Kawasaki disease, also known as mucocutaneous lymph node syndrome, was first described in Japan in 1967. It is currently the leading cause of acquired heart disease in children in the United States. Untreated Kawasaki disease may lead to the formation of coronary artery aneurysms and sudden cardiac death in children. This vasculitis presents with fever for ≥ 5 days, plus a combination of key criteria. Because each of the symptoms commonly occurs in other childhood illnesses, the disease can be difficult to diagnose, especially in children who present with an incomplete form of the disease. At this time, the etiology of the disease remains unknown, and there is no single diagnostic test to confirm the diagnosis. This issue reviews the presentation, diagnostic criteria, and management of Kawasaki disease in the emergency department. Emergency clinicians should consider Kawasaki disease as a diagnosis in pediatric patients presenting with prolonged fever, as prompt evaluation and management can significantly decrease the risk of serious cardiac sequelae.
Case Presentation

A 3-year-old girl presents to the emergency department for evaluation of fever. Her mother reports that the child has had a fever for the past 5 days, with temperatures ranging from 38.3°C (101°F) to 40°C (104°F). The child has some rhinorrhea, but no significant cough. She has been complaining of abdominal pain and had 2 episodes of nonbilious vomiting in the last 2 days. She was evaluated at her pediatrician’s office 2 days ago, and she was diagnosed with a viral illness. Her mother reports the subsequent development of a red rash that started on the child’s face and chest, and it is now present on her trunk, back, and extremities. Her lips are cracked, and her mother attributes this to poor oral intake over the past few days. Today, the child was noted to have red eyes, without discharge, and redness in the genital area. The mother has not noticed swelling of the extremities or peeling skin. The remainder of the review of systems is negative. The child was previously healthy, with no prior hospitalizations, and she is fully immunized. She attends a small, in-home daycare, but none of the other children there have been sick. On physical examination, the child appears tired and ill, although she is not in distress. Her temperature at triage is 39.8°C (103.6°F). She is tachycardic, with a heart rate of 166 beats/min; and tachypneic, with a respiratory rate of 48 breaths/min. Her eyes are injected bilaterally, without purulent discharge. Her tympanic membranes are normal. She has dry, fissured lips. She has shotty cervical lymphadenopathy. Her lungs are clear to auscultation, and the cardiovascular examination reveals tachycardia without murmurs. Her abdomen is soft and mildly tender to palpation throughout, with no hepatosplenomegaly. Her extremities are warm, well perfused, and without swelling. Her skin is notable for a fine, erythematous maculopapular rash on the face, chest, back, and extremities. The patient’s ill appearance and history of prolonged fever are concerning for the possibility of Kawasaki disease, but you aren’t sure that she meets all of the criteria. You wonder if there are infections you should worry about. Are there laboratory tests you could order that would help you differentiate Kawasaki disease from infection? What about diagnostic imaging tests? Should you start any medications? Are there any other complications that you should be concerned about?

Introduction

Kawasaki disease was initially described in Japan in 1967 by Tomisaku Kawasaki.Originally known as mucocutaneous lymph node syndrome, it is an acute, self-limited, febrile vasculitis of infancy and childhood. Kawasaki disease primarily affects small- and medium-sized arteries, including the coronary arteries. Although it is a self-limited disease, early diagnosis and treatment is critical to preventing the formation of coronary artery aneurysms, which may lead to acquired cardiovascular disease and sudden death. Since it was first described, Kawasaki disease has been well characterized. Affected children generally have fever for at least 5 days, plus 4 of 5 key criteria. These criteria include conjunctival injection, oral mucosal changes, polymorphous rash, distal extremity changes, and cervical lymphadenopathy. Non-specific symptoms, such as vomiting, joint pain, cough, decreased oral intake, rhinorrhea, and abdominal pain, may also be present, and may make the diagnosis more challenging. To add to the diagnostic challenge, some patients may develop an incomplete form of the disease. These children will not meet all of the clinical criteria of Kawasaki disease, but they may still develop the cardiovascular complications. Incomplete Kawasaki disease accounts for 15% to 20% of Kawasaki disease diagnoses, and it is more common in children aged < 6 months and in children aged > 5 years.5

No single laboratory test can be used to establish the diagnosis of Kawasaki disease, although laboratory testing can be used to distinguish this disease from other disease entities. Thus, the diagnosis must be made using a combination of a thorough history, physical examination, and laboratory results. If some of the diagnostic criteria are met and Kawasaki disease is suspected, the current recommendations are to obtain an echocardiogram to assess coronary artery involvement. Ideally, this should be done within 10 days of the onset of fever to minimize the risk of cardiovascular complications.

Kawasaki disease is rarely fatal, but virtually all deaths result from cardiac sequelae. In fact, this disease has now surpassed rheumatic heart disease as the leading acquired heart disease in children in the United States.5 Coronary artery aneurysms occur in 15% to 25% of untreated children. Coronary artery aneurysm has been known to lead to myocardial infarction, ischemic heart disease, and sudden cardiac death. Peak mortality occurs 15 to 45 days after the development of fever. However, sudden cardiac death has been documented years after the diagnosis of Kawasaki disease. In-hospital mortality is currently estimated to be 0.17% in the United States.7

Critical Appraisal Of The Literature

A literature search was performed using both PubMed and Ovid. The initial search on PubMed using the term Kawasaki disease resulted in 8170 articles. This was then decreased to 3458 articles by limiting the results to children (aged birth to 18 years) and articles published in English. A similar search in Ovid using the same terms produced 4593 articles. Guidelines from the American Academy of Pediatrics (AAP) in partnership with the American Heart Association (AHA) were reviewed. Search of the Cochrane Database of Systematic Reviews produced reviews of Kawasaki disease treatment using intravenous immunoglobulin (IVIG) and aspirin. The ref-
Kawasaki disease was first discovered in Japan, and the incidence of the disease is significantly higher in Asian populations. As a result, many of the published studies have come from Japan. However, for our purposes, only those studies published in English were reviewed.

A review of the literature for the etiology and pathogenesis of Kawasaki disease produced mixed results. Although there are many studies examining the etiology of the disease, the evidence presented within these studies was weak overall. In contrast, the evidence in support of the optimal treatment of Kawasaki disease is much stronger. Many of these studies have been performed using a prospective, randomized approach. In addition, several meta-analyses on the topic are available and were reviewed.

Epidemiology, Etiology, And Pathophysiology

Epidemiology
Kawasaki disease is the second most common vasculitis condition in children. It is also the leading cause of acquired heart disease in children in the United States. It is slightly more prevalent in males than in females, at a rate of approximately 1.5 to 1. Although Kawasaki disease has been described in all ethnicities, it is most prevalent in children of Asian ancestry. The United States Centers for Disease Control and Prevention reported estimates of disease occurrence in 9 to 19 per 100,000 children aged < 5 years in the continental United States, with an estimated 5447 related hospitalizations in 2009. Rates are highest in Asian/Pacific Islanders, followed by blacks, whites, and American Indians. The rate of hospitalization for Kawasaki disease among Asian/Pacific Islander children in the United States is 30.3 per 100,000, while the rate for white, non-Hispanic children in the United States is 12 per 100,000. Within the United States, Hawaii has higher rates of Kawasaki disease, with one study showing an estimated rate of 47.7 per 100,000 children aged < 5 years. The significantly higher rates in Hawaii are likely related to the high proportion of the population with Asian- or Pacific-Islander ancestry.

Worldwide, the highest incidence of Kawasaki disease is in Japan, where it was first described. In 2007 and 2008, an epidemiologic study in Japan estimated the incidence of Kawasaki disease at 216.7 per 100,000 children aged 0 to 4 years, which is > 10 times the incidence in the United States. In other parts of Asia, rates of Kawasaki disease are lower compared to those seen in Japan, but they are still higher than rates in the United States. A 2012 review reported that Hong Kong had an incidence of 39 per 100,000 children aged < 5 years, Beijing had an incidence of 55 per 100,000, and Korea’s annual incidence was 113.1 per 100,000 children. Europe and Oceania reported significantly lower rates. Hospital admission rates from England averaged 8.4 per 100,000. Australian statistics from the 1990s showed an annual incidence of 3.7 per 100,000 children aged < 5 years.

Etiology And Pathophysiology
Despite all of the research that has been performed in the last 40 years, the exact etiology of Kawasaki disease remains a mystery. Clinical and epidemiological data are suggestive of an infectious agent, but such an agent has never been identified. The self-limited nature of the illness and associated symptoms of fever, rash, and conjunctivitis are common to many viral illnesses. Younger children are disproportionately affected, which is also the case with many infectious diseases. Epidemiological data have shown that the disease is most common in the winter and spring, and occurs in community outbreaks with a wave-like geographic spread. All of these factors are characteristic of an infectious etiology.

Many infectious agents have been proposed as having a causative role in Kawasaki disease, including multiple viruses, bacteria, spirochetes, and rickettsia. However, none have been confirmed as the definitive source. Other theories have been proposed as well. One theory has suggested that selective expansion of specific T-cell receptor families in Kawasaki disease might be the result of a bacterial superantigen. A 1993 study found toxic shock syndrome toxin-1 (TSST-1) in 11 out of 16 patients with Kawasaki disease. However, follow-up studies by different authors failed to show similar results. A more recent prospective, multicenter trial did not show a higher prevalence of supertoxin-producing bacteria in Kawasaki disease patients compared to febrile controls. In addition, the immune response in Kawasaki disease has now been shown to be oligoclonal. The oligoclonal response is more consistent with an immune response to a common antigen, rather than the polyclonal response typically seen when a superantigen is present.

In 2005, another theory was presented when researchers reported a novel human coronavirus in respiratory samples from 8 out of 11 patients with Kawasaki disease, but in only 1 of 22 control patients. This was called the New Haven coronavirus (HCoV-NH), named for its place of discovery. Unfortunately, this virus was later found to be the same as a previously reported coronavirus, HCoV NL-63, and multiple follow-up studies from both the United States and Asia have been unable to find an association between this virus and Kawasaki disease.

Studies have also attempted to link Kawasaki disease to various environmental causes (including pollutants, toxins, and heavy metals), but no conclusive evidence has been found. A significant overlap in symptoms has been observed in both Kawasaki disease and acrodynia (mercury toxicity), but a link...
between the 2 conditions has not been proven.

More recent immunologic research has revealed infiltration of immunoglobulin A (IgA) plasma cells in coronary artery walls, as well as in the respiratory tract, pancreas, and kidneys of patients with Kawasaki disease. In addition, CD8 lymphocytes have also been noted as part of the inflammatory response in coronary artery aneurysms. These patterns of inflammatory cell infiltration support the theory of an immune response to a microbial agent. Similar findings of IgA plasma cells in the respiratory tract are seen in respiratory illnesses such as influenza or respiratory syncytial virus, suggesting that the portal of entry for the microbial agent may be the respiratory tract. Further immunologic study has revealed the presence of intracytoplasmic inclusion (ICI) bodies within the ciliated bronchial epithelium. Similar inclusion bodies were not detected in control patients. A single monoclonal antibody detected approximately 85% of the ICI bodies in patients with fatal Kawasaki disease, suggesting that a single agent or closely related agents may be responsible for the disease. No structures representing known bacterial, fungal, or parasitic elements were identified within the ICI bodies.

Despite our improved understanding of the immune system activation that occurs in Kawasaki disease, it is still somewhat unclear how it leads to coronary artery aneurysms. Patients with Kawasaki disease have been found to have stimulation of the cytokine cascade and endothelial cell activation. It is this endothelial activation that leads to coronary arteritis and aneurysms, although the exact mechanism of how this occurs still needs to be elucidated. Various studies have shown elevated levels of matrix metalloproteinase-9 and vascular endothelial growth factor in Kawasaki disease patients, both of which may contribute to the development of aneurysms.

### Differential Diagnosis

When children present with Kawasaki disease in its classic form, it is not difficult for an astute emergency clinician to make the correct diagnosis. However, children presenting with < 5 days of fever, or those with incomplete Kawasaki disease may prove to be more of a diagnostic challenge. Fever is a very common complaint in pediatric patients, with a broad differential diagnosis. (See Table 1.) Accurately differentiating fever due to viral or bacterial illnesses from fever due to Kawasaki disease is critical. This is especially true since patient outcomes are significantly improved when patients are treated within 10 days of the onset of fever.

It is important to consider a variety of diagnoses when thinking about children with fever. (See Table 2, page 5.) Many fevers will be caused by nonspecific viral infections, and they will resolve on their own in time without long-term consequences. Rash associated with fever may be seen in viral exanthems, as well as in Epstein-Barr virus and acute streptococcal infections. Adenovirus may present quite similarly to Kawasaki disease, with symptoms such as fever, rash, conjunctival changes, mucous membrane changes, and adenopathy. A study by Barone et al noted that children with adenovirus are more likely to have purulent conjunctivitis or exudative pharyngitis compared to children with Kawasaki disease, although the study was small.

Rash, fever, and conjunctival changes are also seen in measles, and, although many children are vaccinated against this disease, several outbreaks have recently been reported. Fever can also be seen in drug hypersensitivity reactions, so a complete medication history should be taken at presentation.

### Prehospital Care

Many children with suspected Kawasaki disease will initially present to their pediatricians or be brought

### Table 1. Differential Diagnosis Of Prolonged Fever In Pediatric Patients

<table>
<thead>
<tr>
<th>Infectious</th>
<th>Endocrinologic</th>
</tr>
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<tbody>
<tr>
<td>Systemic viral infection</td>
<td>Thyrotoxicosis</td>
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<tr>
<td>Pneumonia</td>
<td></td>
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<tr>
<td>Urinary tract infection</td>
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<tr>
<td>Infective endocarditis</td>
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<tr>
<td>Osteomyelitis</td>
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<tr>
<td>Lyme disease</td>
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<tr>
<td>Rocky Mountain spotted fever</td>
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<tr>
<td>Human immunodeficiency virus</td>
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<td>Malaria</td>
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<table>
<thead>
<tr>
<th>Immunologic</th>
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<tbody>
<tr>
<td>Immunodeficiency</td>
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<table>
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<tr>
<th>Oncologic</th>
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<tbody>
<tr>
<td>Leukemia</td>
<td></td>
</tr>
<tr>
<td>Lymphoma</td>
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<tr>
<td>Other neoplasm</td>
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</table>

<table>
<thead>
<tr>
<th>Rheumatologic</th>
<th></th>
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<tbody>
<tr>
<td>Juvenile idiopathic arthritis</td>
<td></td>
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<tr>
<td>Systemic lupus erythematosus</td>
<td></td>
</tr>
<tr>
<td>Kawasaki disease</td>
<td></td>
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<tr>
<td>Familial Mediterranean fever</td>
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<table>
<thead>
<tr>
<th>Gastroenterologic</th>
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<tbody>
<tr>
<td>Inflammatory bowel disease</td>
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<table>
<thead>
<tr>
<th>Toxicologic</th>
<th></th>
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</thead>
<tbody>
<tr>
<td>Drug-related fever</td>
<td></td>
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</tbody>
</table>
to the hospital directly by parents. For children who are transported via emergency medical services, prehospital care should focus on supportive measures. Assessment of the airway, breathing, and circulation is of primary importance, with close monitoring of vital signs during transport. A few children may develop shock in association with Kawasaki disease. For these children, obtaining intravenous access and initiating fluid resuscitation takes precedence. When possible, these children should be transported to a facility with a pediatric intensive care unit.

**Emergency Department Evaluation**

**History**

The diagnosis of Kawasaki disease should be considered in all children presenting with prolonged fever, especially if it has been present for ≥ 5 days. It is important to note that symptoms may present sequentially rather than simultaneously, and, thus, some of the diagnostic symptoms may be resolved prior to presentation to the emergency department. When considering a diagnosis of Kawasaki disease, ask the caregivers about all recent symptoms, even if they are not currently present.

The presence of ≥ 5 days of fever is essential for the diagnosis of Kawasaki disease. In affected children, fevers are often high, commonly > 39°C (102.2°F), and potentially > 40°C (104°F). The fever may not respond to antipyretic drugs, and it generally persists for an average of 10 to 14 days without treatment, but may continue for as long as 3 to 4 weeks. Once treatment for Kawasaki disease is initiated, fever usually resolves within 48 hours.

**Physical Examination**

In addition to fever, the diagnostic criteria for complete Kawasaki disease include the presence of 4 out of 5 supporting signs and symptoms. (See Table 3, page 6.) These include conjunctival injection, oropharyngeal changes, polymorphous rash, extremity changes, and lymphadenopathy. Conjunctival injection is common, and it occurs in an estimated 80% to 90% of patients with Kawasaki disease. It is most commonly bilateral, painless, and nonpurulent. It typically involves the bulbar conjunctiva and is described as limbic sparing. (See Figure 1, page 6.)

Oropharyngeal mucous membrane changes are found in approximately 80% to 90% of patients with Kawasaki disease. These include obvious changes such as dry, fissured, or erythematous lips, which are easily observed. (See Figure 2, page 6.) However, changes can be more subtle. Children may develop strawberry tongue, in which the tongue becomes bright red with prominent papillae. Other changes may include nonexudative pharyngitis or erythema of the posterior oropharynx.

Polymorphous rash is present in approximately 80% to 90% of patients, and it often develops early in the course of the disease. A wide variety of cutaneous eruptions have been described, including rashes that appear as diffuse and macular, scarlatiniform, scaling plaques, or even resembling erythema multiforme. (See Figure 3, page 7.) The rash is less commonly urticarial, and almost never appears as vesicles or bullae. The rash is often found on the trunk or extremities, and may be present in the perineal area.

### Table 2. Comparison Of Kawasaki Disease And Other Similarly Presenting Diseases

<table>
<thead>
<tr>
<th>Disease</th>
<th>Features</th>
<th>First-Line Treatment</th>
<th>Complications</th>
</tr>
</thead>
</table>
| Kawasaki disease      | Fever (> 5 days) plus:                        | Intravenous immunoglobulin plus aspirin | - Coronary artery aneurysms
|                       | • Conjunctivitis                              |                                      | - Sudden cardiac death                            |
|                       | • Oropharyngeal changes                       |                                      |                                                  |
|                       | • Polymorphous rash                           |                                      |                                                  |
|                       | • Extremity changes                           |                                      |                                                  |
|                       | • Lymphadenopathy                             |                                      |                                                  |
| Adenovirus            | Fever plus:                                   | Supportive care                      | - Pneumonia                                      |
|                       | • Rash                                        |                                      |                                                  |
|                       | • Conjunctivitis                              |                                      |                                                  |
|                       | • Lymphadenopathy                             |                                      |                                                  |
|                       | • Pharyngitis                                 |                                      |                                                  |
| Group A Streptococcus | Fever plus:                                   | Antibiotics                          | - Rheumatic heart disease                        |
|                       | • Pharyngitis                                 |                                      | - Postinfection glomerulonephritis               |
|                       | • Rash                                        |                                      |                                                  |
| Measles               | Fever plus:                                   | Supportive care                      | - Pneumonia                                      |
|                       | • Rash                                        |                                      | - Otitis media with or without hearing loss      |
|                       | • Conjunctivitis                              |                                      | - Encephalitis                                   |
|                       | • Rhinorrhea                                  |                                      | - Subacute sclerosing panencephalitis            |
|                       | • Pharyngitis                                 |                                      |                                                  |
Interestingly, children who have previously received the bacillus Calmette-Guérin (BCG) vaccine will often have erythema, induration, or crusting at the site of injection. The mechanism for inflammation at this site is not well understood. It is known to be a very specific finding for Kawasaki disease, and it can be considered a strong indication of Kawasaki disease in the presence of incomplete or atypical criteria. This finding is rarely observed in the United States, as children in the United States do not routinely receive the BCG vaccine. However, the BCG vaccine is commonly used in other countries. Although it does not prevent pulmonary tuberculosis, the BCG vaccine is used to provide infants and young children with protection against tuberculosis, meningitis, and disseminated tuberculosis. In countries where tuberculosis is endemic, the vaccine is routinely given to neonates as soon as possible after birth. Therefore, emergency clinicians should be aware of this finding when evaluating children who were born in or who have lived in countries where the BCG vaccination is common.

Extremity changes are another criterion for Kawasaki disease, but a wide variety of changes can occur. Erythema and/or edema of the hands and feet may be present. The entirety of the hands and feet may be affected, but erythema may also be limited to the palms of the hands and the soles of the feet. Erythema is often sharply demarcated at the wrist and ankle. The hands and feet can be painful, and, in younger children, this may manifest as refusal to bear weight or use the affected limbs. Such changes occur in 80% to 90% of children during the acute phase of illness. Desquamation of the fingers and toes is also common in children. One recent study reported that 68% of children diagnosed with Kawasaki disease had desquamation of the fingers, toes, or both. However, this occurs late in the disease, often 2 to 3 weeks after the onset of illness, making it less useful for diagnosing Kawasaki disease in the acute phase.

Lymphadenopathy is the least common of the diagnostic criteria. It occurs in only 50% to 60% of patients with Kawasaki disease. The adenopathy of Kawasaki disease is most commonly unilateral and found in the cervical chain. Classic criteria cite the lymphadenopathy as consisting of ≥1 lymph node with a diameter of at least 1.5 cm.

Table 3. Features of Kawasaki Disease in Children*

<table>
<thead>
<tr>
<th>Diagnostic Criteria</th>
<th>Description</th>
<th>Time of Occurrence</th>
<th>Occurrence Rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fever</td>
<td>Duration ≥ 5 days</td>
<td>Acute phase</td>
<td>100%</td>
</tr>
<tr>
<td>Conunjunctivitis</td>
<td>Bilateral, painless, nonpurulent</td>
<td>Acute phase</td>
<td>80%-90%</td>
</tr>
<tr>
<td>Oropharyngeal changes</td>
<td>Erythema, pharyngitis, fissured lips, strawberry tongue</td>
<td>Acute phase</td>
<td>80%-90%</td>
</tr>
<tr>
<td>Polymorphous rash</td>
<td>Diffuse, often macular, may be scarlatiniform, possible perineal involvement</td>
<td>Acute phase</td>
<td>80%-90%</td>
</tr>
<tr>
<td>Extremity changes</td>
<td>May include erythema, edema, or desquamation</td>
<td>Acute phase and/or 2-3 weeks after onset</td>
<td>80%-90%</td>
</tr>
<tr>
<td>Lymphadenopathy</td>
<td>Cervical region, usually unilateral</td>
<td>Acute phase</td>
<td>50%-60%</td>
</tr>
</tbody>
</table>

*Complete Kawasaki disease is defined as fever for ≥5 days plus 4 of the 5 diagnostic criteria.

Arthritis and arthralgias can occur, usually early in the course. Arthritis may be oligoarticular or polyarticular. The cardiovascular examination in children with Kawasaki disease can reveal tachycardia, hyperdynamic precordium, murmurs, or a gallop. Gastrointestinal complaints are common, but are often nonspecific. Complaints may include abdominal pain, vomiting, or diarrhea, and may occur in up to one-third of patients. One study found that vomiting was associated with an increased risk of treatment resistance to IVIG, although this study was small and retrospective in nature. Nonspecific gastrointestinal complaints are common in viral illnesses, and so are not as useful in making a definitive diagnosis of Kawasaki disease. Less commonly, hepatomegaly and jaundice can occur. There have been rare reports of obstructive jaundice due to gall bladder hydrops and cholestasis associated with Kawasaki disease.

Increasingly, Kawasaki disease has been recognized as an etiology of shock in some children. These children often require intravenous fluids, pressors, and admission to a pediatric intensive care unit. Children presenting with Kawasaki disease with shock show a significantly higher inflammatory response than children with Kawasaki disease without shock, despite the time to presentation being equal. Kawasaki disease has also been indicated as a cause of multiple organ dysfunction syndrome. A retrospective review at one institution revealed that, over an 8-year period, 11 children had been admitted to the pediatric intensive care unit with shock and were later diagnosed with Kawasaki disease.

Outside of the diagnostic criteria, there are other symptoms that are commonly reported in patients with Kawasaki disease. Irritability is quite common. Although children who have viral illnesses may also be irritable, the irritability of children with Kawasaki disease is often more pronounced. Because of this, some theorize that the irritability may be the result of aseptic meningitis, which is found in approximately 25% of patients with Kawasaki disease. One study found that 50% of patients were described as irritable by their parents in the 10 days prior to the diagnosis of Kawasaki disease, and these patients were more likely to be younger in age. However, marked irritability has been noted in infants with normal cerebrospinal fluid studies, so further research in this area is needed to determine the cause of such pronounced irritability.

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**Figure 3. Diffuse Macular Rash**


**Figure 4. Erythema Of The Extremities**


**Figure 5. Desquamation Of Fingers**

This figure was published in Zitelli and Davis’ Atlas of Pediatric Physical Diagnosis, 6th edition, Torok K, Rosen P, Kawasaki Disease, pages 289-291, Copyright Elsevier 2012. Used with permission. To view a full-color version of this issue’s photos, scan the QR code with a smartphone or tablet or go to: www.ebmedicine.net/KawasakiDiseaseSigns.
Liver panel abnormalities can occur in patients with Kawasaki disease. Up to 40% of patients will show mild to moderate elevations in serum transaminases. An even higher number (approximately 60% to 67%) will have elevated plasma gamma-glutamyl transpeptidase. The mechanism behind liver function abnormalities in Kawasaki disease patients is not well understood. Theories for how this occurs include vasculitis within the liver vessels, toxin-mediated effects, oxidant stress, and inflammatory cell infiltration, but further research in these areas is needed.

**Lipid And Albumin Levels**
Plasma cholesterol and high-density lipoprotein levels can be markedly depressed in affected patients. Hypoalbuminemia is another common finding, and it has been associated with more severe disease. The pathophysiology of this finding is that microvascular inflammation leads to increased microvascular permeability, which, in turn, results in vascular leak, decreased serum levels of albumin, and, ultimately, peripheral edema.

**Sodium Levels**
Hyponatremia has also been documented in patients with Kawasaki disease. This was first described in the United States in a 1982 retrospective study of patients with Kawasaki disease, which found that 6 of 11 patients had hyponatremia at the time of hospital admission. Lim et al prospectively studied 50 patients with Kawasaki disease and found that 26% (13 patients) had hyponatremia during the acute phase of illness. Even higher rates of hyponatremia have been reported in some studies. Watanabe et al conducted a study of 146 Kawasaki patients, and they found that 44% of the patients had hyponatremia. It has been suggested that patients with hyponatremia have higher levels of inflammation overall, although the exact pathophysiology of hyponatremia in Kawasaki disease is not well understood.

**Brain Natriuretic Peptide Levels**
Elevated serum N-terminal brain natriuretic peptide (NTproBNP) levels have been investigated for use in diagnosing Kawasaki disease. Brain natriuretic peptide (BNP) is synthesized within myocytes as proBNP and is released into circulation during periods of ventricular stress. The N-terminal section is cleaved, releasing both the active BNP and the inactive NTproBNP into circulation. BNP has an extremely short half-life, being degraded in 5 to 10 minutes. NTproBNP has a significantly longer half-life than BNP (25 to 125 minutes) making it more easily detectable in circulation. Although NTproBNP levels are frequently elevated in children with Kawasaki disease, these levels vary with age, making it difficult to use this laboratory test in diagnosis. In practice, given the complexity of this marker, it is not routinely used.

**Urinalysis**
Sterile pyuria can be found in approximately one-third of affected patients. Early research reported
that urine obtained via suprapubic tap was normal, indicating urethritis as the primary cause of pyuria. However, more recent research indicates that upper urinary structures, including the bladder and kidney, may be involved.

**Lumbar Puncture**

Although lumbar puncture is not routinely recommended for evaluation of Kawasaki disease, it is occasionally performed. Of those children who undergo this procedure, between one-third and one-half will show signs of cerebrospinal fluid pleocytosis. This includes a predominance of mononuclear cells and normal cerebrospinal fluid protein and glucose levels.

**Cardiovascular Testing**

Children with Kawasaki disease may have changes on electrocardiography (ECG), although these are often nonspecific. Changes may include arrhythmias, nonspecific T-wave changes, PR-interval prolongation, or QT-interval prolongation. These ECG findings are most likely to be found during the acute phase and in the first month following diagnosis, and they frequently normalize after recovery.

The most critical imaging to obtain in children with Kawasaki disease is echocardiography. This is usually performed transthoracically, and should be done in all patients with a definitive or suspected diagnosis of Kawasaki disease. Ideally, initial echocardiography should be performed on the day of diagnosis. Echocardiography can be helpful in formally diagnosing cases of incomplete Kawasaki disease. It is noninvasive and does not involve radiation. It is both highly sensitive and specific for detecting coronary artery lesions. Guidelines from the AHA and the AAP recommend prompt echocardiography once Kawasaki disease is diagnosed or suspected, although delays in obtaining imaging should not delay initiation of treatment. The AAP stresses the importance of this examination being performed by an experienced echocardiographer in order to best visualize all segments of the coronary arteries and accurately assess vessel diameter. Ectasia of the arteries is defined as vessels that are larger than normal without segmental aneurysms. The AHA defines aneurysms as small if they are < 5 mm in diameter, medium if the diameter is 5 to 8 mm, and giant if the diameter is > 8 mm. The most commonly affected vessel is the proximal segment of the left anterior descending artery, followed by the proximal right coronary artery, left main coronary artery, and the left circumflex artery, respectively. The least commonly affected vessel is the distal segment of the right coronary artery.

It should be noted that a normal initial echocardiogram should not be used to exclude the diagnosis of Kawasaki disease, especially if physical examination findings and laboratory tests are consistent with the diagnosis. Early studies estimated the prevalence of coronary artery lesions to be 2% to 4% in patients treated within 10 days of the onset of fever. However, more recent studies have shown much higher rates. Tse et al examined echocardiograms from 178 patients with Kawasaki disease, noting that 34% had lesions on initial evaluation. Baer et al studied initial echocardiograms of 100 patients with Kawasaki disease, and they found that 44% of patients had either ectasia or aneurysms present at the time of the initial evaluation. The dramatic increase in lesions at the time of diagnosis is thought to be related to changing the definition of lesions from absolute measurements to a measurement that is adjusted for body surface area.

Perivascular echocardiographic brightness (PEB) has been proposed as a criterion for diagnosing incomplete Kawasaki disease in some patients. Prior research suggested that perivascular brightness was a predictor of coronary artery aneurysms. However, PEB is somewhat subjective and dependent on the individual echocardiographer. A more recent attempt to quantitatively define PEB and its use in diagnosing incomplete Kawasaki disease did not confirm PEB to be a reliable diagnostic criterion.

In addition to coronary artery lesions, children can develop other cardiac problems, and initial echocardiography should assess for such problems. Myocarditis is common during the acute phase of the illness, and decreased ventricular contractility can occur. As many as 50% to 70% of patients will have wall motion abnormalities related to myocardial inflammation, although this seems to be independent of the risk of coronary artery aneurysms. Pericarditis, valvular regurgitation, and pericardial effusion have also been documented.

**Risk Classification**

Although several risk classification criteria have been proposed, the most commonly applied in the United States are those proposed by Beiser et al. These criteria are generally used to predict which patients are at a high risk of developing coronary artery aneurysms among patients who were treated with IVIG within 10 days of the onset of fever. The scoring system uses baseline neutrophil and band counts, hemoglobin, platelet count, and temperature on the day after the patient receives IVIG to categorize patients into high-risk and low-risk categories. The negative predictive value of the score appears to be appropriate, as no patients in the low-risk group developed coronary artery aneurysms. However, the positive predictive value of the tool is relatively inadequate, with only 13% of high-risk patients developing coronary artery aneurysms. Thus, although this may be a helpful tool for predicting low-risk patients, it should not be used to guide treatment or follow-up decisions.

Egami et al devised a scoring system to predict treatment resistance to IVIG. Using multivariate logis-
Clinical Pathway For Emergency Department Management Of Kawasaki Disease

Fever for ≥ 5 days?
- Consider alternative diagnosis
- Discharge if appropriate
- Recommend follow-up with primary care physician if fever persists

≥ 4 diagnostic criteria present?
- Conjunctivitis
- Mucous membrane changes
- Polymorphous rash
- Extremity changes
- Cervical lymphadenopathy

Obtain laboratory testing
- CRP/ESR
- CBC
- ALT
- Albumin
- Urinalysis

Laboratory tests consistent with Kawasaki disease? (eg, CRP ≥ 3.0 mg/dL and ESR ≥ 40 mm/h)
- Start treatment with IVIG and high-dose ASA (Class I)
- Obtain echocardiogram expeditiously (Class II)

Fever resolved within 48 h?
- Consider alternative diagnosis
- Monitor for fever for 2-3 days
- Recommend follow-up with primary care physician if fever persists
- If suspicion for Kawasaki disease remains high, consider obtaining an echocardiogram

Consider other treatment options
- IVIG plus corticosteroids (Class II)
- Infliximab (Class II)
- Abciximab (Class III)

2-3 diagnostic criteria present?
- Conjunctivitis
- Mucous membrane changes
- Polymorphous rash
- Extremity changes
- Cervical lymphadenopathy

Evaluate for incomplete Kawasaki disease (Class II)

Consider alternative diagnosis

Abbreviations: ALT, alanine aminotransferase; ASA, acetyl salicylic acid (aspirin); CBC, complete blood count; CRP, C-reactive protein; ED, emergency department; ESR, erythrocyte sedimentation rate; IVIG, intravenous immunoglobulin.

Class Of Evidence Definitions

Each action in the clinical pathways section of Pediatric Emergency Medicine Practice receives a score based on the following definitions.

Class I
- Always acceptable, safe
- Definitely useful
- Proven in both efficacy and effectiveness

Level of Evidence:
- One or more large prospective studies are present (with rare exceptions)
- High-quality meta-analyses
- Study results consistently positive and compelling

Class II
- Safe, acceptable
- Probably useful

Level of Evidence:
- Generally higher levels of evidence
- Nonrandomized or retrospective studies: historic, cohort, or case control studies
- Less robust randomized controlled trials
- Results consistently positive

Class III
- May be acceptable
- Possibly useful
- Considered optional or alternative treatments

Level of Evidence:
- Generally lower or intermediate levels of evidence
- Case series, animal studies, consensus panels
- Occasionally positive results

Indeterminate
- Continuing area of research
- No recommendations until further research

Level of Evidence:
- Evidence not available
- Higher studies in progress
- Results inconsistent, contradictory
- Results not compelling

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NO

YES

NO

YES

NO

YES

NO

YES

NO

YES
tic regression, they found that age, total days of symptoms, platelet count, CRP, and alanine aminotransferase can be used to predict which patients are likely to be resistant to IVIG therapy. In the initial study, the score had a sensitivity of 78% and a specificity of 76%. Although this may be helpful in anticipating treatment resistance, it was designed for use in Japan, so treatment resistance patterns will vary. Several recent studies have investigated the use of the Egami score in North America. The studies found that, when applied to a North American cohort, the Egami score had adequate specificity, but a low sensitivity for predicting IVIG resistance. Thus, this scoring system may be inadequate for detecting patients at risk of treatment resistance in the North American population.

Incomplete Kawasaki Disease

Within the literature, there is some debate regarding the diagnosis of incomplete Kawasaki disease. Generally, a patient is diagnosed with incomplete disease if Kawasaki disease is suspected but fails to fulfill the conventional diagnostic criteria. These patients typically display prolonged fever in addition to 2 to 3 of the principal criteria, failing to meet the more traditional definition of at least 4 principal criteria. In these situations, emergency clinicians should be suspicious of Kawasaki disease. It is important to note that laboratory findings should be supportive of the diagnosis of Kawasaki disease, if no alternative diagnosis is found in the course of the evaluation. By most estimates, approximately 20% of patients with Kawasaki disease will likely fall into the category of incomplete disease.

Prior research indicates that children with incomplete Kawasaki disease may be at higher risk for the development of coronary artery aneurysms. However, it is not clear whether this relates to the disease itself or to the delay in diagnosis that often occurs in cases of incomplete disease. Sudo et al examined a large cohort of patients with Kawasaki disease in Japan to study the epidemiologic differences between patients with complete versus incomplete forms of Kawasaki disease. Of the more than 23,000 patients in the study, 80% fell into the category of complete disease, and the other 20% fell along a spectrum of having 1 to 4 supporting criteria. The patients with incomplete Kawasaki disease had an increased incidence of coronary artery aneurysms compared to the typical Kawasaki disease patients (13.1% vs 8.8%). It should be noted that these patients also tended to be hospitalized later in the course of their disease and were less likely to receive IVIG than the children with more typical disease. The authors attributed the higher incidence of aneurysms to the delay in diagnosis and treatment, as well as to the increased use of echocardiography for establishing a diagnosis of Kawasaki disease.

Further, a meta-analysis found that there was an increased risk of coronary artery aneurysms in incomplete disease, with an odds ratio of 1.447 (95% confidence interval [CI], 1.158-1.808; P = .001). This included analysis of > 20 studies, for a total of 4504 Kawasaki disease patients and 32,519 controls. However, the analysis did not address the issue of delay in diagnosis and treatment.

A second large study reported the differences between complete and incomplete Kawasaki disease at a single center in North America. Manlhiot et al retrospectively reviewed 955 patients with Kawasaki disease, finding that 77% presented with complete Kawasaki disease while the remaining 23% fell into the incomplete category. Although this study also showed that the time to diagnosis and treatment was delayed for patients with incomplete disease, there was no significant difference in the rate of development of coronary artery aneurysms between the 2 groups (13% vs 11%).

The evidence of incomplete Kawasaki disease as an independent predictor of aneurysm development is complicated by the difficulty in making a diagnosis of incomplete Kawasaki disease. It is well documented that a longer duration of fever and delay in treatment increase the risk of aneurysm development. Thus, emergency clinicians who suspect Kawasaki disease should proceed with further evaluation, including laboratory testing and echocardiography. The AHA reports that conventional diagnostic criteria should be considered as a guideline for Kawasaki disease, and that all patients with fever for ≥ 5 days plus 2 to 3 criteria should be promptly evaluated. The AAP and AHA provide a framework for decisions regarding the evaluation of children with suspected incomplete Kawasaki disease.

Treatment

Initial Treatment

Since the etiology of Kawasaki disease remains unclear, the goals of treatment focus on the prevention of coronary artery aneurysm development. Early identification and treatment of Kawasaki disease has been shown to reduce the development of coronary artery aneurysms. Treatment should be started as soon as a diagnosis of Kawasaki disease is made. Current recommendations suggest treatment should be given within 10 days of the onset of fever, and, ideally, within 7 days of the onset of fever. Initial treatment in the United States generally includes IVIG in combination with high-dose aspirin.

Intravenous Immunoglobulin

Evidence for the use of IVIG in Kawasaki disease is strong. The use of IVIG in Kawasaki disease began in the 1980s. Several randomized controlled studies during that time showed a significant reduction in coronary artery aneurysm development in children receiving IVIG plus aspirin compared to aspirin alone. Newburger et al used an IVIG dose of 400 mg/kg/day for 4 days. A follow-up randomized controlled study performed by Egami and colleagues showed that the same dose for 5 days had improved recovery from fever but failed to prevent coronary artery aneurysm development. The III study showed that the use of IVIG in the United States generally includes IVIG in combination with high-dose aspirin.

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several years later showed that a single infusion of 2 g/kg of IVIG was more effective at preventing aneurysms than the traditional 4-dose regimen.\(^5\) This infusion is generally given over a period of 10 to 12 hours. More recently, a meta-analysis of randomized controlled trials has shown that treatment with IVIG compared to placebo significantly reduced the risk of coronary artery aneurysms at 30 days.\(^7\) In addition, the single, higher dose of IVIG was associated with a reduction in the duration of fever when compared with the multiple-dose regimen.\(^5\)\(^7\)

The efficacy of IVIG for the treatment of Kawasaki disease is well established, although the mechanism of action is not clearly understood. IVIG is thought to work primarily through a generalized anti-inflammatory action. Several mechanisms have been proposed, including regulation of Fc-receptor function, suppression of proinflammatory cytokine production, inhibition of the complement system, and inhibition of tumor necrosis factor (TNF) production.\(^1\) However, strong evidence to support these theories is still needed.

IVIG is considered to be a safe treatment, although it is not without side effects. Common side effects of the infusion include headaches, fever, chills, myalgias, nausea, vomiting, changes in blood pressure, and tachycardia.\(^7\) If such side effects occur, they can generally be managed by slowing the infusion and by providing supportive care. Serious side effects are uncommon, but can include acute renal failure, aseptic meningitis, neutropenia, anaphylaxis, and autoimmune hemolytic anemia.\(^7\) In addition, IVIG is also a pooled-blood product and thus carries the risk of transfusion-related infections as well.

**Aspirin**

Aspirin has long been used as part of the treatment for Kawasaki disease. It is theorized that since aspirin has anti-inflammatory effects as well as antiplatelet effects, it should be useful in the treatment of Kawasaki disease. However, there is insufficient evidence in the literature to show that aspirin at any dose reduces the incidence of coronary artery aneurysms.\(^5\) A Cochrane review of the literature identified only 1 randomized controlled trial examining the use of aspirin in Kawasaki disease. This single study failed to demonstrate an added benefit of aspirin plus IVIG compared to IVIG alone to reduce the development of coronary artery lesions.\(^7\)

Given the lack of randomized controlled trials, the Cochrane review was unable to support or negate the use of aspirin in the treatment of Kawasaki disease.\(^7\) Despite this, many centers continue to use aspirin in conjunction with IVIG.

Without sufficient evidence for its use, there are no consistent recommendations on aspirin dosing. In North America, aspirin is generally started at high doses (80-100 mg/kg/day) and divided into 4 doses. The dose is then decreased to 3 to 5 mg/kg/day after defervescence.\(^5\)\(^8\) In Japan, more-moderate doses of aspirin (30-50 mg/kg/day) are given during the febrile phase of the illness.\(^1\) Low-dose aspirin is then continued for 6 to 8 weeks until follow-up echocardiography is normal. For children who develop coronary artery lesions, low-dose aspirin may be continued indefinitely for its antiplatelet effects. Despite the lack of evidence to support the use of aspirin, the AHA and the AAP continue to recommend its use in combination with IVIG.\(^5\)

**Corticosteroids**

The use of corticosteroids as a routine part of a treatment regimen for Kawasaki disease is still under debate. This treatment dates back to before the use of IVIG as primary treatment. In 1979, Kato et al published their research on the treatment of Kawasaki disease, exploring 5 different treatment options, including the use of prednisone as monotherapy. The research showed a substantially higher rate of coronary artery aneurysms in children treated with corticosteroids alone (prednisolone 2-3 mg/kg/day) compared to aspirin alone (64.7% vs 11%).\(^8\) The prednisolone group also had significantly higher rates of coronary artery lesions compared to those treated with a combination of steroids plus aspirin or no treatment. However, this study had significant limitations. It was a relatively small sample, with a total of 92 patients. There was no randomization, and the size of each treatment group varied significantly, with some groups having as few as 7 patients. Despite these limitations, this study led to the near-abandonment of corticosteroids as a part of the treatment for Kawasaki disease.

More recently, the question of using corticosteroids in combination with IVIG for primary treatment has been explored. Newburger et al conducted a multicenter, randomized, placebo-controlled, double-blinded study in the United States to compare standard therapy (IVIG plus high-dose aspirin) to standard therapy plus methylprednisolone.\(^8\) The findings showed no significant difference in the number of days spent in the hospital, the duration of fever, rates of initial treatment failure, or the incidence of coronary artery aneurysms. Based on this evidence, they concluded that corticosteroids are not useful as a routine adjunct to IVIG in standard-risk Kawasaki patients.

There is continued interest in the use of steroids for patients who are considered to be at a high risk of treatment resistance. A randomized trial from a single institution in Japan explored the use of standard treatment plus corticosteroids in patients predicted to be at a high risk of refractory disease.\(^3\) A total of 48 patients out of 122 were predicted to have Kawasaki disease that was refractory to treatment, and they were randomized to receive standard therapy of IVIG plus aspirin or standard therapy of IVIG plus a single dose of intravenous methylprednisolone (30 mg/kg). Significantly more patients in
the standard treatment plus methylprednisolone group had a prompt defervescence compared to patients who received standard therapy alone (86.4% versus 23.1%). In addition, the group that received steroids had a 9% rate of coronary artery aneurysms on echocardiogram at 1 month compared to 39% in the standard treatment group. This study, performed by Ogata et al, was well designed, but limited in its application due to its small size.\textsuperscript{82}

A second Japanese study by Kobayashi et al used a larger, multicenter approach.\textsuperscript{83} As in the prior study, this one addressed the use of corticosteroids as an adjunct to the standard initial therapy for patients classified as being at high risk. In this case, patients were randomized to standard treatment of IVIG (123 patients) or standard treatment plus steroids (125 patients). The steroid regimen included intravenous prednisolone (2 mg/kg/day in divided doses) for 5 days followed by a 15-day oral prednisolone taper. The results showed only 3% of patients treated with corticosteroids developed coronary artery aneurysms, compared to 23% of patients who received the standard treatment.

It should be noted that the Newburger et al study did not separate patients into risk categories, but used a general group of patients with Kawasaki disease.\textsuperscript{81} In comparison, both the Ogata et al and Kobayashi et al studies examined only patients characterized as high risk (by applying the Egami criteria). This suggests that, although corticosteroids do not need to be given to all Kawasaki patients, there may be a select group of high-risk patients who would benefit from the addition of corticosteroids to the standard therapy.

### Treatment Resistance

Although the standard therapy of IVIG plus high-dose aspirin is effective for most patients with Kawasaki disease, it is estimated that approximately 10% to 20% of patients will fail to respond to this therapy.\textsuperscript{3} Second-line therapy usually consists of retreatment with IVIG, potentially in combination with corticosteroids. Persistent fever and elevations of inflammatory markers place patients at a high risk of developing coronary artery aneurysms and other cardiac complications. Therefore, the choice of treatment for resistant disease becomes important.

#### Infliximab

Infliximab (Remicade\textsuperscript{®}) is a monoclonal antibody directed against tumor necrosis factor alpha-1 (TNF-alpha) and blocks its function. Infliximab was theorized to work in Kawasaki disease, as TNF-alpha levels are known to be elevated in patients with this disease.\textsuperscript{73} To explore the effectiveness of infliximab as a treatment for recalcitrant Kawasaki disease, Burns et al published a case series of 16 patients treated with infliximab after they failed to respond to IVIG.\textsuperscript{84} In this series, 14 patients were treated with 5 mg/kg of infliximab and 2 patients were treated with 10 mg/kg. Of the 16 patients who were febrile prior to treatment with infliximab, 13 had cessation of fever after treatment. The limitations of this study include its small size and retrospective nature. However, given the overall favorable response to treatment in these patients, the authors of the study concluded that further research was warranted.

A follow-up study by Burns et al investigated the use of infliximab for resistant Kawasaki disease using a multicenter, randomized, prospective approach.\textsuperscript{85} This study compared infliximab 5 mg/kg to a second dose of IVIG 2 g/kg in patients who had persistent fever after an initial dose of IVIG. In this study, 8 of 12 patients given a second dose of IVIG had prompt resolution of fever compared to 11 of 12 patients treated with infliximab. There were no differences in adverse outcomes between the 2 groups. Although further research is needed, infliximab is generally safe and should be considered as an alternative therapy in treatment-resistant disease.

#### Abciximab

Abciximab (ReoPro\textsuperscript{®}), another monoclonal antibody, has been investigated for use in patients who develop aneurysms. Abciximab inhibits the glycoprotein IIb/IIIa inhibitor. It has previously been used in adults to prevent thrombotic complications and promote vascular remodeling in acute coronary disease.\textsuperscript{86} Case reports have shown improvement in coronary artery aneurysms in children treated with abciximab. A retrospective study compared 9 patients with coronary artery aneurysms who received standard therapy to 6 patients with similar lesions who received standard therapy plus abciximab. In this study, standard therapy was defined as IVIG 2 g/kg plus aspirin 80 to 100 mg/kg/day. The patients who received abciximab had a significantly higher rate of resolution of their aneurysms compared to the patients who received standard therapy (68% vs 37%).\textsuperscript{86} Although these results are encouraging, the study was very small and was performed in a retrospective fashion. Further study on the use of abciximab for Kawasaki disease is needed, preferably in the form of prospective trials.

### Special Populations

In addition to having a propensity to occur in certain populations, Kawasaki disease has been noted to be affected by genetics. Children whose parents had Kawasaki disease have a slightly higher risk of developing the disease.\textsuperscript{87} Siblings of children affected by Kawasaki disease are at significantly higher risk for developing Kawasaki disease themselves. Familial studies in Japan show siblings of affected children to have 10 times the relative risk for development of the disease.\textsuperscript{88} Such cases were also more likely to have recurrent disease.\textsuperscript{87}
Researchers in North America studied clusters of families with multiple cases of Kawasaki disease in siblings or cousins. The researchers obtained information from 2 hospitals, as well as from families who contacted a Kawasaki disease research program. They were able to identify 9 families in which 2 siblings were diagnosed with Kawasaki disease, for a total of 18 affected children. They also identified 9 other families with 24 affected children. Many of these cases were separated by both time and geography, so the researchers were unable to identify a clear pattern of inheritance. Despite this, clinicians should be aware of the tendency for Kawasaki disease to run in families, as this may lead to a more timely diagnosis and reduce the risk of coronary artery aneurysm development.

Emerging Research

To date, there is no definitive test for Kawasaki disease, leading to potentially dangerous delays in diagnosis and treatment. Prior research has shown that delays in diagnosis increase the risk of complications (including coronary artery aneurysms) and mortality. To this end, several researchers have been working to find a more definitive laboratory test to help emergency clinicians make the diagnosis of Kawasaki disease.

Kentsis et al have been studying urine proteomics in an attempt to find a sensitive diagnostic test for making the diagnosis of Kawasaki disease. The study looked at a total of 107 patients, of whom 53 had a diagnosis of Kawasaki disease and 54 had Kawasaki-like symptoms, but a different final diagnosis (such as viral illness). The researchers identified that filamin C, which is associated with myocardial and endothelial damage, and meprin A, which is an immune modulator, were present in high concentrations in the urine of patients with Kawasaki disease compared to patients with other febrile diagnoses. This was true for both the complete and incomplete forms of Kawasaki disease. In addition, the diagnostic performance of these tests was superior to the diagnostic performance of ESR, CRP, or a combination of the 2 tests. In addition, the levels of meprin A and filamin C present in the urine were found to decline after treatment with IVIG. Future research is needed to validate these findings.

Reindel et al investigated serum periostin levels as a possible biomarker for diagnosing Kawasaki disease. The authors hypothesized that, since periostin plays a role in vascular and cardiac damage, it might be elevated in patients with Kawasaki disease. In this study, the researchers compared serum periostin levels of 30 control patients (15 afebrile controls, 15 febrile controls) to the periostin levels of 27 patients with Kawasaki disease (12 with coronary artery aneurysms, 15 without coronary artery aneurysms). The mean periostin level in all control patients was 5647 ng/mL, which was significantly different from the mean periostin level of 42,549 ng/mL in all patients with Kawasaki disease ($P = .0086$). Although promising, this was a small study, and the results need to be validated.

Displacement

Patients with suspected Kawasaki disease, either complete or incomplete, should be admitted to an appropriate pediatric inpatient facility. Treatment for Kawasaki disease involves, at a minimum, an infusion of IVIG, which is typically given over a period of hours. Side effects of this medication may include fever, headache, urticaria, nausea, vomiting, and blood pressure instability. Although uncommon, anaphylaxis, Stevens-Johnson syndrome, and nephrotoxicity have been reported, so it is in the best interest of the patient to be admitted for monitoring during treatment. In addition, most hospitals will keep children in the hospital until the fever resolves, as children with ongoing fevers may be resistant to traditional treatments. Ideally, children should be admitted to a unit with the capability for pediatric echocardiography and access to a pediatric cardiologist for complete evaluation of the heart and coronary artery aneurysms. Children who present with myocarditis, impaired ventricular function, or giant coronary artery aneurysms in the setting of acute Kawasaki disease should be managed at a facility with a pediatric cardiology service and pediatric intensive care unit.

Children with Kawasaki disease can be discharged after completion of therapy provided there is resolution of fever. High-dose aspirin (80-100 mg/kg/day in the United States) is generally continued for 48 to 72 hours after defervescence. All children with Kawasaki disease should be discharged on low-dose aspirin (3-5 mg/kg/day), which should be maintained for a minimum of 6 to 8 weeks following diagnosis. Echocardiography should be repeated at 2 weeks post diagnosis, and then again at 6 to 8 weeks post diagnosis. Aspirin can be discontinued at that time if no coronary artery abnormalities are found on echocardiography.

Recurrence rates of Kawasaki disease are low. Large epidemiologic studies done in Japan estimate a recurrence rate of 3% to 4%. Similar studies estimate a recurrence rate of 2% in the North American population. Recurrence tends to be more common in children aged < 3 years of age at the time of the initial episode. Emergency clinicians need to be aware of the risk of recurrence when evaluating a patient with a history of Kawasaki disease.

Long-Term Prognosis

Since Kawasaki disease was first described more than 40 years ago, outcomes have improved significantly. With proper identification and treatment, the incidence of coronary artery lesions has declined
to approximately 3% to 5%, from an initial rate of 25% to 30% previously.\cite{95} Long-term management of children following diagnosis of Kawasaki disease depends largely on whether or not they develop coronary artery lesions. Risk stratification schemes exist to help guide follow-up. These can be found in the AHA guidelines on Kawasaki disease, and they are summarized in Table 4.

Children who are promptly diagnosed and treated and who do not develop coronary artery lesions are considered at low risk. These children are thought to have long-term cardiac outcomes similar to the population without Kawasaki disease.\cite{7} These patients are generally treated with a 6- to 8-week course of antiplatelet therapy, and are followed by cardiology every 3 to 5 years after the first year. Despite proper recognition and treatment, a small percentage of children develop coronary artery aneurysms. It is estimated that 50% to 70% of such lesions will regress within 1 to 2 years.\cite{5,6} Coronary arteries may develop areas of stenosis, and these lesions are frequently progressive. Depending on the type, location, and size of the lesion, these children may require long-term antiplatelet or anticoagulation therapy and frequent evaluations by a pediatric cardiologist. (See Table 4, page 15.)

Mortality rates for Kawasaki disease are generally low, and they are currently estimated to be 0.01% to 0.2% currently.\cite{94} Mortality peaks between 15 and 45 days after the onset of disease, and it is most often due to coronary artery thrombosis.\cite{5,94} Myocardial infarction can occur secondary to thrombotic occlusion of an aneurysm or stenotic vessel, and the highest risk of this occurs within the first year after diagnosis.\cite{5} Other causes of death include congestive heart failure, arrhythmias, or coronary artery rupture.\cite{94} As children with Kawasaki disease age, there is a recognized risk of late myocardial infarction.

<table>
<thead>
<tr>
<th>Risk Level (I-V)</th>
<th>Pharmacological Therapy</th>
<th>Physical Activity</th>
<th>Follow-Up and Diagnostic Testing</th>
<th>Invasive Testing</th>
</tr>
</thead>
<tbody>
<tr>
<td>I (no coronary artery changes at any stage of illness)</td>
<td>None beyond first 6-8 wk</td>
<td>No restrictions beyond first 6-8 wk</td>
<td>Cardiovascular risk assessment, counseling at 5-y intervals</td>
<td>None recommended</td>
</tr>
<tr>
<td>II (transient coronary artery ectasia, disappears within first 6-8 wk)</td>
<td>None beyond first 6-8 weeks</td>
<td>No restrictions beyond first 6-8 wk</td>
<td>Cardiovascular risk assessment, counseling at 5-y intervals</td>
<td>None recommended</td>
</tr>
<tr>
<td>III (1 small-medium coronary artery aneurysm/major coronary artery)</td>
<td>Low-dose aspirin (3-5 mg/kg/day), at least until aneurysm regression is documented</td>
<td>For patients aged &lt; 11 y, no restriction beyond first 6-8 wk; patients aged 11-20 y, physical activity guided by biennial stress test, evaluation of myocardial perfusion scan; contact or high-impact sports discouraged for patients taking antiplatelet agents</td>
<td>Annual cardiology follow-up with echocardiogram + ECG, combined with cardiovascular risk assessment, counseling; biennial stress test/evaluation of myocardial perfusion scan</td>
<td>Angiography, if noninvasive test suggests ischemia</td>
</tr>
<tr>
<td>IV (large or giant coronary artery aneurysm, or multiple or complex aneurysms in same coronary artery, without obstruction)</td>
<td>Long-term antiplatelet therapy or warfarin (target INR 2-2.5) or low–molecular-weight heparin (target anti-factor Xa level 0.5-1 U/mL), should be combined in giant aneurysms</td>
<td>Contact or high-impact sports should be avoided because of risk of bleeding; other physical activity recommendations guided by stress test/evaluation of myocardial perfusion scan outcome</td>
<td>Biannual follow-up with echocardiogram + ECG; annual stress test/evaluation of myocardial perfusion scan</td>
<td>First angiography at 6-12 mo or sooner, if clinically indicated; repeated angiography if noninvasive test, clinical, or laboratory findings suggest ischemia; elective repeat angiography under some circumstances</td>
</tr>
<tr>
<td>V (coronary artery obstruction)</td>
<td>Long-term low-dose aspirin; warfarin or low-molecular-weight heparin if giant aneurysm persists; consider use of low-molecular-weight consumption</td>
<td>Contact or high-impact sports should be avoided because of risk of bleeding; other physical activity recommendations guided by stress test/myocardial perfusion scan outcome</td>
<td>Biannual follow-up with echocardiogram and ECG; annual stress test/evaluation of myocardial perfusion scan</td>
<td>Angiography recommended to address therapeutic options</td>
</tr>
</tbody>
</table>

Abbreviations: ECG, electrocardiogram; INR, international normalized ratio.

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1. “I thought the child had a viral illness, so I treated her with antipyretics and discharged her.”

Fevers are common in children, and many children with fever will likely have a viral illness. Many of the other symptoms of Kawasaki disease are found in viral illnesses, such as rash and conjunctivitis. However, Kawasaki disease should be considered in all patients with parental report of prolonged fever. Failure to recognize and treat Kawasaki disease in a timely manner can have catastrophic consequences.

2. “The child did not meet the criteria for all of the symptoms on presentation to the ED, so I thought she could not have Kawasaki disease.”

The diagnosis of incomplete Kawasaki disease can be difficult. It is necessary to have a high index of suspicion with regard to Kawasaki disease in children with a fever lasting ≥ 5 days. It is important to note that symptoms may present sequentially rather than simultaneously, and, thus, some of the diagnostic symptoms may be resolved prior to presentation to the ED. If a patient has fever plus 2 to 3 of the diagnostic criteria, further evaluation with laboratory studies and possibly an echocardiogram is warranted to evaluate for Kawasaki disease. By most estimates, approximately 20% of patients with Kawasaki disease will fall into the category of incomplete disease.

3. “I suspected Kawasaki disease, but I was unsure of the diagnosis, so I waited for the laboratory tests to return before beginning any treatment.”

There is no single diagnostic test to confirm the diagnosis of Kawasaki disease. Diagnosis centers on the presence of the criteria for Kawasaki disease, which include fever for at least 5 days, plus 4 of 5 of the following key criteria: conjunctival injection, oral mucosal changes, polymorphous rash, distal extremity changes, and cervical lymphadenopathy. Treatment should not be delayed if the diagnosis can be confirmed by the history and physical examination. Early identification and treatment of Kawasaki disease has been shown to reduce the development of coronary artery aneurysms.

4. “I was unsure of the diagnosis, so I waited to start treatment with IVIG.”

Delays in making the diagnosis and delays in starting treatment significantly increase the risk of developing coronary artery aneurysms. If the emergency clinician has a high suspicion for Kawasaki disease and laboratory values support the diagnosis, treatment should be initiated promptly. Echocardiogram should be performed as soon as possible, but this should not delay treatment.

5. “I know that the guidelines recommend echocardiography for assessment of coronary arteries when the suspicion is high for Kawasaki disease, so I delayed treatment to obtain the imaging.”

Ideally, initial echocardiography should be performed on the day of diagnosis. Guidelines from the AHA and the AAP recommend prompt echocardiography once Kawasaki disease is diagnosed or suspected, although delays in obtaining imaging should not delay initiation of treatment.

6. “The patient failed to respond to initial standard treatment of IVIG and aspirin, and I didn’t know what to choose next.”

Although the standard therapy of IVIG plus high-dose aspirin is effective for most patients with Kawasaki disease, it is estimated that approximately 10% to 20% of patients will fail to respond to this therapy. Second-line therapy usually consists of retreatment with IVIG, potentially in combination with corticosteroids. Although further research is needed, infliximab is generally safe and should be considered as an alternative therapy in treatment-resistant disease.

7. “I ordered an echocardiogram for the patient, but there were no findings, so I ruled out Kawasaki disease.”

It should be noted that a normal initial echocardiogram should not be used to exclude the diagnosis of Kawasaki disease, especially if physical examination findings and laboratory tests are consistent with the diagnosis.
Case Conclusion

After evaluating this 3-year-old patient, you had some concerns that the patient had incomplete Kawasaki disease. Review of the diagnostic criteria revealed that this patient had the characteristic criteria of 5 days of fever, and met 3 of the supporting diagnostic criteria (conjunctivitis, oral mucous membrane changes, and polymorphous rash). You discussed this possibility with the mother, and proceeded with laboratory workup. The patient’s laboratory tests showed a white blood cell count of 18,900/mm$^3$, but normal hemoglobin of 12.3 g/dL and normal platelet count of 320,000/mm$^3$. She was mildly hyponatremic, with a sodium level of 132 mEq/L, although the remainder of her electrolyte levels were normal. Her inflammatory markers were extremely elevated, with a CRP of > 25 mg/dL and an ESR of 87 mm/h. She was mildly hypoalbuminemic, with an albumin level of 2.7 g/dL. Her liver enzymes revealed a normal AST of 54 U/L, but an elevated ALT of 131 U/L. Her urinalysis was positive for leukocyte esterase and negative for nitrites. Urine also had 10 to 25 WBC/HPF and 0 RBC/HPF. Blood and urine cultures remained negative. These laboratory results were consistent with a diagnosis of incomplete Kawasaki disease, so you admitted the patient for treatment. You consulted cardiology to obtain an echocardiogram. In the meantime, she was started on IVIG 2 g/kg and high-dose aspirin of 100 mg/kg/day. The echocardiogram showed no coronary artery aneurysms. However, she was noted to have mildly decreased left ventricular function, mild mitral insufficiency, and a small pericardial effusion. She continued to have a fever for 48 hours after IVIG administration, and was given a second dose, after which she promptly defervesced. Her cardiac function subsequently improved. She was discharged home on low-dose aspirin, and was scheduled for follow-up with a pediatric cardiologist.

Summary

Kawasaki disease is an acute, febrile vasculitis of childhood, primarily affecting small- to medium-sized arteries. It is a self-limited disease, but can result in the development of coronary artery aneurysms if left untreated. Despite significant research, the exact etiology of the disease remains unknown. In the United States, clinical criteria for diagnosis of complete Kawasaki disease include fever for ≥ 5 days and at least 4 of 5 supporting symptoms. These symptoms include conjunctival injection, oral mucosal changes, polymorphous rash, distal extremity changes, and cervical lymphadenopathy. Emergency clinicians should be aware that a smaller proportion of children will present with incomplete Kawasaki disease, comprised of fever for ≥ 5 days plus 2 to 3 of the supporting symptoms. These patients will typically have laboratory findings that support the diagnosis.

All children with suspected or confirmed Kawasaki disease should have echocardiography performed to assess for coronary artery abnormalities. Primary treatment for Kawasaki disease includes IVIG infusion. Despite a lack of strong evidence in its favor, many institutions continue to include high-dose aspirin as part of the treatment protocol. Treatment should ideally be started within 10 days of the onset of fever. Patients who have persistent fever despite treatment may need repeated IVIG infusion or treatment with corticosteroids. In addition, infliximab and abciximab are currently being investigated for use in resistant disease, although further studies are needed. Children who are untreated or have delays in diagnosis and treatment are at an increased risk for development of coronary artery aneurysms, thrombosis, and sudden cardiac death.
References

Evidence-based medicine requires a critical appraisal of the literature based upon study methodology and number of subjects. Not all references are equally robust. The findings of a large, prospective, randomized, and blinded trial should carry more weight than a case report.

To help the reader judge the strength of each reference, pertinent information about the study will be included in bold type following the reference, where available. The most informative references cited in this paper, as determined by the author, will be noted by an asterisk (*) next to the number of the reference.

1.* Kawasaki T. Acute febrile mucocutaneous syndrome with lymphoid involvement with specific desquamation of the fingers and toes in children. *Arrang.* 1967;16(3):178-122. (Retrospective review; 50 patients)


73. Egami K, Muta H, Iishi M, et al. Prediction of resistance to...


CME Questions

5. Lymphadenopathy in Kawasaki disease:
   a. Is usually axillary
   b. Occurs in 80% to 90% of children with Kawasaki disease
   c. Requires antibiotic management
   d. Is usually unilateral

6. Elevation of which of the following laboratory results aids in the diagnosis of Kawasaki disease?
   a. Sodium
   b. Albumin
   c. Cholesterol
   d. CRP

7. Incomplete Kawasaki disease may be diagnosed when a child presents with:
   a. Myocarditis of unknown etiology
   b. Fever and rash and the patient is an Asian/Pacific Islander
   c. Fever for ≥ 5 days plus 2 to 3 of the diagnostic criteria
   d. Two to 3 of the diagnostic criteria without fever

8. In the United States, what is the standard treatment for Kawasaki disease?
   a. Supportive care
   b. IVIG plus aspirin
   c. Corticosteroids
   d. Aciximab

9. At this time, an option for treatment of resistant disease is:
   a. Propranolol
   b. Infliximab
   c. Dialysis
   d. Ampicillin

10. The risk of a child developing Kawasaki disease is significantly increased if:
    a. The child has a sibling with Kawasaki disease
    b. The child is unimmunized
    c. The child attends daycare
    d. The child has congenital heart disease

1. Diagnostic clinical criteria for Kawasaki disease include all of the following EXCEPT:
   a. Conjunctivitis
   b. Oropharyngeal changes
   c. Vomiting
   d. Extremity changes

2. Rates of Kawasaki disease are highest in which population?
   a. Asian/Pacific Islanders
   b. Hispanics
   c. Blacks
   d. Whites

3. The polymorphous rash associated with Kawasaki disease is commonly:
   a. Vesicular
   b. Bullous
   c. Diffuse macular
   d. Urticarial

4. Which finding in patients who have previously received the BCG vaccination is highly specific for Kawasaki disease?
   a. Jaundice
   b. Erythema at the BCG injection site
   c. Shock
   d. Arthritis
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