



Confronting the Causes and Complications of **Kawasaki Disease**

Will research eventually uncover the causes of KD and how to better treat it?

By Ronale Tucker Rhodes, MS

KAWASAKI DISEASE (KD) was first described by Japanese pediatrician Tomisaku Kawasaki in 1967. His report identified the disease in 50 infants suffering from persistent fever, rash, lymphadenopathy (abnormal size lymph nodes), edema, conjunctival injection (redness in the white sclera of the eye), redness and cracking of the lips, strawberry tongue (a swollen, bumpy tongue) and convalescent desquamation (shedding of the outermost membrane or layer of a tissue such as skin). KD is also a leading cause of acquired heart disease in the U.S.^{1,2}

Today, KD occurs worldwide and is more prevalent in boys than girls. The highest incidence of KD is in Japan with an annual rate of 130 to 140 out of 100,000 children under 5 years old. The incidence in the continental U.S. varies between 9 and 19 out of 100,000 children under 5 years old, and in Hawaii, it varies between 120 and 130 out of 100,000 Japanese Americans under 5 years old. The Centers for Disease Control and Prevention's most recent estimate (2009) of the number of hospitalizations with KD is 5,447, 4,040 of whom were children under 5 years old.^{1,2}

What Is KD?

Also known as mucocutaneous lymph node syndrome because it also affects lymph nodes, skin and the mucous membranes inside the mouth, nose and throat,³ KD is an uncommon childhood disease that mainly affects infants and young children (although in rare cases, it can occur in older children and teens). It is a form of vasculitis in which the walls of blood vessels throughout the body become inflamed. The disease can affect any type of blood vessel in the body, including the arteries, veins and capillaries.⁴

In some cases, KD affects the coronary arteries that carry oxygen-rich blood to the heart.⁴ Aneurysms of the coronary arteries, the blood vessels that supply oxygen to the heart itself, are the most serious complication of Kawasaki disease. In fact, fatal coronary artery aneurysms develop in up to 25 percent of untreated children.²

KD Symptoms

KD typically occurs in three phases. The first phase, known as the acute febrile stage, may include a high fever of more than 102.2 degrees Fahrenheit that lasts more than five days; conjunctivitis (extremely red eyes without a thick discharge); red, dry, cracked lips and an extremely red, swollen tongue (strawberry tongue); swollen and red skin on the palms of the hands and soles of the feet; swollen lymph nodes in the neck and sometimes elsewhere; and a rash on

the trunk of the body and, often worse, in the genitals. The second phase, known as the subacute stage, may include peeling of the skin on the hands and feet, especially the tips of the fingers and toes and often in large sheets, joint pain, diarrhea, vomiting and abdominal pain. In the final phase, the convalescent stage, signs and symptoms slowly go away unless complications develop. It can be as long as eight weeks before energy levels are normal.^{3,5}

Some also recognize a fourth phase, known as the chronic stage, which refers only to patients who have developed cardiac complications. The chronic stage is significant because an aneurysm formed in childhood may rupture in adulthood. And, in some cases in which this has occurred, reviews of past medical histories have revealed febrile childhood illnesses of unknown cause.⁶

Unfortunately, not all children have classic signs of KD, and some who do may actually have other illnesses that present with similar signs. As such, many children go undiagnosed until long-term damage has occurred.⁷

Causes of KD

Despite four decades of research, it is still unknown what causes KD (it is known that KD is not contagious).⁵

One theory is that KD results due to abnormal immune system activation; however, the triggers of this abnormal response are unknown. Since cases of KD tend to cluster geographically and by season, researchers have also suggested an infection may be involved; however, no infectious agent (such as a virus or bacteria) has been identified.

Genetic factors appear to be important as suggested by an increased frequency of the disease in Asian and Asian-American populations and among family members of an affected child. A variation in the ITPKC gene has been associated with an increased risk of KD. The ITPKC gene provides instructions for making an enzyme called inositol 1,4,5-trisphosphate 3-kinase C, which helps limit the activity of T cells that identify foreign substances and defend the body against infection. Research suggests the ITPKC gene variation may interfere with the body's ability to reduce T cell activity, leading to inflammation that damages blood vessels and results in the signs and symptoms of KD.⁸

In 2017, the American Heart Association (AHA) published new guidelines for the diagnosis and management of KD that propose three linked pathological processes: 1) necrotizing arteritis, which "destroys the arterial wall into the adventitia, causing aneurysms," 2) subacute/chronic vasculitis "characterized by an asynchronous infiltration of lymphocytes,

plasma cells and eosinophils with fewer macrophages that begins in the first two weeks after fever onset but can continue for months to years in a small subset of patients and is closely linked to the third process” and 3) myofibroblastic proliferation, which involves a unique medial smooth muscle cell-derived myofibroblastic process that can cause progressive arterial stenosis.⁹

Diagnosing KD

The first guidelines for the diagnosis and management of KD were published by AHA in 2004, which were similar to those published by the Japanese Circulation Society. According to those guidelines, KD is a clinical diagnosis based on its symptoms. Classic (typical) KD is diagnosed based on the presence of a fever lasting five or more days, accompanied by four out of five other symptoms that occur in the first phase. Incomplete (atypical) KD occurs in persons with fever lasting five or more days and with two or three of these symptoms. What’s more, these clinical features tend to appear sequentially, which helps to differentiate KD from other disorders.¹⁰

There is no specific diagnostic test for KD. However, because a prompt diagnosis is so critical, AHA’s 2017 revised guidelines include an updated algorithm outlining supplemental information, including clinical, laboratory and echocardiographic findings, that may facilitate the diagnostic process in cases lacking complete classic clinical criteria. These can be found at circ.ahajournals.org/content/early/2017/03/29/CIR.000000000000484.¹¹

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Importantly, as mentioned previously, there are other illnesses with similar clinical features, so they should be considered before making a KD diagnosis.¹⁰ These can include viral infections such as rubeola, roseola, rubella, adenovirus and others; bacterial infections such as streptococcal scarlet fever, staphylococcal scalded skin syndrome, toxic shock syndrome and mycoplasma infection; Lyme disease; toxoplasmosis; Rocky Mountain spotted fever; typhus, juvenile rheumatoid arthritis; drug reactions (allergy); and mercury poisoning.¹²

Treating KD

Because of the risk of serious complications, initial treatment for KD usually is given in a hospital with a goal of reducing inflammation and arterial damage and preventing thrombosis in those with coronary artery abnormalities. For both complete and incomplete KD, initial treatment is a single high-dose (2 g/kg) infusion of intravenous immune globulin (IVIG), usually given over 10 to 12 hours, together with a total daily dose of 80 mg/kg to 100 mg/kg of aspirin (acetylsalicylic acid) administered every six hours until the patient is afebrile for 48 to 72 hours.^{10,11} IVIG is shown to reduce the prevalence of coronary artery abnormalities, whereas aspirin has important anti-inflammatory activity (at high doses) and antiplatelet activity (at low doses).¹¹

Under AHA’s revised guidelines, if fever persists after 10 days without other explanation or coronary artery abnormalities and with ongoing systemic inflammation, a second high-dose IVIG infusion should be given. In addition, low-dose aspirin is typically prescribed for at least six weeks or longer if the child develops a coronary artery aneurysm. One concern about aspirin for children is it could cause Reye syndrome, a rare but potentially life-threatening condition that can affect the blood, liver and brain of children and teenagers after a viral infection.³ However, the low-dose therapy used for antiplatelet effect has not been associated with its development.¹¹

In patients who are IVIG-resistant, AHA’s revised guidelines include recommendations for additional therapies, including corticosteroids, infliximab and etanercept, as well as detailed recommendations for management based on coronary artery involvement.¹¹

Corticosteroids. While the use of corticosteroids in children has been controversial, they were initially used as treatment for KD long before IVIG was found to be useful. And, many studies have shown benefit and no ill effects from their use.¹¹ A recent meta-analysis published in January 2017 reviewed the use of corticosteroids in 922 male and female children with KD in seven randomized trials for reducing the chance of future heart problems, as well as their effect on the duration of fever, signs of infection in the blood and the number of days spent in the hospital. Findings showed corticosteroids reduced the subsequent occurrence of coronary artery abnormalities without serious adverse events (737 participants had no events) and mortality (915 lived). In addition, corticosteroids reduced the duration of fever, time for laboratory parameters to normalize and length of hospital stay.¹³

Another meta-analysis published in December 2016 compared corticosteroids plus IVIG versus IVIG therapy alone in treating patients with KD either using corticosteroids as initial therapy or as rescue therapy. The study involved 2,746 patients in 16 comparative studies to determine the rate of coronary artery abnormalities. Findings were as follows: 1) The duration of illness before corticosteroid therapy was significantly shorter in the initial corticosteroids subset than in the rescue corticosteroids subset. 2) The rate of coronary artery abnormalities was significantly lower in adjunctive corticosteroids than in IVIG therapy. 3) The overall efficacy was negatively correlated with the duration of illness before corticosteroid therapy. 4) Studies using corticosteroids plus IVIG as initial therapy showed a more advantageous effect than IVIG alone regarding coronary artery abnormality prevention, whereas the benefit was not found using corticosteroids as rescue therapy. 5) Patients predicted at baseline to be at high risk of IVIG resistance seemed to obtain the greatest benefit from adjunctive corticosteroid therapy regarding coronary artery abnormality prevention. 6) Fever duration was significantly reduced in the corticosteroids group without an increased risk of adverse events.¹⁴

Infliximab. In early studies conducted in Japan, high levels of the proinflammatory cytokine TNF- α in the plasma of patients with acute KD were documented, with the highest levels shown in patients who went on to develop coronary artery abnormalities. Infliximab, a chimeric monoclonal antibody that binds with high affinity to TNF- α , was the first anti-TNF- α monoclonal antibody therapy to be approved for pediatric patients.¹¹

A study led by physicians at the University of California, San Diego (UCSD) School of Medicine and Rady Children's Hospital in San Diego looked at whether adding infliximab to current standard therapy (IVIG and aspirin) would prevent IVIG-resistance and associated coronary artery abnormalities. Results showed that "while the addition of infliximab to primary treatment in acute KD did not reduce treatment resistance, it was safe and well-tolerated, achieved a greater reduction in the size of the left coronary artery, and reduced the number of days of fever and laboratory markers of inflammation," according the study's first author Adriana H. Tremoulet, MD, of the UC San Diego Department of Pediatrics and the UC San Diego/Rady Children's Hospital-San Diego Kawasaki Disease Research Center. "We conclude that use of infliximab is safe in infants and children and that early treatment could help children with Kawasaki disease with high levels of inflammation or early signs of coronary artery damage."¹⁵

Kawasaki Disease Facts

- 80% to 90% of Kawasaki disease cases occur in children under age 5 and older than 6 months.
- Kawasaki disease is not contagious; it does not spread among family members or children in child care centers.
- Kawasaki disease occurs more frequently in those of Asian ancestry.
- The cause of Kawasaki disease is not known, but it is thought to be a reaction by the body's immune system.
- Signs & Symptoms:
 - Begins with a high fever (>102 degrees Fahrenheit) for at least five days, along with other signs and symptoms.
 - Rash all over the body but more severe in the diaper area.
 - Red, bloodshot eyes without any pus, drainage or crusting.
 - Tender, swollen gland (lymph node) on one side of the neck.
 - Swollen hands and feet with redness on the palms of the hands and the soles of the feet.
 - Very red, swollen and cracked lips; strawberry-like tongue with rough, red spots.
 - Significant irritability and fussiness.
 - Peeling fingers and toes (typically two to three weeks after the beginning of fever).

Etanercept. In 2010, a prospective, open-label study of 15 patients administered 0.8 mg/kg of etanercept subcutaneously after IVIG infusion and again at one and two weeks later. The pharmacokinetics were similar to those reported in older children, and no adverse reactions were attributable to etanercept. As a result, a Phase III randomized, placebo-controlled trial was initiated and is still enrolling subjects.

In 2013, a study was conducted to determine the most effective alternative therapy to those refractory to IVIG in a mouse model. Vasculitis was induced by injection of *Candida albicans* water-soluble fractions (CAWS) into the mice, followed by administration of IVIG, etanercept, methylprednisolone (MP), and cyclosporine-A (CsA). At two and four weeks, the mice were sacrificed, and plasma cytokines and chemokines were measured. At two weeks, inflammation of blood vessels was reduced only by etanercept, with the effect persisting for the subsequent two weeks. At four weeks, IVIG and CsA also reduced the inflammation, but the effect of etanercept was more significant. MP exerted no apparent effect at two or four weeks. According to the researchers, "Etanercept was most effective in suppressing CAWS-induced vasculitis and can be a new therapeutic intervention for KD."¹⁶

Other treatments for patients who fail to respond to either a second infusion of IVIG, steroids or infliximab include cyclosporine, other monoclonal antibody therapy, plasma exchange and cytotoxic agents.¹¹

Ongoing Research

The cause of KD, why some children are more susceptible to it and why the standard treatment is ineffective in some children are the main topics of research today.

Researchers at the UCSD School of Medicine in conjunction with colleagues at Rady Children's Institute for Genomic Medicine have identified plausible gene variants that predispose some children to developing KD. They did this by analyzing the whole genome sequence for the first time in a six-member African-American family whose two children had KD but the parents and siblings did not. "Despite their apparent increased susceptibility, children of African-American descent have been excluded from previous KD genetic analysis," wrote the authors of the study. Whole genome sequencing is a process in which the person's complete DNA sequence is determined at a single time. The researchers also looked at genome-wide association studies that search for genetic variation in large populations with a goal of finding distinct gene variants that, in combination, might indicate predisposition to and higher likelihood of developing KD. They found a variation of the toll-like receptor 6 gene that plays a fundamental role in the immune system, which may be linked to the pro-inflammatory state during the acute stage of KD. They also found another variant in a gene called tumor-associated calcium signal transducer 2, which is involved in cellular calcium signaling.

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"The analysis of whole genome sequence to understand disease genetics is only recently becoming a tool that is affordable and manageable due to new developments in computer science," said lead author of the study Jane C. Burns, MD, professor and director of the Kawasaki Disease Research Center at UCSD School of Medicine and Rady Children's Hospital. "Our next approach will be to compare

the whole genome sequence from KD patients with severe heart damage to those with no damage despite no or delayed treatment. We hope this will lead us to the genetic pathways that result in damage to the coronary arteries, which in turn will suggest new therapies to target those pathways."¹⁷

While IVIG is the first line of treatment for KD, some 10 percent to 20 percent of children are IVIG-resistant and are at increased risk of developing coronary artery aneurism. As such, researchers at the Kawasaki Disease Research Program at UCSD are trying to determine how IVIG works in KD patients and why some don't respond, and it's possible they may have found some useful information to develop new treatments. They hypothesized that "IVIG preparations given to IVIG-resistant KD patients had lower levels of sialylation (the process by which sialic acid groups are introduced onto molecules) and, thus, limited anti-inflammatory effect." Alternatively, they hypothesized that "IVIG-resistant KD patients have lower levels of endogenous sialylation of IgG [molecules] compared to those [who] were responsive."

To test their hypotheses, the researchers collected a sample of the actual IVIG the patients were given for the disease, as well as serum from the patients before they were given IVIG. They then looked at control patients who came into the emergency room who don't have KD and compared that to the KD serum one year later after having been treated with IVIG. They found there didn't seem to be any difference in children who received IVIG exogenously. However, children who responded to IVIG had higher endogenous levels of alpha-2 6-sialic acid compared to those who were resistant. And, those endogenous levels remained there after one year. In essence, said Dr. Tremoulet, in a presentation about the research, "there seemed to be something inherent to these children." They next looked at whether there is a difference in the transcript levels of ST6GAL1 that correlate with IVIG treatment response or whether there is a protein level difference of ST6GAL1 that also correlated with treatment response. What they found was the levels of sialylation of IVIG were unrelated to treatment outcomes. It didn't matter how much of the sialic acid was on the IVIG given to patients, whereas endogenous IgG levels did matter.

"It turns out that antigen processing is really critical," explained Dr. Tremoulet. "When you give someone IVIG, they have to actually cut it up into little pieces, and they have to be able to then present that so the body can have an anti-inflammatory response. The children who don't respond well to IVIG, they don't process that antigen smoothly. They can't really take the whole IVIG complex

and cut it up efficiently and present it so the body will have an anti-inflammatory response. And, that's critical because that's how we lower inflammation. It turns out if we give our KD patients very small peptides of a part of [IVIg] so the patient doesn't actually have to chop [it up] (we have an in vitro model where we actually try to give the small peptides already chopped up), then we don't actually have a problem with IVIG-resistance. What's probably happening is that there may be a link here between sialic acid that's present and its antigen processing. Which is a beautiful story because, in the end, what we're hoping is that by actually developing these small peptides that can be given to patients may be an alternative to treatment for KD rather than giving a very expensive amount of IVIG."¹⁸

In 2017, researchers at UCSD School of Medicine, Rady Children's Hospital and the Betty Irene Moore School of Nursing at UC Davis received a \$2 million grant from the Patient-Centered Outcomes Research Institute (PCORI) for a three-year study to look at the effectiveness of two treatment options for children with KD who are resistant to initial therapy. "After talking to more than 100 parents, clinicians and researchers, we learned that their top priority for research is to test the effectiveness of treatments to prevent heart damage in this fragile patient population," said Dr. Burns who is co-principal investigator of the study. "Our findings will further Kawasaki disease research and give insight into how to approach patients who do not respond to initial treatment."

The two treatment options are second infusions of IVIG or infliximab. "We want to see which treatment option will stop the fevers and inflammation fastest in patients whose symptoms return after IVIG treatment or never subside," explains Dr. Burns. In addition to comparing the effectiveness of the two drugs, the researchers are also evaluating patient-reported outcomes using an app for parents to record their child's discomfort, psychosocial concerns and other experiences during a hospital stay and after discharge. "Because children can be resistant to treatment, parents can understandably become anxious and frustrated," said Katherine Kim, PhD, MPH, co-principal investigator and assistant professor at UC Davis. "The mobile app will help us determine and better understand KD and the burden treatment can have on patients and their families."

A Hopeful Future

While KD research has been ongoing for more than four decades, recent discoveries show tremendous promise for

understanding its cause and developing new treatments. KD is a rare disease in the U.S., but in many countries, KD is more prevalent, and treatment with IVIG is mostly not an

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option. For these children and others, more effective and less expensive treatment is their best hope. ■

RONALE TUCKERRHODES, MS, is the editor-in-chief for *IG Living* magazine.

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