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Management of Kawasaki Disease in Texas: Policy implications

Alberto Coustasse
Marshall University, coustassehen@marshall.edu

Doohee Lee
Marshall University, leed@marshall.edu

Cody Arvidson

Julius J. Larry III

Witold Migala

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Alberto Coustasse, Lewis College of Business / Marshall University Graduate College

Doohee Lee, Lewis College of Business / Marshall University Graduate College

Cody Arvidson, University of North Texas at Dallas

Julius J. Larry III

Witold Migala

ABSTRACT

Kawasaki Disease (KD) is the leading cause of acquired cardiovascular disease among children, but KD has received little attention on its management from a policy perspective. The core objective of this paper is to review the literature, identify problems related to KD, and evaluate and offer some policy alternatives to effectively prevent and treat KD epidemiologically in Texas. Policy options suggested in this paper include, among others, (1) establishing a mandatory national KD registry system (along with active surveillance), (2) introducing sentinel providers, (3) requiring mandatory reporting of KD by hospitals, and (4) sponsoring policy KD research and practice.

INTRODUCTION

Kawasaki Disease (KD) involves the skin, mouth, and lymph nodes, and typically presents in children up to five years of age. In the U.S. alone, over 5,500 KD cases were reported in 2006 (Centers for Disease Control and Prevention [CDC] 2009). KD represents the leading cause of acquired cardiovascular disease in children (Kawasaki Disease Foundation 2009). With the etiology of KD unknown after 40 years of intense research (Burns 2007), no specific laboratory test, such as a blood test, throat culture, or nasal culture, has been developed for accurately diagnosing KD and atypical cases (CDC 2009). Delayed diagnosis and treatment have remained unavoidable and prevalent (Coustasse, Larry, Migala, Arvidson, and Singh 2009). Furthermore, diagnosis is complicated by the same symptoms and signs being present in other illnesses (Freeman and Shulman 2006).

For the purpose of this policy paper, KD is defined according to American Heart Association (2001) and CDC (2009) criteria. These diagnostic criteria include high fever of 4 or 5 days duration along with four or more of the following seven symptoms: (1) rash, (2) red eyes, (3) red, swollen, and cracked lips, (4) "strawberry" tongue, (5) swollen hands and feet, (6) swollen lymph nodes, (7) redness of the palms and soles of the feet (AHA 2001). Treatment consists of Intra Venous Immuno Globulin (IVG) for 8 to 12 hours being administered within 10 days of the first onset of fever. High doses of aspirin must continue to be administered until the fever subsides. The initial

treatment is followed by aspirin dosages maintained, with regulated reductions in administration amounts, for at least 2 months to reduce spontaneous coronary thrombosis (Gersony 1991).

Virtually all deaths in patients who have experienced KD result from cardiac sequelae, or secondary cardiac conditions such as arrhythmia, chest pain, myocardial infarction, and sudden death (Fujiwara and Hamashima 1978; Burns et al. 1996;). The peak mortality occurs 15 to 45 days after the initial onset of fever. However, sudden death from myocardial infarction may occur many years later in individuals who as children had coronary artery aneurysms and stenosis. The potential for later death due to KD complications suggests tracking KD patients throughout childhood is important. Many cases of fatal and nonfatal myocardial infarctions in young adults have been attributed to "missed" KD in childhood (Burns et al. 1996).

Coustasse, Larry, Migala, Arvidson, and Singh (2009) report only 49.4 percent of the patients in their Texas sample being correctly diagnosed with KD upon admission to a hospital. The majority of patients presenting with KD were misdiagnosed. Further, Coustasse et al. reported for the majority of the patients, the sample was represented by 41 different admitting diagnoses other than KD. Even though the misdiagnosis right appears to be high, the overwhelming majority of children with KD (>96 percent) are hospitalized (Chang 2002; Holman et al. 2003). The remaining four percent of cases are treated on an outpatient basis. Since Coronary Artery Aneurysms (CAA) occur significantly more frequently in untreated patients (Newburger 2007), effective interventions are required to enhance the healthcare providers' ability to accurately identify cases of KD in children less than 5 years old and presenting with high fever and rash illnesses (Anderson, Todd, and Glode 2005). Untreated, KD can lead to serious complications that involve the heart and cardiovascular system (Newburger et al. 2004). Therefore, timely and accurate diagnosis is critical, and treatment within 10 days after onset of fever is essential to decrease the risk of heart problems. With appropriate detection and treatment, the incidence of CAA is reduced to as little as 1 percent and no more than 5 percent of cases (Freeman and Shulman 2006).

Lloyd, Walker, and Wilkinson (2001) investigate the clinical and epidemiological features of KD and emphasize the likelihood of an infectious cause for KD. Consequently, several microbial agents have been studied in KD patients. The microbial agents studied include rickettsiae, propionibacterium acnes, klebsiella pneumoniae, ehrlichia sp., parainfluenza virus types 2 and 3, Epstein-Barr virus, rotavirus, among others (Belay et al. 2005; Dominguez, Anderson, Glode, Robinson, and Holmes 2006). Additional possible causes for the disease are identified as prior respiratory disease, exposure to carpet cleaning chemicals, use of humidifiers, or living in close proximity to lakes, rivers, bays, and oceans (Rauch 1987; Kawasaki Disease Foundation 2009). Although multiple infectious agents and toxins are implicated as potential origins for exposure to the disease, none have been conclusively identified as a causative or contributing agent (Chua 2001; Holman et al. 2005).

While KD has been investigated empirically as suggested above, no single, published policy paper provides policymakers with insights on how to manage KD. Therefore, a need to research policy options exists, and this paper's main objective is to identify problems related to KD and review the potential health crisis created by misdiagnoses of KD in children. We use the available literature and offer epidemiologic policy implications for the efficient and effective prevention of KD and diagnosis and treatment of KD in U.S. children.

METHODOLOGY

The research was conducted to complete a comprehensive literature review on the policy and public health implications of KD. The research strategy was limited to selecting articles from reputable journals in which online access was available from electronic databases. The research strategy yielded journal articles of high impact and an analysis of findings from the literature was performed. The studies were investigated to determine their pertinent findings and ethical conclusions, whether stated or implied by the article's general perspective.

Search Strategy

When completing the online research, the following terms were combined using the Boolean "OR" with "Kawasaki disease" and "Kawasaki Syndrome" in conjunction with the Boolean "AND" with "policy," "passive surveillance," "public health," and "active surveillance." All pertinent articles came from (1) four electronic databases including EbscoHost, Ovid Medline, Springer, and PubMed and (2) the Internet, such as GoogleScholar and Dogpile search engines, in an effort to find all possible scholarly and newsworthy information available regarding problems associated with KD and the nature of the crisis related to the misdiagnosis of KD in U.S. hospitals. Also, recognized health organizations websites, such as the CDC, AHA, and World Health Organization, were included in the search for data. Reference lists from retrieved articles were utilized to identify other relevant research articles.

Inclusion, Exclusion, and Assessment

Abundant information is available regarding the disease; however, the review was restricted to literature including information about the policy and public health implications in KD. Reviews and primary research articles were included in this study. All selected articles were in English. No articles were excluded due to the age of the article, but unpublished works were excluded from this study.

RESULTS

A Rationale for Developing a National Kawasaki Disease Policy

Since KD is the leading cause of acquired heart disease for children in the U.S. and with sudden deaths resulting from coronary aneurysm and/or thrombosis, the societal benefit in reducing KD is apparent (Kawasaki Disease Foundation 2009). The financial costs and benefits of more accurate KD diagnosis and treatment will be further quantifiable when accurate incidence and disparities are identified and addressed. Maintaining on-going surveillance is one of the basic duties of a public health system (Wagner et al. 2001; Lewis et al. 2002).

Estimation of national and state incidence of KD has been difficult because the reporting of cases to the CDC remains sporadic (Burns 2007), and all KD tracking and reporting is left to state agencies to enforce (Kao 2005). As is the case with any large passive surveillance system, only a fraction of the total cases are reported (Rauch 1987). Researchers have been forced to rely on hospital discharge data for records of KD surveillance and reporting (Holman, Curns, Belay, Steiner, and Schonberger 2003).

The CDC has maintained a "passive surveillance, or voluntary, system for tracking KD in the U.S. since 1976 (Belay, Maddox, Curns, Ballah, and Schonberger 2006). While a standardized case report form was devised by CDC to collect patient information regarding age, gender, race, residence, clinical signs and symptoms, and KD complications and outcomes, and efforts to insure full completion of the forms were instigated, many forms have not filed properly (Belay et al. 2006). Beginning in 1984, a computerized database was created by the CDC, and a passive reporting system for KD was implemented in 22 states, but poor compliance with reporting procedures has prevented an accurate estimate of the number of cases diagnosed each year (Burns et al. 2000). The number of states reporting KD has declined from a high of 29 in 1994 to a low of 11 in 2002 (Belay et al. 2006). "Active surveillance" would require formal protocol for recording observations of the disease and reporting all suspected cases of KD and the circumstances under which hospital admission occurred admission. Moreover, through active surveillance better estimates of KD incidence and rates of long-term complications can be made available to the medical community and the public (Morens, Anderson, and Hurwitz 1980).

In 1994, San Diego County, California implemented passive surveillance of KD. KD was reported through the recognition, identification, and reporting of each KD case by health care providers to the San Diego Health and

Human Services Agency's Division of Community Epidemiology. Bronstein, Besser, and Burns (1997) conducted a retrospective review of hospital discharge data for San Diego County using 1994-1995 data and demonstrated a reporting of only two-thirds of the eligible patients for county and state levels and a complete failure to report any cases to the CDC. From this study, Bronstein et al. recommend the implementation of a sentinel hospital reporting system, or an active surveillance system, as an alternative to the national passive surveillance system for tracking patients diagnosed with KD. Kao (2005) has reiterated the importance of their recommendation for the 21st century.

Policy Recommendations for Kawasaki Disease Surveillance

The central public health policy problem involving KD are the needs for educating healthcare providers and for a government policy to insure the acquisition of accurate and timely data on all suspected KD cases for purposes of early diagnosis, patient tracking, and determining the cause of the disease (Coustasse, Larry, Migala, Arvidson, and Singh 2009). Timely and accurate data are critical to the early diagnosis of KD. Through awareness of the disease, children can receive early diagnosis and treatment before complications arise. Proper early treatment has been shown to reduce the potential of cardiac sequelae, including CAA and ectasia, which develops in approximately 15 percent to 25 percent of untreated children and may lead to ischemic heart disease or sudden death (Newburger et al. 2004).

The issue of acquiring accurate KD data remains problematic. Active surveillance would require reporting, collecting, storing, tracking, and disseminating confidential data regarding KD patients from registries or centralized databases and intervention at the regulatory and legislative levels. There are several policy issues of concern to legislative bodies, public health professionals, and the public, such as privacy issues; perceptions of governmental intrusions; and ethical issues such as the potential for stigmatization. Perhaps the most serious policy issue of concern is privacy. Presently, the standardized case report form devised by CDC to collect information on KD includes age, gender, race, residence, clinical signs and symptoms, and complications and outcomes (Belay et al. 2006). Although these forms contain personal identifiable health information, privacy concerns are adequately safeguarded because the information is subject to the strict handling and disclosure provisions of the Health Insurance Portability and Accountability Act of 1996 (HIPAA).

While privacy a serious concern in considering policies promoting the active surveillance of KD, the professional education of healthcare providers, the development of a KD specific national registry, and the sponsorship of research are necessary for increasing awareness by professionals and the public and decreasing complications related to misdiagnosis.

On the other hand, *Active surveillance* is costly and involves outreach by the public authority, such as regular telephone calls or visits to laboratories, hospitals, and providers to stimulate reporting of specific diseases (CDC, 2007). Because it places intensive demands on resources, implementation of active surveillance, according to the CDC, it should be limited only to brief or sequential periods of time and for specific purposes.

Professional Education About KD

KD is now the leading cause of acquired heart disease among children in developed countries (Falcini 2006; Burns 2009). Departments of pediatrics at most medical schools in the U.S. are committed to excellence in research and education and in the clinical care of infants, children and young adults. Therefore, it is imperative that more emphasis be placed on the signs, symptoms, diagnosis, and treatment of KD in medical school training so that medical graduates will be cognizant of the disease in their medical practices. In order to obtain correct, early diagnoses of KD, healthcare providers must be educated to recognize the signs and symptoms of KD and make differential diagnoses. This training should begin in medical schools and continue through continuing medical education courses.

In order for pediatricians, emergency room physicians and primary care physicians to stay abreast of the latest developments in pediatric medicine and infectious diseases, continuing medical education courses are necessary. The first line of treatment for KD is accepted to be a combination of aspirin and intravenous immunoglobulin. However, a substantial number of patients have an incomplete response to intravenous immunoglobulin and require additional treatment. Unresponsive patients are at high risk of developing coronary abnormalities and experiencing adverse events from treatment with multiple therapies (Latino, Manlhiot, Sabharwal, Chahal, Yeung, and McCrindle 2008). In 13-30 percent of KD patients, fever persists or recurs. Fever may recur several days following discharge. Doctors must bear the responsibility of warning parents to return to the hospital if fever or other signs of KD recur following discharge, because patients may develop coronary artery abnormalities due to inadequate discharge instruction (Mason and Takahashi 2008).

Physicians must attend continuing education courses and availing themselves of the latest knowledge might prevent them from providing optimal treatment to their KD patients. Continuing medical education becomes increasingly more important with KD because of the serious and sometimes fatal consequences of delayed treatment due to erroneous diagnoses. If professional associations and state licensure boards were to require such education, perhaps the level of misdiagnosis in states such as Texas could be reduced to single digits.

Active Surveillance Through a KD Registry System

The Texas Birth Defects Registry is an excellent example of how legislation can be used to create a centralized state-wide registry, control its use, safeguard privacy, provide for appropriate oversight, and limit access to the information contained in the registry. A statewide KD registry could be created and maintained in like manner in as state of Texas' size. A registry is an organized system for the collection, storage, retrieval, analysis and dissemination of information on individual persons who have either a particular disease, a condition (e.g., a risk factor) that predisposes to the occurrence of a health-related event, or prior exposure to substances or circumstances known or suspected to cause adverse health effects (U.S. Department of Health and Human Services 2008). Texas and the U.S. may need to take a cue from the Japanese Ministry which established a registry of children with a history of KD to determine the long-term outcome for those children and at least 6,600 were being evaluated longitudinally (Nakamura et al. 2000). To investigate the association between service in Vietnam and risk of subsequent cancer, registries have been used to identify people with selected cancers and their prior experiences (exposures) of these "cases" were compared with those of appropriately selected persons serving as "controls." Another purpose for a KD registry could be establishing the etiology of KD. As the literature has shown, however, a legislative mandate creating a statewide KD registry alone is not enough to guarantee these purposes for a registry will be achieved.

An excellent example of a sentinel provider surveillance program is the U.S. Sentinel Provider Surveillance Network for influenza surveillance. An influenza sentinel provider is a trained health care professional who volunteers to report clinically diagnosed Influenza-Like Illness (ILI) to the CDC. The CDC and states' health departments use the data to determine flu activity levels for each state (Texas Department of State Health Services 2009). Sentinel physicians report the total number of patient visits to their facilities each week, as well as the number of patient visits for influenza-like illness within four age categories (0-4 years, 5-24 years, 25-64 years, and 65+ years). They collect respiratory specimens from a sample of patients with influenza-like illness for virus culture (Michigan Department of Community Health 2009).

It is important to note that the data provided by the influenza sentinels can only be used to determine where and when influenza-like illness activity is occurring. It cannot be used to determine the total number or magnitude of influenza cases for an entire state. A major drawback to the sentinel provider program is the shortage of volunteers available to adequately canvass a state, thereby limiting the number of surveillance sites. Effectively, trade-off of between the non-compliance of the passive surveillance system and the greater degree of specificity created using sentinel providers occurs.

Disease surveillance is an epidemiological practice by which the spread of disease is monitored in order to establish patterns of progression. The main role of disease surveillance is to predict, observe, and minimize the harm caused by outbreak, epidemic, and pandemic situations and to increase knowledge as to what factors might contribute to such circumstances. A key part of modern disease surveillance is the practice of disease-case reporting (World Health Organization 2008).

Most infectious disease surveillance systems rely primarily on receiving the case reports from physicians and other health care providers. These data are usually incomplete and may not represent all populations. Completeness of reporting had been estimated to vary from 6 percent to 90 percent for many of the common notifiable diseases (Thacker and Berkelman 1988). Voluntary reporting of KD, whose etiology is believed to involve an infectious agent, suffers from poor compliance with reporting procedures preventing an accurate estimate of the number of cases diagnosed annually (Burns et al. 2000).

Several reasons explain the failure of health care providers and laboratories to report notifiable diseases. The reasons include lack of awareness of the legal requirement to report, lack of knowledge of which diseases are reportable, lack of accurate diagnoses, lack of understanding of how or to whom to report, an assumption that someone else will report the case, intentional failure to report to protect patient privacy, and insufficient reward for reporting or penalty for not reporting. Interventions aimed at reducing these barriers have had limited success at improving provider and laboratory reporting behavior (Doyle, Glynn and Groseclose, 2002).

The best recommendation for reporting of KD in Texas is through mandatory reporting by all hospitals in Texas to a centralized state registry mandated by legislation. Presently, the Texas Health Care Information Collection (THCIC) is responsible for collecting hospital discharge data from all state licensed hospitals (Texas Department of Health Services 2009). For purposes of KD reporting by hospitals, it is recommended that legislation require all hospitals in Texas to report KD symptoms and cases without exception. It is estimated that about 96 percent of KD children were hospitalized in Texas in 2004. The other 4 percent were probably treated on an outpatient basis or were admitted to exempt hospitals. If all hospitals in Texas were required to report, all KD case admissions to formerly-exempt hospitals would be captured and reporting error rate would be minimal.

The UNEX project which investigates Unexplained Deaths and Critical Illnesses by the CDC has developed methods for evaluating severe syndromes indicating infection, including non-culture-based methods to identify etiologic agents (CDC 2002). Many clinicians have treated patients with puzzling situations, in which the acute onset of a critical illness suggestive of an infectious origin occurred in otherwise healthy young people for whom diagnostic tests failed to identify an etiologic agent. Occasionally, such episodes are retrospectively diagnosed many years later with the recognition of a new infectious disease and testing of stored clinical specimens (Pinner, Rebmann, Schuchat, and Hughes 2003). Considering the seriousness of cardiac sequelae, lack of an etiologic agent, and the long-term follow-up required, we advocate that KD should rightfully be placed in the UNEX project. Active surveillance is needed and recommended in the literature. A national registry, such as the one maintained in Japan, would greatly enhance the management and tracking of KD children into adulthood while providing accurate estimates for the calculation of incidence rates and recurrence rates.

"Active surveillance," as opposed to a "passive surveillance," system is recommended. The voluntary passive surveillance for KD has failed to accomplish the purposes of surveillance as evidenced by the continuing decline in the number of states that voluntarily reported to CDC from a high of 29 in 1994 to a low of 11 in 2002 (Belay et al. 2006). Therefore, it is recommended that all hospitals report KD cases immediately following discharge of the patient. "Active surveillance" can provide better estimates of disease incidence, rates of complications (Morens, Anderson, and Hurwitz 1980), and more timely identification of outbreaks.

Sponsorship and Diversification of KD Research and Practice

Given that financial resources play a vital role in preventing and treating certain diseases, we suggest that federal and state governments should initiate systematic efforts to sponsor KD research and practice. A reasonable need to increase research funding exists as only limited (competitive) funding opportunities exist for KD researchers and practitioners. In addition, scant attention for funding KD projects investigating access to care, quality of care, cost analyses of care, and program evaluations of prevention and treatment. For instance, 103 KD research projects have been funded by the National Institute of Health from 2000 through 2009, according to the Computer Retrieval of Information on Scientific Projects (CRISP 2009), but no single proposal was funded in the context of health services research. This finding simply suggests that governments must diversify funding mechanisms to meet the different needs for KD research and practice (CRISP 2009).

CONCLUSION

The national surveillance system is an important tool to monitor the likely occurrences of regional and nationwide KD outbreaks and to monitor the trend of cardiac complications among all KD patients representing specific racial and ethnic groups. These patients could be at risk for long-term coronary artery disease and require special attention and follow-up. It is imperative to start an "active surveillance system" first at the state level, such as within a large and populated state like Texas, as a pilot experience. Once the system has been refined within Texas, for example, a national registry should be implemented to ensure compliance with "mandatory" KD reporting and to be able to provide accurate data to accomplish the mission of monitoring KD. A clinical registry containing important information on treatment and coronary outcomes is needed along with a serum bank and DNA bank (Newburger 2007). Such integrated state and system-wide improvements will greatly enhance continuing education for physicians and increase their proficiency in making accurate and early diagnoses of KD. Education of physicians and other healthcare providers in the recognition of the symptoms of KD is imperative because delayed or erroneous diagnoses might cause not only delayed treatment but in some cases also death. Active surveillance, therefore, can provide the best avenue to ensure providers, patients, and society as whole gain beneficial long-term benefits.

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