006; Gibbons et al. 2002; Newburger et al. 2004; Cimaz and Rundel 2009). Intravenous immunoglobulin (IVIG) is used to treat KS patients with the goal of decreasing the occurrence of coronary artery abnormalities (CAAs), the most serious complication of KS (Fukushige et al. 1994; Newburger et al. 2004; Belay et al. 2006).

Currently, no diagnostic test exists for KS, so cases are determined by the presence or absence of specific criteria (Levy and Koren 1990; Fukushige et al. 1994; Joffe et al. 1995; Khan et al. 1995; Witt et al. 1999; Stapp et al. 2000; Gibbons et al. 2002; Hsieh et al. 2002; Rowley 2002; Newburger et al. 2004; Belay et al. 2006; Sonobe et al. 2007;

Cimaz and Sundel 2009; Ghelani et al. 2012). The Centers for Disease Control and Prevention (CDC) uses a case definition to classify reported cases as KS, atypical KS, or physician-diagnosed KS (i.e., those reported cases not meeting the definition for KS or atypical KS) (Khan et al. 1995; Gibbons et al. 2002; Belay et al. 2006); similarly, public health officials in Japan use the fifth revised Japanese guidelines to categorize reported KS cases into three groups depending on criteria present (Ayusawa et al. 2005; Sonobe et al. 2007). While most reported KS cases meet a KS case definition, a sizable percentage of patients do not, particularly infants with the disease (Joffe et al. 1995; Stapp et al. 2000; Rowley et al. 2002; Newburger et al. 2004; Sonobe et al. 2007; Cimaz and Sundel 2009). A previous study using US surveillance data found that 2.4% of reported cases were atypical, and 13.2% of cases did not meet the CDC case definition for KS or atypical KS (Belay et al. 2006); a study in Georgia reported similar results for atypical cases (2.1%) but reported a higher percentage of patients not meeting either case definition (26.5%) (Gibbons et al. 2002). In, Japan, a study reported that 14.0% of cases failed to meet criteria for definitive KS (Sonobe et al. 2007).

The goal of this study was to test the hypothesis, using a large, national database, that atypical KS patients and physician-diagnosed KS patients not meeting the KS case definition in the United States differ from patients meeting the KS case definition with regards to demographics, timing of treatment, and the occurrence of CAAs. In addition, a Japanese KS case definition was applied to KS patients in the database to assess similarities with previously reported Japanese statistics. Atypical and physician-diagnosed KS cases are important because they may not be identified in a timely manner

to allow for optimal treatment; many other illnesses can have a similar presentation (Cimaz and Sundel 2009). Because treatment with IVIG is thought to be more effective when given early in the course of illness, identification of suspected KS cases not meeting the KS case definition could be helpful in preventing the occurrence of CAAs (Joffe et al. 1995; Stapp et al. 2000; Hsieh et al. 2002; Rowley 2002).

6.3 Methods

Since 1976, the CDC has conducted passive national surveillance for KS using a standardized case report form (Centers for Disease Control and Prevention 2012). The case report form collects information on KS patient demographics, clinical signs, treatment, and complications and is periodically revised, most recently in 2004. Since 1984, information has been entered into an electronic database. For the present study, US children <18 years of age in the database with onset during 1984-2008 were selected for analysis and classified by KS case definition status. The CDC KS case definition requires that a case has fever for ≥5 days (or fever until IVIG administration if given before the 5th day of fever) and the presence of at least 4 of the following 5 clinical signs: bilateral conjunctival injection, oral mucosal changes, peripheral extremity changes, rash, and cervical lymphadenopathy (at least 1.5 cm in diameter) (Khan et al. 1995; Gibbons et al. 2002; Belay et al. 2006). Cases with fewer than 4 clinical criteria, but with fever and CAAs, are classified as having atypical KS (Gibbons et al. 2002; Belay et al. 2006). CAA is defined as the presence of coronary artery dilatation or aneurysm. Cases in the database with fever but not meeting criteria for KS or atypical KS were classified as physician-

diagnosed KS cases and subdivided according to the number of clinical criteria met. Criteria classified as unknown on the case report form were considered to be absent. For comparison with KS analyses by Sonobe et al using Japanese data, the third revised Japanese KS case definition was applied to the US CDC KS data (Sonobe et al. 2007). This case definition differs from the US CDC KS case definition in that it does not require the presence of fever, but includes it as 1 of 6 criteria along with the 5 KS criteria mentioned previously; unlike the CDC KS case definition, no size is specified for cervical lymphadenopathy. Cases meeting 5 or 6 criteria are considered complete cases, while other KS cases, regardless of CAA status, are classified as incomplete KS (Sonobe et al. 2007).

The Wilcoxon rank-sum test was used for comparison of continuous variables, and the Chi square test and Fisher's exact test (two-sided) were used as appropriate to compare categorical variables. To identify independent predictors of atypical and physician-diagnosed KS, multivariate logistic regression analysis with backward elimination was performed. Statistical analyses were conducted using SAS version 9.2 (SAS institute, Cary, NC) using a p-value <0.05 as the significance level.

6.4 Results

Of 9636 KS cases <18 years of age reported to the CDC with onset between 1984 and 2008, 8329 (86.4%) met the CDC KS case definition, and 267 (2.8%) met the definition for atypical KS. The remaining 1040 cases (10.8%) did not meet either definition or

lacked enough known criteria to classify. Of the 1040 cases, 106 (10.2%) had no fever of any duration reported and were excluded from further analyses.

The proportion of atypical KS cases out of all KS cases meeting a KS case definition ranged annually from 0.3% to 4.0% from 1984-2003; from 2004-2008, the range was 4.7% to 9.6% (Figure 6.1). The majority of the 267 atypical KS patients (153, 57.3%) had fever for ≥5 days (or fever until start of treatment) and 3 criteria; similarly, 58.0% of physician-diagnosed KS cases lacked only one criterion to be classified as a case (Table 6.1). Of the atypical KS cases, 34 (12.7%) did not meet the fever criterion, with 12 (35.3%) of these cases being <1 year of age; 186 (19.9%) of the physician-diagnosed KS cases did not meet the fever criterion. Atypical KS cases and physician-diagnosed cases were both hospitalized for a median of 3 days (mean 5.7, range 1-33 and mean 4.0, range 1-34, respectively) as were cases meeting the KS case definition (mean 4.4, range 1-67). While males represented a higher percentage of atypical KS cases compared to KS cases (64.6% and 60.2%, respectively), this difference was not significant (p=0.154); significant differences were also not identified for race and ethnicity between atypical KS cases and KS cases (Table 6.2). However, there were significantly more white children (p=0.023) and significantly fewer black children (p=0.018) with physician-diagnosed KS compared to white and black children, respectively, meeting the KS case definition. Logistic regression determined age <1 year to be an independent predictor of both atypical KS and physician-diagnosed KS cases. Almost all atypical and physician-diagnosed KS cases (96.0% and 93.1%, respectively) were treated with IVIG; both categories were significantly less likely to receive treatment before the 5th day of illness

compared to KS cases ($p<0.001$). The most common complications among atypical cases were pericardial effusion (16.2%), arthralgia (15.5%), mitral regurgitation (9.3%), and meatitis or sterile pyuria (9.0%). The most common complications among physician-diagnosed cases were meatitis or sterile pyuria (6.2%), pericardial effusion (5.6%), arthralgia (5.5%), and hepatitis or hepatomegaly (3.6%).

Applying the third revised Japanese case definition to the US CDC KS data, 8420 (87.5%) of 9619 children met the complete KS case definition and 1199 (12.5%) met the incomplete KS case definition; among Asians in the US, 1140 (88.8%) met the definition for complete KS and 144 (11.2%) had incomplete KS. Cervical lymphadenopathy was the least reported clinical sign, with almost 75% of US incomplete KS cases lacking this criterion (Table 6.3). A higher proportion of KS cases were incomplete among children <1 year of age compared to children ≥1 year of age ($p<0.001$) and children with KS ≥5 years of age were more likely to be incomplete compared to children with KS aged 1 through 4 years ($p=0.049$) (Table 6.4). Among US cases, significantly higher proportions of CAA were found for all age groups except the ≥5 year old group in comparisons between incomplete and complete Kawasaki syndrome cases; however, only the 6-11 month old age group was found significant for this comparison among US Asian cases (Table 6.4).

6.5 Discussion

While most KS cases reported to the CDC met the CDC KS case definition, 13.6% did not, including 2.8% that were classified as atypical KS. The majority of cases not

meeting the KS case definition were only lacking the presence of one criterion to be considered a case, emphasizing the fact that many of these cases are likely KS. Criteria may not be fully acknowledged on the report form due to lack of documentation in the medical record or the appearance of a criterion late in the course of illness. The early initiation of IVIG treatment may also influence whether a criterion appears (Joffe et al. 1995; Witt et al. 1999; Stapp et al. 2000; Yeo et al. 2008; Ghelani et al. 2012). The higher proportion of atypical KS cases out of all KS cases meeting a KS case definition seen in the later years of the study may reflect increased recognition of coronary artery dilatations due to the application of criteria developed by deZorzi et al. (deZorzi et al. 1998; Belay et al. 2006; Ghelani et al. 2012).

Atypical and physician-diagnosed KS cases were significantly younger than KS cases. Interestingly, physician-diagnosed cases were more likely to be white and less likely to be black compared to white and black patients, respectively, meeting the KS case definition, which may reflect quality of care issues if some providers are more likely than others to diagnose KS, and in turn, administer appropriate treatment, or if some patients are less likely to receive the consistent care that may be necessary to diagnose and treat the illness. This finding is in keeping with a study by Wilder et al. that found that socioeconomic factors influenced the likelihood of a delay in KS diagnosis (Wilder et al. 2007).

Applying the third revised Japanese guidelines to the US CDC data, 12.5% of the children in the US CDC database had incomplete KS. The percentage of incomplete KS

among Asian KS cases in the US database (11.2%) was less than the 16.1% reported by Sonobe et al. among Japanese KS patients in the 17th Japanese KS survey (Sonobe et al. 2007). A recent study by Nakamura et al. reported an even higher proportion of incomplete cases using the 21st Japanese survey (18.6%) (Nakamura et al. 2012). In Japan, where KS incidence is higher than in the US and has been reported to be increasing (Nakamura et al. 2012), physicians may be more astute in diagnosing KS without all clinical signs being present; it is also possible that the illness is now overdiagnosed as awareness has grown. Additionally, the Asian cases in the US data belong to a heterogeneous group that includes various Asian populations as well as Pacific Islanders, which may influence KS incidence (Holman et al. 2005, 2010b).

Limitations of the study include the passive nature of the CDC KS surveillance system; not all states report cases or fully report the case information. Because some criteria are reported as unknown, the percentage of cases classified as meeting the KS case definition is likely an underestimate. However, previous epidemiologic findings from the CDC database suggest that results can be generalized to the US population (Belay et al. 2006).

Because of the risk of CAAs, it is important for physicians to have a high index of suspicion for KS and to be able to recognize potential KS cases in the absence of a diagnostic test (Joffe et al. 1995; Hsieh et al. 2002; Rowley 2002; Newburger et al. 2004). Atypical and physician-diagnosed KS cases in this study were significantly less likely than cases meeting the KS case definition to receive treatment before the fifth day of illness. Young children, particularly those <1 year of age, are especially vulnerable to

the occurrence of CAAs and to not meeting a KS case definition, so physicians should be open to the possibility of KS in children exhibiting some but not all necessary criteria and consider appropriate treatment (Joffe et al. 1995; Witt et al. 1999; Hsieh et al. 2002; Rowley 2002; Newburger et al. 2004). Current American Heart Association guidelines suggest an algorithm be used for diagnosing KS in patients not meeting a KS case definition which applies to suspected KS patients who have fever ≥5 days (Newburger et al. 2004). In our study, 12.7% of atypical KS cases did not meet this fever requirement, emphasizing the need for better early detection of potential KS cases.

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Figure 6.1. Atypical KS cases as a percentage of all cases meeting a KS case definition, United States, 1984-2008

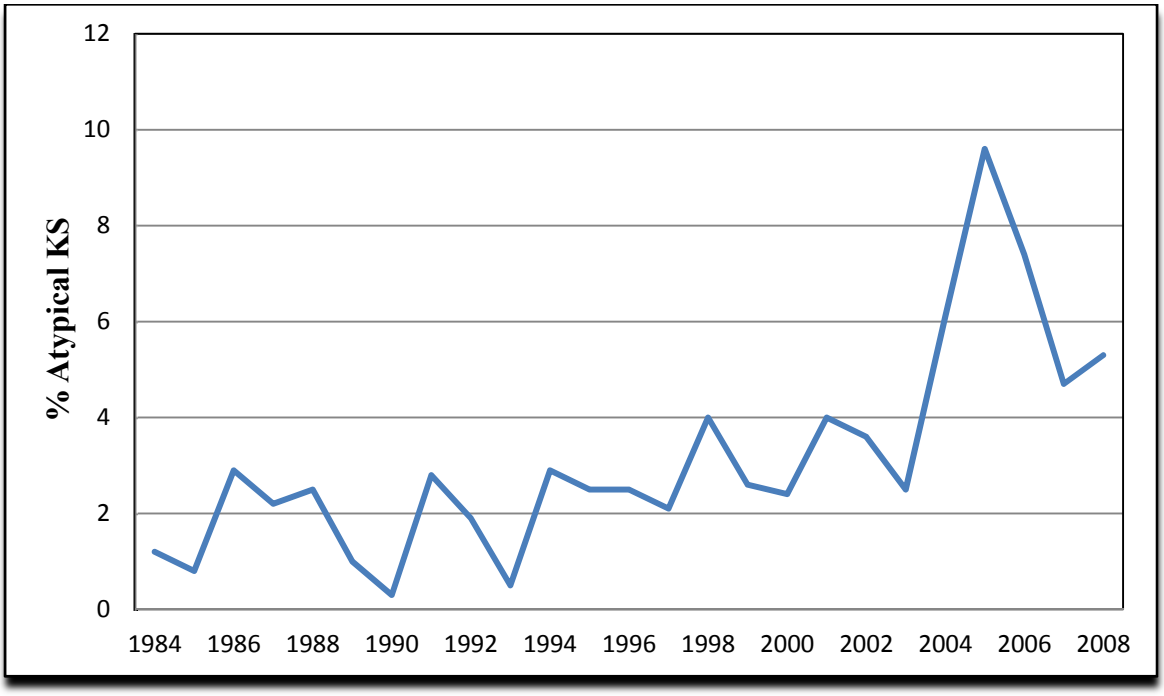

Table 6.1. CDC Kawasaki syndrome (KS) case definition criteria among atypical and physician-diagnosed KS cases, United States, 1984-2008

Criteria*	Atypical KS (n=267)	Physician-diagnosed KS (n=934)
Fever ≥5 days** and 3 criteria	153 (57.3%)	542 (58.0%)
Fever ≥5 days and 2 criteria	41 (15.4%)	144 (15.4)
Fever ≥5 days and 1 criterion	33 (12.4%)	41 (4.4%)
Fever ≥5 days and no criteria	6 (2.3%)	21 (2.2%)
Fever <5 days and 4 or 5 criteria	25 (9.4%)	140 (15.0%)
Fever <5 days and 3 criteria	5 (1.9%)	34 (3.6%)
Fever <5 days and 2 criteria	2 (0.8%)	7 (0.7%)
Fever <5 days and 1 criterion	1 (0.4%)	2 (0.2%)
Fever <5 days and no criteria	1 (0.4%)	3 (0.3%)

CDC: Centers for Disease Control and Prevention

* Criteria reported as unknown were considered to be absent

**Fever for ≥5 days or until start of treatment if given before the 5th day of fever

Table 6.2. Kawasaki syndrome (KS), atypical KS, and physician-diagnosed KS by demographic characteristics, United States, 1984-2008

	KS (n=8315)	**Atypical KS (n=267)**	**P-Value[§]**	**Physician-diagnosed KS (n=934)**	**P-Value[§]**
Sex (% male)	4879/8108 (60.2%)	166/257 (64.6%)	0.154	524/910 (57.6%)	0.130
Median age, months (range)	33 (0-210)	18 (1-214)	<0.001◦	30 (1-205)	0.042◦
Race	(n=7525)	(n=233)		(n=820)	
White	4706 (62.5%)	153 (65.7%)	0.331	546 (66.6%)	0.023
Black	1400 (18.6%)	35 (15.0%)	0.165	125 (15.2%)	0.018
Asian	1131 (15.0%)	36 (15.5%)	0.860	111 (13.5%)	0.254
AI/AN*	29 (0.4%)	0 (0.0%)	1.000	5 (0.6%)	0.338
Other	259 (3.4%)	9 (3.9%)	0.729	33 (4.0%)	0.389
Ethnicity (% Hispanic)	1348/4949 (27.2%)	53/190 (27.9%)	0.842	138/571 (24.2%)	0.842

*AI/AN = American Indian/Alaska Native

§ Chi square test or Fisher's exact test (two-sided), as appropriate, for comparisons of atypical KS and physician-diagnosed KS cases to KS cases

◦Wilcoxon rank sum test

Table 6.3. Kawasaki syndrome (KS) case criteria among complete and incomplete KS cases using the third revised Japanese KS case definition, United States (1984-2008) and Japan (2001-2002)

Criterion	Complete KS %			Incomplete KS %		
	US all races	US Asian	Japan	US all races	US Asian	Japan
Fever*	98.9	99.2	98.8	81.8	76.4	80.3
Conjunctival injection	97.2	98.5	96.9	72.3	78.7	75.6
Oral mucosal changes	98.7	98.1	95.7	71.9	81.5	62.8
Rash	97.9	97.6	94.0	77.8	76.7	64.9
Extremity changes	94.1	93.5	90.8	55.6	50.4	44.3
Cervical lymphadenopathy**	67.5	59.6	75.3	25.8	28.4	38.6

United States data from Centers for Disease Control and Prevention KS surveillance database, 1984-2008, Japanese data from the Japanese 17th nationwide survey as reported by Sonobe et al. 2007.
Table format derived from Sonobe et al. 2007.
*Fever ≥5 days or until start of treatment if given before the 5th day of fever
**≥ 1.5 cm for United States, no size requirement for Japan

Table 6.4a. Kawasaki syndrome (KS) and coronary artery abnormalities (CAAs) by age group using the third revised Japanese KS case definition, United States (1984-2008) and Japan (2001-2002)

Age group (% of total, US all races/US Asian/Japan)	Proportion incomplete KS (%)			CAA, all KS (%)		
	US all races	US Asian	Japan	US all races	US Asian	Japan
≤5 months (5.4/6.6/9.6)	26.2	17.6	24.1	37.8	34.6	19.1
6-11 months (10.9/13.2/16.0)	14.9	9.4	20.4	19.5	22.0	14.8
1 and 2 years (38.1/42.4/41.5)	11.7	11.4	14.2	14.7	18.5	13.2
3 and 4 years (22.9/22.2/21.3)	9.4	8.4	12.5	12.7	16.0	15.0
≥5 years (22.8/15.5/11.6)	12.4	13.6	17.2	14.2	14.3	18.5

United States data from Centers for Disease Control and Prevention KS surveillance database, 1984-2008, Japanese data from the Japanese 17th nationwide survey as reported by Sonobe et al. 2007.
Table format derived from Sonobe et al. 2007.

Table 6.4b. Kawasaki syndrome (KS) and coronary artery abnormalities (CAAs) by age group using the third revised Japanese KS case definition, United States (1984-2008) and Japan (2001-2002)

Age group	CAA, complete KS (%)			CAA, incomplete KS (%)				
	US all races	US Asian	Japan	US all races	P-value*	US Asian	P-value**	Japan
≤5 months	33.5	30.3	17.4	50.4	0.001	53.3	0.090	24.3
6-11 months	18.3	19.6	13.6	26.6	0.023	43.8	0.027	19.3
1 and 2 years	13.6	17.8	12.8	23.0	<0.001	23.6	0.294	15.6
3 and 4 years	11.8	15.8	14.9	21.9	<0.001	17.4	0.771	15.7
≥5 years	13.8	14.0	17.2	16.8	0.220	16.0	0.761	23.1

United States data from Centers for Disease Control and Prevention KS surveillance database, 1984-2008, Japanese data from the Japanese 17th nationwide survey as reported by Sonobe, et al. 2007.
Table format derived from Sonobe, et al. 2007.
*Comparison of incomplete US KS cases (all races) with CAAs to complete US KS cases (all races) with CAAs
**Comparison of incomplete US KS cases (Asian) with CAAs to complete US KS cases (Asian) with CAAs

7. Study 3: Kawasaki syndrome treatment response at two pediatric specialty hospitals, Atlanta, Georgia, 2006-2008

Preface

This study was conducted in collaboration with colleagues at CDC (Ermias Belay, Laura Callinan, Robert Holman, Lawrence Schonberger), Children's Healthcare of Atlanta (Alesia Fleming, Michael DeGuzman), and Emory University (John Boring, Jodie Guest, Godfrey Oakley).

7.1 Abstract

Background. Although most children with Kawasaki syndrome (KS) have an effective therapeutic response to treatment with intravenous immunoglobulin (IVIG), some patients do not and require a secondary treatment. Identification of KS patients at risk for nonresponse to initial treatment could contribute to the development of more effective treatment strategies.

Methods. Electronic medical records for children <18 years of age discharged with an International Classification of Diseases, 9th revision, Clinical Modification (ICD-9-CM) code for KS (446.1) or aneurysm (414.11) from two Atlanta, Georgia pediatric specialty hospitals during 2006-2008 were reviewed, and data were abstracted and analyzed. A scoring system was developed to predict IVIG treatment nonresponse.

Results. Of 191 patients meeting the CDC KS or atypical KS definitions and receiving IVIG treatment within 10 days, 45 (23.6%) required secondary treatment.
C-reactive protein (CRP) ≥7 mg/dL, percent bands >11, alanine aminotransferase >50 IU/L, aspartate aminotransferase >60 IU/L, total bilirubin >1 mg/dL, and age ≥36 months were identified by univariate analysis as being significantly associated with IVIG non-response. CRP ≥7 mg/dL, total bilirubin >1 mg/dL, illness day at IVIG treatment <5, and age ≥36 months were found to be independent predictors of IVIG nonresponse through logistic regression. A scoring system using these predictors was developed with 79.4% sensitivity and 68.0% specificity in identifying KS patients with IVIG nonresponse in the database.

Conclusions. The scoring system developed from the predictors may be useful in future studies examining the potential benefits of early additional treatments given in conjunction with IVIG for high-risk children with KS.

7.2 Introduction

Kawasaki syndrome (KS) is an acute febrile vasculitis of unknown etiology that primarily affects young children (Belay et al. 2006; Kobayashi et al. 2006; Muta et al. 2006; Sano et al. 2007; Uehara et al. 2008; Tremoulet et al. 2008; Ashouri et al. 2008). KS patients are typically treated with high-dose intravenous immunoglobulin (IVIG) and aspirin with the goal of decreasing the occurrence of coronary artery abnormalities (CAAs), the most serious complications of KS (Durongpisitkul et al. 2003; Belay et al. 2006; Muta et al. 2006; Sano et al. 2007; Uehara et al. 2008; Tremoulet et al. 2008); however, 10-23% of patients fail to respond to initial treatment (Burns et al. 1998; Wallace et al. 2000; Durongpisitkul et al. 2003; Egami et al. 2006; Kobayashi et al. 2006; Muta et al. 2006; Sano et al. 2007; Uehara et al. 2008; Tremoulet et al. 2008; Ashouri et al. 2008; Do et al. 2010). Patients who do not respond to initial treatment have been reported to be at higher risk of developing CAAs (Burns et al. 1998; Wallace et al. 2000; Durongpisitkul et al. 2003; Egami et al. 2006; Kobayashi et al. 2006; Sano et al. 2007; Ashouri et al. 2008). Identification of KS patients who may not respond to initial treatment could allow for appropriate interventions that may prevent CAA occurrence (Fukunishi et al. 2000; Belay et al. 2006; Muta et al. 2006; Sano et al. 2007; Uehara et al. 2008; Tremoulet et al. 2008; Okada et al. 2009; Kobayashi et al. 2012).

Previous studies seeking to identify which KS patients may fail to respond to initial treatment have reported various laboratory and demographic characteristics as risk factors (Fukunishi et al. 2000; Durongpisitkul et al. 2003; Muta et al. 2006; Ashouri et al. 2008; Do et al. 2010), and, in some instances, scoring systems have been developed to predict

treatment nonresponse (Egami et al. 2006; Kobayashi et al. 2006; Sano et al. 2007; Tremoulet et al. 2008). While some predictive variables have been consistently identified across the studies, risk factors and scoring systems have generally differed. In some studies, a different IVIG protocol (1 g/kg over 2 days compared to 2 g/kg in a single infusion) was used than what is recommended in the United States (Kobayashi et al. 2006; Sano et al. 2007). Furthermore, the majority of the scoring systems have been created using data obtained from racially non-diverse populations, making them potentially less applicable to many treatment centers in the United States (Egami et al. 2006; Kobayashi et al. 2006; Sano et al. 2007; Tremoulet et al. 2008).

In this study, we analyze electronic medical records for KS patients <18 years of age discharged from two racially diverse pediatric specialty hospitals. By comparing characteristics of IVIG responsive and non-responsive KS patients, we tested the hypothesis that a scoring system using such data could be created that would predict IVIG nonresponse in US KS patients with better sensitivity than previous systems.

7.3 Methods

Electronic medical records for children <18 years of age discharged with an International Classification of Diseases, 9th revision, Clinical Modification (ICD-9-CM) code for KS (446.1) or aneurysm (414.11) from two Atlanta, Georgia pediatric specialty hospitals during 2006-2008 were reviewed (US Department of Health and Human Services Public Health Service and Health Care Financing Administration 2005). Data for each patient, including demographics, clinical signs, treatments, and complications, were collected on

an abstraction form. When recurrent KS cases were identified, an attempt was made to review records from the previous KS admission, even if the year of onset for that KS episode was outside the 2006-2008 period. The Centers for Disease Control and Prevention (CDC) KS case definition and atypical KS case definition were applied to all physician-diagnosed KS cases for inclusion in the final analysis (Khan et al. 1995; Belay et al. 2006). The CDC KS case definition requires 5 days of fever (or fever until the time of treatment if administered before the fifth day) and the presence of at least 4 of the following 5 criteria: bilateral conjunctival injection, oral mucosal changes, peripheral extremity changes, rash, and cervical lymphadenopathy (at least 1.5 cm diameter) (Khan et al. 1995; Gibbons et al. 2002; Belay et al. 2006). The atypical KS case definition requires the presence of fever of any duration and CAAs in KS patients not meeting the CDC KS case definition (Gibbons et al. 2002; Belay et al. 2006). CAA was defined as the presence of coronary artery dilatation or aneurysm as indicated by the treating physician or noted in an echocardiogram report. The first day of illness was considered to be the date that the first KS case definition criterion appeared. A patient was classified as IVIG nonresponsive if, for any reason, a secondary KS treatment, including high-dose intravenous methylprednisolone, infliximab, or additional IVIG, was administered after the initial IVIG dose. Because IVIG treatment is recommended to be given within the first ten days of illness (Newburger et al. 2004), patients with initial IVIG treatment on the tenth day of illness or later were excluded from the analysis. The study was approved by the Institutional Review Board of Children's Healthcare of Atlanta.

Univariate analysis was performed to compare the proportion of abnormal levels of laboratory values between IVIG responders and nonresponders. Variables were compared between the two groups through the chi-square test and Fisher's exact test (two-sided), as appropriate, using a p-value <0.05 as the significance level. Abnormal levels were determined by patient age and defined by the hospital laboratory reports, with the exception of C-reactive protein (CRP). Because 98.9% of patients were above the hospital-defined abnormal value of ≥ 1 mg/dL for CRP, 7 mg/dL was selected as a cutoff value based on previous studies and receiver-operator characteristic (ROC) curve analysis. The other laboratory variables were white blood cell count (WBC), the percentage of white blood cells that were segs and bands, erythrocyte sedimentation rate (ESR), hemoglobin, hematocrit, platelet count, and serum concentrations of albumin, alanine aminotransferase (ALT), aspartate aminotransferase (AST), total bilirubin, and sodium. When laboratory tests were performed more than once before initial IVIG was administered, the highest value was used for WBC, seg percentage, band percentage, ESR, ALT, AST, total bilirubin, and CRP, while the lowest values were used for albumin, hemoglobin, hematocrit, platelet count, and sodium. To identify independent predictors of IVIG nonresponse, multivariate logistic regression analysis with backward elimination was performed using variables identified by the univariate analysis and the demographic variables sex, age in months, and number of days of illness at initial IVIG treatment, which served as a surrogate for the duration of time until KS diagnosis. Variables with a p-value <0.2 were retained in the model. A scoring system was created using weights based on the odds ratios of the independent predictors identified through the logistic regression model.

The sensitivity and specificity of the scoring system were calculated for patients meeting the KS case definition and atypical KS case definition as well as for all physician-diagnosed KS cases. Values were compared for different races and were also compared to sensitivity and specificity values obtained by using scoring systems devised for the same purpose in Japan by Egami et al., Kobayashi et al., and Sano et al. (Egami et al. 2006; Kobayashi et al. 2006; Sano et al. 2007). Statistical analyses were performed using SAS version 9.2 (SAS institute, Cary, NC).

7.4 Results

For 2006-2008, there were 361 patients <18 years of age discharged from the two hospitals with an ICD-9-CM diagnostic code of 446.1 or 414.11; all patients with the 414.11 code also had the 446.1 code. Of the 361 patients, 67 patients were excluded from analysis for belonging to one of the following categories: 1) patients with a history of KS admitted for a non-KS illness, 2) patients admitted for a KS-like illness but who were found to have a different, more likely diagnosis, 3) patients who were seen on an outpatient basis and not admitted to the hospital, and 4) patients who were incorrectly discharged with the KS code 446.1 as the apparent result of a coding error. The remaining 294 patients were classified as physician-diagnosed KS cases. Of these, 241 (82.0%) met the CDC case definition for KS (226/241, 93.8%) or atypical KS (15/241, 6.2%). Most of the patients not meeting a KS case definition lacked the lymphadenopathy (42/51, 82.4%) and the peripheral extremity changes (31/46, 67.4%) criteria.

For patients meeting the KS case definitions, 156 patients (64.7%) were male, and 75.9% were <5 years of age. Black patients comprised the highest percentage of cases (44.4%), followed by white patients (42.2%), Asians (12.4%), and other races (0.9%). Out of 107 patients with ethnicity information available, 29 (27.1%) were Hispanic. The highest percentage of patients had KS onset in December (12.6%), followed by January and May, with 10.5% of patients having onset in each month. Five patients (2.1%) were identified as having recurrent KS (Table 7.1).

After excluding 6 cases (2.5%) not treated with IVIG and 44 (18.3%) who received treatment on or after the 10^{th} day of illness, 191 KS patients remained; 45 (23.6%) of the 191 patients required secondary treatment, and all 45 received a second dose of IVIG. A significant difference was not seen between the proportion of white KS patients and black KS patients who did not respond to initial treatment (p=0.531), between the proportion of white KS patients and Asian KS patients who did not respond (p=0.380), or between the proportion of Hispanic KS patients and non-Hispanic KS patients who did not respond (p=0.746). Twenty-eight of the 45 patients were not treated further, while two patients were subsequently treated with IV methylprednisolone, and one patient was treated with infliximab. The remaining 14 patients received a third dose of IVIG, and half of these also received IV methylprednisolone.

Of the KS patients requiring secondary treatment, 11 of 44 (25.0%) had CAAs, significantly more than the 16 of 146 (11.0%) of cases receiving only one dose of IVIG (p=0.019). In all 27 patients with CAAs, the CAA was identified through echocardiogram

testing on the day of initial IVIG or later. There was no significant difference in CAA occurrence by racial group.

Univariate analysis identified CRP ≥7 mg/dL, percent bands >11, ALT >50 IU/L, AST >60 IU/L, total bilirubin >1 mg/dL, and age ≥36 months as being significantly associated with IVIG non-response (Table 7.2). These variables along with male sex, as a possible confounder, and IVIG treatment before the fifth day of illness, consistently identified as a predictor in previous studies, were included in a multivariate logistic regression analysis which identified CRP ≥7 mg/dL, total bilirubin >1 mg/dL, age ≥36 months, and IVIG treatment before the fifth day of illness as independent predictors of IVIG nonresponse. The area under the ROC curve for this model was 0.79 (95% CI 0.70-0.87) (Figure 7.1). Point values were assigned to the predictor variables, and a point total of ≥2 was used to identify patients who were more likely to not respond to initial IVIG treatment (Table 7.3).

Using the scoring system created from the point values, the sensitivity and specificity for predicting IVIG nonresponse were 79.4% and 68.0%, respectively (Table 7.4a). The scoring system was less effective at predicting CAAs (sensitivity 47.8%, specificity 58.6%). When applied to black children in the dataset only, the sensitivity for predicting IVIG nonresponse increased to 84.2% while specificity remained almost the same at 67.9% (Table 7.4b). Among white children, the sensitivity was even higher (90.0%), although specificity was 63.4%. The sensitivity among Asian children was only 33.3%; however, this value was obtained from a small number of patients (n=23). Because not all

physician-diagnosed KS cases met the CDC KS case definition, we also used the scoring system to assess the dataset with all physician-diagnosed KS cases receiving IVIG before the 10th day of illness (n=230). For these patients, the sensitivity was 71.1% and the specificity was 66.0%. All of the sensitivity values were higher compared to Japanese scoring systems applied to the dataset (Table 7.4a).

7.5 Discussion

This study examined IVIG response among a racially diverse population of KS patients at two pediatric specialty hospitals. Consistent with previous US studies, the majority of the KS patients were male (63.9%) (Belay et al. 2006; Holman et al. 2010), with 14.2% of patients having CAAs and 2.1% being identified as recurrent (Gibbons et al. 2002; Belay et al. 2006). While the high proportion of patients with KS onset in winter months is consistent with other reports of KS seasonality (Belay et al. 2006; Holman et al. 2010), the spike in KS onset in May was consistent with a previous Georgia study that showed 26% of KS hospitalizations occurring in May and June (Gibbons et al. 2002).

A high proportion of the KS patients (23.6%) in the present database required additional treatment beyond the initial IVIG. Several scoring systems have been devised in Japan in an attempt to predict which KS patients are likely to not respond to initial IVIG treatment (Egami et al. 2006; Kobayashi et al. 2006; Sano et al. 2007). The Egami et al. score was shown previously by Tremoulet et al. to have low sensitivity when applied to KS patients in the United States (Egami et al. 2006; Tremoulet et al. 2008). This scoring system, along with the Kobayashi et al. score and Sano et al. score, also failed to accurately predict IVIG

nonresponse in this study. The Tremoulet et al. scoring system, created from KS patient data in San Diego, could not be applied to our data because one variable of the scoring system, gamma glutamyl transferase, was not routinely collected by the study hospitals (Tremoulet et al. 2008). A strength of the simple scoring system created in this study is that the four components are likely to be collected by hospitals treating patients with potential KS. However, the sensitivity of the model, 79.4%, indicates that 21.6% of patients who will not respond to initial IVIG treatment will not be predicted to be at risk. Given this finding, it remains important for other factors, such as genetic differences, to be explored as possible determinants of treatment response (Tremoulet et al. 2008).

The high percentage (7.3%) of KS patients requiring a third dose of IVIG emphasizes the need for better treatment options for high-risk KS patients. A study by Okada et al. in Japan found that high-risk KS patients identified through a scoring system were more likely to promptly defervesce and less likely to develop CAAs when treated with pulse methylprednisolone and IVIG compared to a historical control group which only received IVIG (Okada et al. 2009). More recently, Kobayashi et al. used another scoring system to identify patients and then randomly assigned the severe KS patients to either receive IVIG treatment alone or to receive IVIG treatment with prednisolone; patients in the IVIG plus prednisolone group fared significantly better than those who received IVIG alone, with a lower incidence of CAAs, shorter duration of fever, less need for additional rescue therapy, and lower CRP levels (Kobayashi et al. 2012). Applying Japanese scoring systems to North American data has not been found to show a benefit of primary steroid therapy among high-risk patients (Sleeper et al. 2011). However, application of scoring systems developed

from diverse populations, such as the one developed in this study, may be more useful in showing the benefit of steroid therapy or other treatment strategies. Physicians and researchers applying the scoring system should keep in mind that the inclusion of IVIG before the fifth day of illness as a predictor of IVIG nonresponse should not be interpreted to indicate that the early IVIG itself is responsible. This variable was included as a surrogate for the duration of illness until diagnosis, and early treatment may correspond with more severe cases of KS.

Limitations of the study include its retrospective nature, which restricted the authors to the information present in the medical record. KS clinical signs may not have been completely recorded or present at the time of admission, influencing which patients met the KS case definition. Periungual desquamation, for example, typically appears later in the course of illness. The definition of IVIG nonresponse used in this study may have allowed for the classification of some KS patients as IVIG nonresponsive who may have been considered responsive in other studies with stricter criteria. The high percentage (23.6%) of KS cases who did not respond to initial IVIG in our study may reflect this, although the percentage decreased to 19.4% when all physician-diagnosed KS cases were considered.

In conclusion, findings from multivariate analysis identified CRP ≥7 mg/dL, total bilirubin >1 mg/dL, age ≥36 months, and IVIG given before the fifth day of illness to be independent predictors of IVIG nonresponse. The scoring system developed from these predictors may be a useful tool in future studies to examine the potential benefits of early additional treatments given in conjunction with IVIG.

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Table 7.1. Patients <18 years of age with initial and recurrent Kawasaki syndrome (KS) discharged from two pediatric specialty hospitals, Atlanta, Georgia, 2006-2008

Patient demographics	Asian female	Asian male	Black female	White male	Asian male
Initial KS episode					
Initial criteria present	4/5	4/5	Unk	5/5	Unk
CAA	No	No	No	No	Yes
Response to initial treatment	Yes	Yes	Yes	Yes	Unk
Diagnosis*	KS	Unk	Unk	KS	Unk
Recurrent KS episode					
Recurrent criteria present	5/5	4/5	5/5	4/5	4/5
CAA	No	No	No	No	No
Response to initial treatment	Yes	Yes	Yes	No[§]	Yes
Diagnosis*	KS	KS	KS	KS	KS
Time between episodes (months)	24	24	70-82	3	8

*Diagnosis according to CDC KS case definition or atypical KS case definition
[§] Second dose of IVIG administered
CAA=coronary artery abnormality
Unk=unknown

Table 7.2. Comparison of abnormal lab values and characteristics for Kawasaki syndrome patients <18 years of age by IVIG treatment response at two pediatric specialty hospitals, Atlanta, Georgia, 2006-2008

Variable	IVIG nonresponsive Number (%)	IVIG responsive Number (%)	P-value*
Lab value**			
Albumin, g/dL	24/36 (66.7)	71/129 (55.0)	0.213
Alanine aminotransferase, IU/L	27/37 (73.0)	64/128 (50.0)	0.014
Aspartate aminotransferase, IU/L	23/37 (62.2)	46/128 (35.9)	0.005
C-reactive protein, ≥7 mg/dL	30/38 (78.9)	87/141 (61.7)	0.048
Erythrocyte sedimentation rate, mm/hr	33/35 (94.3)	133/137 (97.1)	0.603±
Hematocrit, %	26/38 (68.4)	04/141 (73.8)	0.514
Hemoglobin, gm/dL	16/39 (41.0)	70/142 (49.3)	0.361
Neutrophil bands, %	17/37 (46.0)	37/137 (27.0)	0.028
Neutrophil segs, %	33/37 (89.2)	125/139 (89.9)	1.000±
Platelets (low), $x10^3/mm^3$	1/40 (2.5)	7/142 (4.9)	0.688±
Platelets (high), $x10^3/mm^3$	10/40 (25.0)	46/142 (32.4)	0.372
Platelets (abnormal), $x10^3/mm^3$	11/40 (27.5)	53/142 (37.3)	0.252
Sodium, mmol/L	21/39 (53.9)	52/132 (39.4)	0.110
Total bilirubin, mg/dL	15/35 (42.9)	19/125 (15.2)	<0.001
White blood cell count, $x10^3/mm^3$	19/42 (45.2)	73/144 (50.7)	0.535
Characteristic			
Age ≥ 36 months	31/45 (68.9)	56/146 (38.4)	<0.001
Illness day at IVIG ≤5 days	4/45 (8.9)	9/146 (6.2)	0.509±
Male	29/45 (64.4)	92/146 (63.0)	0.862
Race: White	15/68 (22.1)	53/68 (77.9)	Reference
Black	23/87 (26.4)	64/87 (73.6)	0.530
Asian	3/25 (12.0)	22/25 (88.0)	0.380±
Other	1/3 (33.3)	2/3 (66.7)	0.541±

*Chi-square test, unless otherwise specified;
±Fisher's exact test (two-sided)
**Abnormal laboratory values determined by patient age/laboratory report

Table 7.3. Multivariate predictors of IVIG nonresponse and corresponding scoring system point values, Kawasaki syndrome patients <18 years of age, Atlanta, Georgia, 2006-2008

Variable	OR (95% CI)	Points
Total bilirubin >1 mg/dL	3.7 (1.4-9.9)	1
CRP ≥7 mg/dL	3.5 (1.2-10.1)	1
Age ≥36 months	4.5 (1.8-11.3)	1
IVIG before day 5	5.2 (1.2-23.1)	1

OR: odds ratio
CI: confidence interval

Figure 7.1. Receiver-operator characteristic (ROC) curve for independent predictors of nonresponse to initial intravenous immunoglobulin (IVIG) treatment CRP ≥ 7 mg/dL, total bilirubin > 1 mg/dL, age ≥36 months, and IVIG treatment before the fifth day of illness

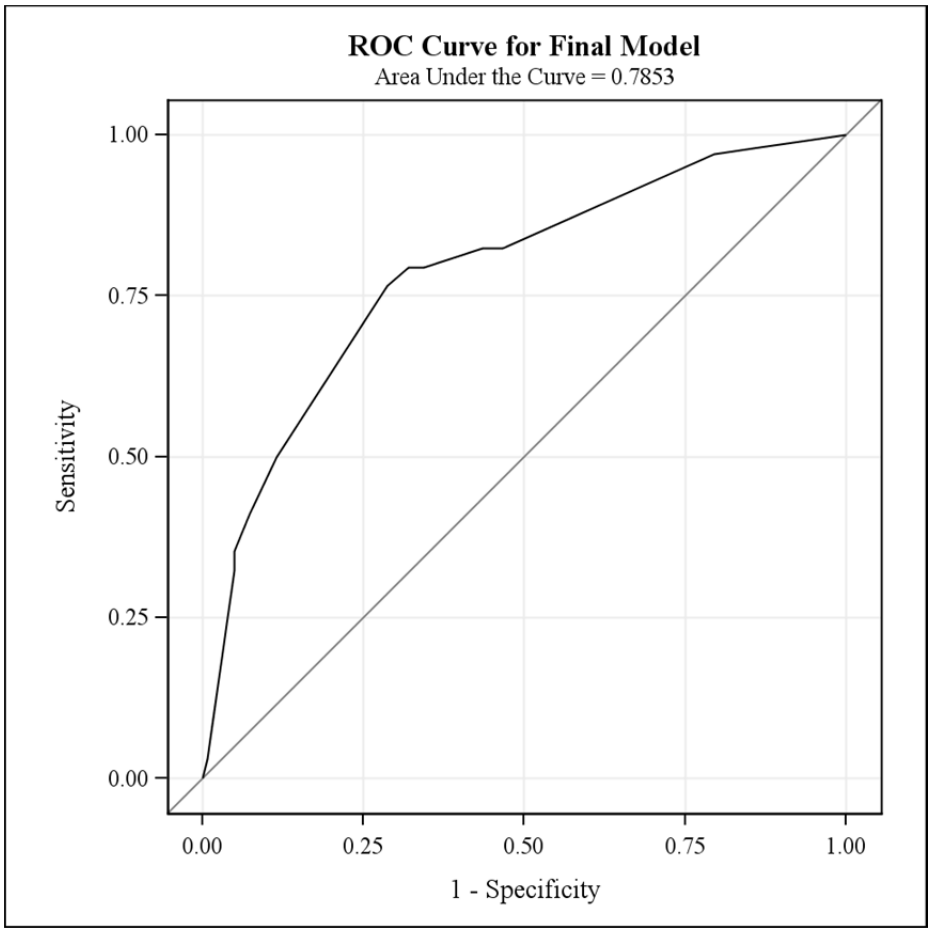

Table 7.4a. Prediction of IVIG nonresponse among Kawasaki syndrome patients <18 years of age at two pediatric specialty hospitals using four scoring systems, Atlanta, Georgia, 2006-2008

	Present score (%)	Sano score (%)	Egami score (%)	Kobayashi score (%)
Sensitivity	79.4	47.1	38.2	45.5
Specificity	68.0	88.4	76.4	74.6
Positive predictive value	40.9	53.3	31.0	33.3
Negative predictive value	92.2	85.6	81.7	83.0

Table 7.4b. Prediction of IVIG nonresponse by race among Kawasaki syndrome patients <18 years of age at two pediatric specialty hospitals using present scoring system, Atlanta, Georgia, 2006-2008

	All races score (%)	White score (%)	Black score (%)	Asian score (%)
Sensitivity	79.4	90.0	84.2	33.3
Specificity	68.0	63.4	67.9	75.0
Positive predictive value	40.9	37.5	47.1	16.7
Negative predictive value	92.2	96.3	92.7	88.2

8. Discussion

8.1 General conclusions

KS is the leading cause of acquired heart disease among children in the United States, Japan, and other countries. Research that can contribute to early detection of KS or better treatment of high-risk patients is therefore necessary. This dissertation focused on three potential high-risk KS categories: recurrent KS patients, atypical and physician-diagnosed KS patients, and KS patients not responding to initial treatment. Study 1 demonstrated that Asian KS patients, both in the US and Japan, had higher rates of recurrence compared to white KS patients when applying a consistent KS case definition, and suggested that CAAs were more common at the initial KS episode among recurrent KS cases compared to nonrecurrent cases.

Sudy 2 provided an in-depth look at physician-diagnosed KS cases not meeting a KS case definition. Few, if any, national US studies have looked at this important population of KS cases**.** The finding that physician-diagnosed KS cases were more likely to be white and less likely to be black compared to patients meeting the KS case definition may reflect quality of care issues if some providers are more likely than others to diagnose KS, and in turn, administer appropriate treatment. Further study of this possibility is warranted.

The third study examined IVIG treatment nonresponse while also providing a picture of KS at two diverse pediatric specialty hospitals. A scoring system using values for CRP, total bilirubin, age, and IVIG treatment day (as a surrogate for time until KS diagnosis) was created to predict KS cases that would not respond to initial IVIG treatment.

8.2 Strengths

This dissertation had several strengths. One overall strength was the use of three sources of data to examine different aspects of KS. The CDC electronic surveillance database dates to 1984 and therefore provides a large number of KS cases on a national scale. Use of the 17th national Japanese survey, while applying the CDC KS case definition, allowed for a more consistent assessment of KS in the US and Japanese populations. The availability of two separate electronic systems (Epic and ChartMaxx) to review medical record data for Study 3 ensured that the most accurate profile for each KS patient was obtained.

A key strength of the two US databases (CDC surveillance and retrospective medical record review) was the racial diversity of the KS patients. Many KS studies have been conducted in Japan, where the disease is most prevalent, and other research has often been performed in areas with low populations of black children. The database created from the retrospective medical record review at two Atlanta specialty pediatric hospitals was comprised of more black KS cases (44.4%) than any other race.

A third strength was the creation of a scoring system in Study 3 that is composed of routinely collected laboratory and clinical values. This will make it possible for other institutions to apply the scoring system to determine its usefulness as a tool to select high-risk KS patients for further study.

8.3 Limitations

As outlined in the individual studies, this dissertation did have limitations. For the first two studies, analyses were limited by the source of the US data, case report forms submitted to the CDC KS surveillance system. The nature of this system limited the studies in three main ways: 1) passive surveillance meant that information was only collected for approximately 10% of cases during the time period (Belay et al. 2006), 2) additional information on recurrent KS cases was lacking, both to confirm the recurrent diagnosis and to obtain information on the first KS admission, and 3) forms were subject to interpretations by the person filling them out; incompletely reported KS cases were excluded from some analyses if they failed to meet the KS case definition. However, despite the limitations of the data source, we were able to reach meaningful conclusions about the extent of KS recurrence and atypical and physician-diagnosed KS cases in the United States.

For Study 3, we were limited by the information available in each patient's medical record. While most records were complete in terms of echocardiography results and laboratory testing, it is possible that certain KS signs were not recorded, and the retrospective nature of the study meant that additional medical information could not be collected or verified. Despite this, our finding of 23.6% nonresponse to initial IVIG among the patients is consistent with previous studies, although it is on the high end of the range (Burns et al. 1998; Wallace et al. 2000; Durongpisitkul et al. 2003; Muta et al. 2006; Kobayashi et al. 2006; Egami et al. 2006; Sano et al. 2007; Uehara et al. 2008; Tremoulet et al. 2008; Ashouri et al. 2008; Do et al. 2010).

8.4 Future research

As a follow up to the findings of this dissertation, several important studies could be conducted. The finding of higher rates of recurrence among Asian KS patients in both the United States and Japan emphasizes the likely role of genetics in determining disease susceptibility and response. Future research should continue to investigate the genetic components of KS in an effort to isolate genetic characteristics that may predispose a child to adversely respond to the potential infectious agent of KS.

A long-term study that follows KS patients from initial KS onset would be difficult, but extremely beneficial. Such a study would allow for very specific findings on KS recurrence, and it would help identify incomplete KS cases that may have otherwise not been classified as KS. The biggest benefit of such a study would be the identification of potential long-term cardiac effects in KS patients, including those with and without CAAs identified during their KS episode. Some studies that follow this line of reasoning are currently underway or being planned; unfortunately, it will be years before true implications of childhood KS can be determined.

In regards to treatment, the scoring system created in Study 3 could be applied to differentiate study groups for research on the effectiveness of alternative therapies using a North American cohort. Previous scoring systems created in Japan have not been shown to predict North American KS cases with high sensitivity (Tremoulet et al. 2008; Sleeper et al. 2011), and the only other US scoring system includes a variable not routinely collected by US hospitals (Tremoulet et al. 2008). The use of the scoring system, as done

by Kobayashi et al. in Japan, could identify high-risk KS patients, who in turn could receive different combinations of treatments (2012).

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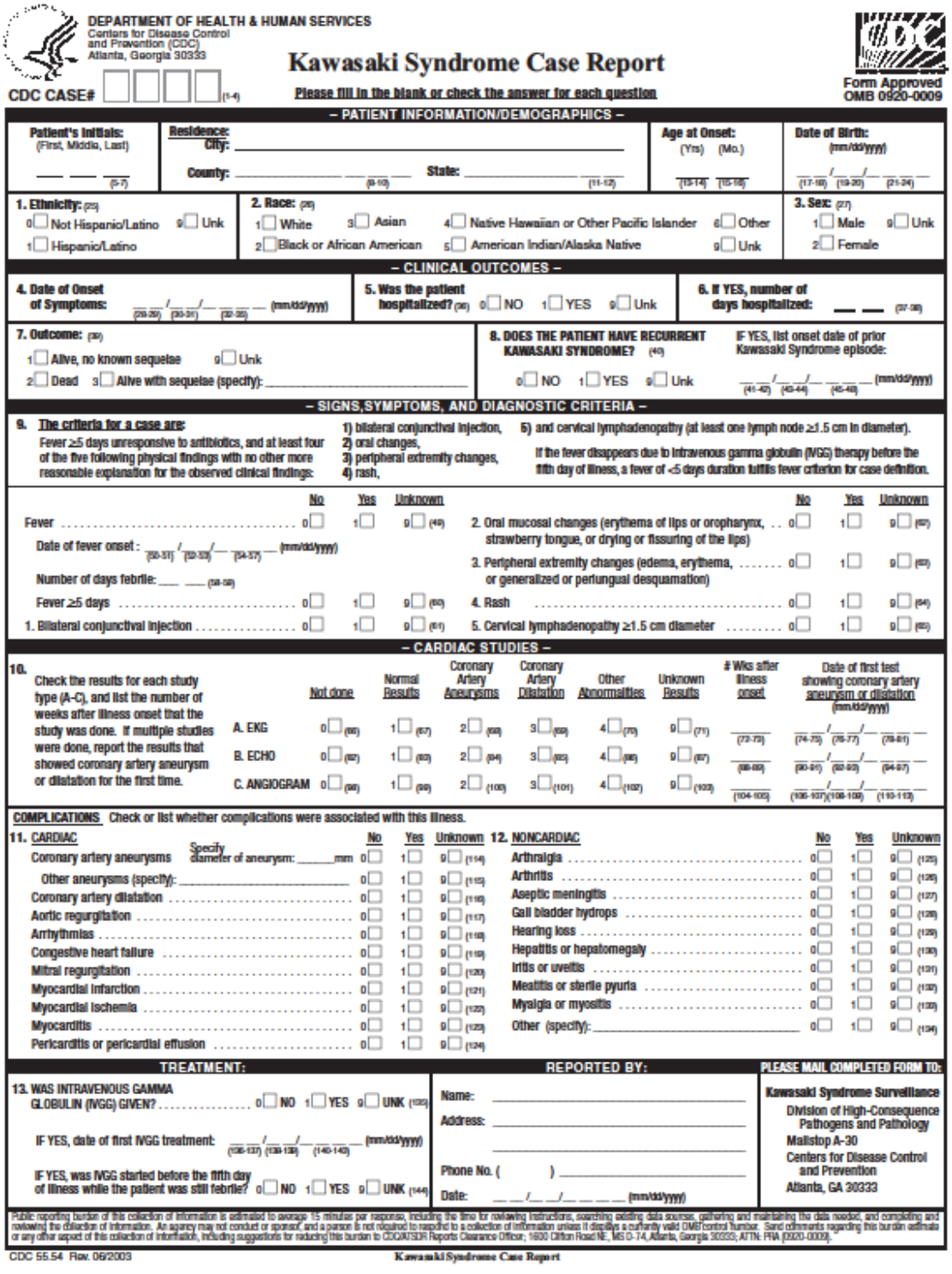
10. Appendix

Appendix 1. Centers for Disease Control and Prevention Kawasaki syndrome surveillance case report form



DEPARTMENT OF HEALTH & HUMAN SERVICES
Centers for Disease Control and Prevention (CDC)
Atlanta, Georgia 30333

Kawasaki Syndrome Case Report

Please fill in the blank or check the answer for each question

Form Approved
OMB 0920-0009

CDC CASE# ☐☐☐☐ (1-4)

– PATIENT INFORMATION/DEMOGRAPHICS –

Patient's Initials: (First, Middle, Last) ___ ___ ___ (5-7)

Residence: City: _____ County: _____ (9-10) State: _____ (11-12)

Age at Onset: (Yrs) (Mo.) (13-14) (15-16)

Date of Birth: (mm/dd/yyyy) __/__/__ (17-18) (19-20) (21-24)

1. Ethnicity: (25)
0☐ Not Hispanic/Latino 9☐ Unk
1☐ Hispanic/Latino

2. Race: (26)
1☐ White 3☐ Asian 4☐ Native Hawaiian or Other Pacific Islander 6☐ Other
2☐ Black or African American 5☐ American Indian/Alaska Native 9☐ Unk

3. Sex: (27)
1☐ Male 9☐ Unk
2☐ Female

– CLINICAL OUTCOMES –

4. Date of Onset of Symptoms: __/__/__ (mm/dd/yyyy) (28-29) (30-31) (32-35)

5. Was the patient hospitalized? (36) 0☐ NO 1☐ YES 9☐ Unk

6. If YES, number of days hospitalized: ___ ___ (37-38)

7. Outcome: (39)
1☐ Alive, no known sequelae 9☐ Unk
2☐ Dead 3☐ Alive with sequelae (specify): _____

8. DOES THE PATIENT HAVE RECURRENT KAWASAKI SYNDROME? (40)
0☐ NO 1☐ YES 9☐ Unk
IF YES, list onset date of prior Kawasaki Syndrome episode: __/__/__ (mm/dd/yyyy) (41-42) (43-44) (45-48)

– SIGNS, SYMPTOMS, AND DIAGNOSTIC CRITERIA –

9. The criteria for a case are:
Fever ≥5 days unresponsive to antibiotics, and at least four of the five following physical findings with no other more reasonable explanation for the observed clinical findings:
1) bilateral conjunctival injection,
2) oral changes,
3) peripheral extremity changes,
4) rash,
5) and cervical lymphadenopathy (at least one lymph node ≥1.5 cm in diameter).
If the fever disappears due to intravenous gamma globulin (IVGG) therapy before the fifth day of illness, a fever of <5 days duration fulfills fever criterion for case definition.

	No	Yes	Unknown
Fever	0☐	1☐	9☐ (49)
Date of fever onset: __/__/__ (mm/dd/yyyy) (50-51) (52-53) (54-57)			
Number of days febrile: ___ ___ (58-59)			
Fever ≥5 days	0☐	1☐	9☐ (60)
1. Bilateral conjunctival injection	0☐	1☐	9☐ (61)
2. Oral mucosal changes (erythema of lips or oropharynx, strawberry tongue, or drying or fissuring of the lips)	0☐	1☐	9☐ (62)
3. Peripheral extremity changes (edema, erythema, or generalized or periungual desquamation)	0☐	1☐	9☐ (63)
4. Rash	0☐	1☐	9☐ (64)
5. Cervical lymphadenopathy ≥1.5 cm diameter	0☐	1☐	9☐ (65)

– CARDIAC STUDIES –

10. Check the results for each study type (A-C), and list the number of weeks after illness onset that the study was done. If multiple studies were done, report the results that showed coronary artery aneurysm or dilatation for the first time.

	Not done	Normal Results	Coronary Artery Aneurysms	Coronary Artery Dilatation	Other Abnormalities	Unknown Results	# Wks after Illness onset	Date of first test showing coronary artery aneurysm or dilatation (mm/dd/yyyy)
A. EKG	0☐ (66)	1☐ (67)	2☐ (68)	3☐ (69)	4☐ (70)	9☐ (71)	___ (72-73)	__/__/__ (74-75) (76-77) (78-81)
B. ECHO	0☐ (82)	1☐ (83)	2☐ (84)	3☐ (85)	4☐ (86)	9☐ (87)	___ (88-89)	__/__/__ (90-91) (92-93) (94-97)
C. ANGIOGRAM	0☐ (98)	1☐ (99)	2☐ (100)	3☐ (101)	4☐ (102)	9☐ (103)	___ (104-105)	__/__/__ (106-107) (108-109) (110-113)

COMPLICATIONS Check or list whether complications were associated with this illness.

11. CARDIAC	No	Yes	Unknown
Coronary artery aneurysms (Specify diameter of aneurysm: _____mm)	0☐	1☐	9☐ (114)
Other aneurysms (specify): _____	0☐	1☐	9☐ (115)
Coronary artery dilatation	0☐	1☐	9☐ (116)
Aortic regurgitation	0☐	1☐	9☐ (117)
Arrhythmias	0☐	1☐	9☐ (118)
Congestive heart failure	0☐	1☐	9☐ (119)
Mitral regurgitation	0☐	1☐	9☐ (120)
Myocardial infarction	0☐	1☐	9☐ (121)
Myocardial ischemia	0☐	1☐	9☐ (122)
Myocarditis	0☐	1☐	9☐ (123)
Pericarditis or pericardial effusion	0☐	1☐	9☐ (124)

12. NONCARDIAC	No	Yes	Unknown
Arthralgia	0☐	1☐	9☐ (125)
Arthritis	0☐	1☐	9☐ (126)
Aseptic meningitis	0☐	1☐	9☐ (127)
Gall bladder hydrops	0☐	1☐	9☐ (128)
Hearing loss	0☐	1☐	9☐ (129)
Hepatitis or hepatomegaly	0☐	1☐	9☐ (130)
Iritis or uveitis	0☐	1☐	9☐ (131)
Meatitis or sterile pyuria	0☐	1☐	9☐ (132)
Myalgia or myositis	0☐	1☐	9☐ (133)
Other (specify): _____	0☐	1☐	9☐ (134)

TREATMENT:

13. WAS INTRAVENOUS GAMMA GLOBULIN (IVGG) GIVEN? 0☐ NO 1☐ YES 9☐ UNK (135)

IF YES, date of first IVGG treatment: __/__/__ (mm/dd/yyyy) (136-137) (138-139) (140-143)

IF YES, was IVGG started before the fifth day of illness while the patient was still febrile? 0☐ NO 1☐ YES 9☐ UNK (144)

REPORTED BY:

Name: _____

Address: _____

_____

Phone No. ( ) _____

Date: __/__/__ (mm/dd/yyyy)

PLEASE MAIL COMPLETED FORM TO:

Kawasaki Syndrome Surveillance
Division of High-Consequence Pathogens and Pathology
Mailstop A-30
Centers for Disease Control and Prevention
Atlanta, GA 30333

Appendix 2. Abstraction form for retrospective medical record review, Children's Healthcare of Atlanta

Kawasaki Syndrome Medical Record Abstraction Form

Patient ID: _____ **Hospital ID:** _____ **Abstraction date:** __ __/__ __/__ __ __ __ *(mm/dd/yyyy)*

PATIENT INFORMATION/DEMOGRAPHICS

1a. Date of Birth: __ __/__ __ __ __ *(mm/yyyy)* **1b. Age in years:** __ __ **1c. Age in months (if <5 years):** __ __

2. Gender: 1☐ Male 2☐ Female 9☐ Unknown

3. a. Race: 1☐ White 2☐ Black/African-American 3☐ Asian 4☐ Native Hawaiian/Other Pacific Islander 5☐ American Indian/Alaska Native 6☐ Other 9☐ Unknown

b. Ethnicity: 1☐ Hispanic/Latino 2☐ Not Hispanic/Latino 9☐ Unknown

4. Outcome of recent illness: 1☐ Alive [as of __ __/__ __/__ __ __ __ *(mm/dd/yyyy)*] 2☐ Deceased 9☐ Unknown

5. Has the patient had a previous KS illness? 1☐ Yes 2☐ No 9☐ Unknown

If yes: Onset date(s): 1) __ __/__ __/__ __ __ __ *(mm/dd/yyyy)* 2) __ __/__ __/__ __ __ __ *(mm/dd/yyyy)*

MOST RECENT KS ILLNESS **SIGNS AND SYMPTOMS**

6. Date of symptom onset: __ __/__ __/__ __ __ __ *(mm/dd/yyyy)*

7. Indicate below which of these conditions were present:	**Yes**	**No**	**Unk**
a. Fever *If yes, Date of fever onset:* __ __/__ __/__ __ __ __ *(mm/dd/yyyy), Number of days febrile:* __ __	1☐	2☐	9☐
b. Fever ≥ 5 days	1☐	2☐	9☐
c. Bilateral conjunctival injection	1☐	2☐	9☐
d. Oral mucosal changes *(erythema of lips/oropharynx, strawberry tongue, or drying/ fissuring of lips)*	1☐	2☐	9☐
e. Peripheral extremity changes *(edema, erythema, or generalized or periungual desquamation)*	1☐	2☐	9☐
f. Rash	1☐	2☐	9☐
g. 1. Cervical lymphadenopathy *(≥1.5 cm in diameter)*	1☐	2☐	9☐
2. Cervical lymphadenopathy *(size unknown)*	1☐	2☐	9☐

HOSPITALIZATION INFORMATION

8. Was the patient hospitalized for this illness? 1☐ Yes 2☐ No 9☐ Unknown

If yes, date(s) of hospitalization, listing the most recent first:

Admit date: __ __/__ __/__ __ __ __ *(mm/dd/yyyy)* Discharge date: __ __/__ __/__ __ __ __ *(mm/dd/yyyy)*

Admit date: __ __/__ __/__ __ __ __ *(mm/dd/yyyy)* Discharge date: __ __/__ __/__ __ __ __ *(mm/dd/yyyy)*

Admit date: __ __/__ __/__ __ __ __ *(mm/dd/yyyy)* Discharge date: __ __/__ __/__ __ __ __ *(mm/dd/yyyy)*

If yes, was the patient admitted to the intensive care unit?
1☐ Yes 2☐ No 9☐ Unknown

9. Was the patient hospitalized for a prior KS episode? 1☐ Yes 2☐ No 9☐ Unknown

If yes, date(s) of hospitalization, listing the most recent first:

Admit date: __ __/__ __/__ __ __ __ *(mm/dd/yyyy)* Discharge date: __ __/__ __/__ __ __ __ *(mm/dd/yyyy)*

Admit date: __ __/__ __/__ __ __ __ *(mm/dd/yyyy)* Discharge date: __ __/__ __/__ __ __ __ *(mm/dd/yyyy)*

Admit date: __ __/__ __/__ __ __ __ *(mm/dd/yyyy)* Discharge date: __ __/__ __/__ __ __ __ *(mm/dd/yyyy)*

LABORATORY STUDIES

10. Are laboratory results available?

	Yes	No	Unk	
a. C-reactive protein (CRP)	1☐	2☐	9☐	Specify highest level: _____
b. Total white blood cell count	1☐	2☐	9☐	Specify highest level: _____
If yes, % neutrophils __ __		% lymphocytes __ __		% bands __ __
c. Hematocrit	1☐	2☐	9☐	Specify level: _____
d. Albumin	1☐	2☐	9☐	Specify level: _____
e. Hemoglobin concentration	1☐	2☐	9☐	Specify level: _____
f. P-selectin	1☐	2☐	9☐	Specify level: _____
g. E-selectin	1☐	2☐	9☐	Specify level: _____
h. Alanine aminotransferase (ALT)	1☐	2☐	9☐	Specify level: _____
i. Aspartate aminotransferase (AST)	1☐	2☐	9☐	Specify level: _____
j. Total bilirubin	1☐	2☐	9☐	Specify level: _____
k. Lactate dehydrogenase	1☐	2☐	9☐	Specify level: _____
l. Sodium	1☐	2☐	9☐	Specify level: _____
m. Platelet count	1☐	2☐	9☐	Specify level: _____
n. Erythrocyte sedimentation rate (ESR)	1☐	2☐	9☐	Specify level: _____

CARDIAC STUDIES

11. Provide results of each test below. If tests were repeated, list the date that an abnormality was detected *for the first time* AND *the preceding normal test date, if applicable.*

a. ECHO 1☐ Not Done 2☐ Normal 3☐ Coronary Artery Aneurysm (specify lumen diameter __ __ mm)
__ __/__ __/__ __ __ __ *(mm/dd/yyyy)* 4☐ Coronary Artery Dilatation 5☐ Other *(specify)*_____ 9☐ Unknown
If abnormal, preceding normal test date: __ __/__ __/__ __ __ __(mm/dd/yyyy)

b. Angiogram 1☐ Not Done 2☐ Normal 3☐ Coronary Artery Aneurysm (specify lumen diameter __ __ mm)
__ __/__ __/__ __ __ __ *(mm/dd/yyyy)* 4☐ Coronary Artery Dilatation 5☐ Other *(specify)*_____ 9☐ Unknown
If abnormal, preceding normal test date: __ __/__ __/__ __ __ __(mm/dd/yyyy)

c. EKG 1☐ Not Done 2☐ Normal 3☐ Abnormal 9☐ Unknown
__ __/__ __/__ __ __ __ *(mm/dd/yyyy)*
If abnormal, preceding normal test date: __ __/__ __/__ __ __ __(mm/dd/yyyy)

COMPLICATIONS

	Yes	No	Unk		Yes	No	Unk
12. Patient has cardiac complications?	1☐	2☐	9☐	**13. Patient has non-cardiac complications?**	1☐	2☐	9☐
If yes, specify below:				If yes, specify below:			
a. Coronary artery aneurysm	1☐	2☐	9☐	a. Arthralgia	1☐	2☐	9☐
b. Other aneurysm *(specify)*_____	1☐	2☐	9☐	b. Arthritis	1☐	2☐	9☐
c. Coronary artery dilatation	1☐	2☐	9☐	c. Aseptic meningitis	1☐	2☐	9☐
d. Aortic regurgitation	1☐	2☐	9☐	d. Gallbladder hydrops	1☐	2☐	9☐
e. Arrhythmias	1☐	2☐	9☐	e. Hearing loss	1☐	2☐	9☐
f. Congestive heart failure	1☐	2☐	9☐	f. Hepatitis or hepatomegaly	1☐	2☐	9☐
g. Mitral regurgitation	1☐	2☐	9☐	g. Iritis or uveatitis	1☐	2☐	9☐
h. Myocardial infarction	1☐	2☐	9☐	h. Meatitis or sterile pyuria	1☐	2☐	9☐
i. Myocardial ischemia	1☐	2☐	9☐	i. Myalgia or myositis	1☐	2☐	9☐
j. Myocarditis	1☐	2☐	9☐	j. Other *(specify)*_____	1☐	2☐	9☐
k. Pericarditis or pericardial effusion	1☐	2☐	9☐				

TREATMENT

14. Was the patient given high-dose aspirin for this illness? 1☐ Yes 2☐ No 9☐ Unknown

If yes, date aspirin treatment initiated __ __/__ __/__ __ __ __ *(mm/dd/yyyy)*

15. Was the patient given intravenous immunoglobulin (IVIG) for this illness? 1☐ Yes 2☐ No 9☐ Unknown

If yes, a. Date of ***first*** IVIG treatment __ __/__ __/__ __ __ __ *(mm/dd/yyyy)*

b. Was ***first*** dose of IVIG given before the 5th day of illness? 1☐ Yes 2☐ No 9☐ Unknown

c. Was ***first*** dose of IVIG given while the patient was still febrile? 1☐ Yes 2☐ No 9☐ Unknown

d. Did the patient respond to the ***first*** dose of IVIG? 1☐ Yes 2☐ No 9☐ Unknown

e. Temperature on day after IVIG infusion _____

16. Was a secondary treatment given? 1☐ Yes 2☐ No 9☐ Unknown

If yes, 1☐ Second dose of IVIG Date *first* given: __ __/__ __/__ __ __ __ *(mm/dd/yyyy)*

2☐ Steroids Date *first* given: __ __/__ __/__ __ __ __ *(mm/dd/yyyy)*

3☐ Other (specify)_____ Date *first* given: __ __/__ __/__ __ __ __ *(mm/dd/yyyy)*

ADDITIONAL INFORMATION

17. Were any additional diagnoses listed at discharge? 1☐ Yes *(specify)*_____

2☐ No 9☐ Unknown

18. Comments: _____

_____