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CHAPTER 35

Kawasaki Disease

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HISTORICAL BACKGROUND

Kawasaki disease (KD) is one of the most common vasculitides of childhood. It has the potential to cause severe complications, significant morbidity, and even mortality. Expeditious treatment can largely prevent these complications, underscoring the importance of early and accurate diagnosis. The diagnosis is based on clinical criteria (Box 35-1), and in the absence of a diagnostic test, correct identification of KD can be as exacting a challenge today as it has been for more than 40 years.

This vasculitis bears the name *Kawasaki disease* because of the highly detailed description of this illness in 50 children by Tomisaku Kawasaki in 1967.[1] Scattered case reports of young children who died of ruptured or thrombosed coronary artery aneurysms have appeared in the medical literature since 1871.[2,3] A clinical syndrome comprising most of the components of what is today recognized as KD was described by Munro-Faure in 1959[4] and by Itoga in 1960,[5] and an even earlier fatal inflammatory vasculopathy primarily affecting young boys, infantile polyarteritis nodosa (IPN), likely represents extreme cases of the same disorder.[6]

DEFINITION AND DIAGNOSTIC CRITERIA

KD is a self-limited vasculitis of unknown etiology characterized by fever, rash, conjunctivitis, oral mucositis, extremity changes, cervical lymphadenopathy, and, in a proportion of cases, dilation or aneurysms of the coronary and other arteries.

Criteria for the diagnosis of KD are shown in Box 35-1.[7] More recently proposed criteria include perineal rash in the criterion for changes in the extremities, and recognition that, in the presence of fever and coronary artery changes demonstrated by echocardiography, fewer than four criteria suffice to make the diagnosis of KD.[7,8] Muta and colleagues[9] showed that fewer cases of KD were missed when children were included whose fevers were abrogated with intravenous immunoglobulin (IVIG) within 5 days of the onset of fever.[10]

None of these guidelines has 100% sensitivity and specificity for the diagnosis of KD. If a child has the characteristic clinical features and develops coronary artery aneurysms, the diagnosis is certain. Children who do not meet the criteria may have an incomplete or atypical form of KD (discussed later). Alternatively, some patients who fulfill all criteria may have other conditions. In a study of patients referred because of possible KD, Burns and colleagues[11] found that the standard clinical diagnostic criteria for KD were fulfilled in 18 (46%) of 39 patients in whom other diagnoses were established. Furthermore, Benseler et al. found that in a consecutive series of children diagnosed with KD, up to one third had concurrent, identifiable infections,[12] including Group A streptococcal tonsillitis, viral illnesses, pneumonia, and gastroenteritis.

More concerning from the perspective of trying to prevent disease sequelae is that many children who develop coronary artery aneurysms never meet criteria for KD.[13] Witt et al. found in a single center study of 127 patients treated for KD that 36% did not meet the criteria for KD. Furthermore, the KD cases that did not meet the criteria for diagnosis had a significantly higher proportion of coronary artery abnormalities as compared to those cases that did meet criteria (20% vs. 7%, $P < 0.05$).[13] Sudo et al. utilized epidemiological data from the twentieth nationwide survey of KD in Japan and found that the prevalence of coronary artery lesions 1 month after disease onset tended to be higher in the cases with one or two principal criteria as compared with those cases that had five to six criteria (7.4% vs. 2.5% $P < 0.05$).[14] Consistent with this, a recent meta-analysis of over 20 studies of patients with KD found that incomplete KD is a risk factor for coronary artery abnormalities.[15]

The youngest patients are the least likely to meet the classic criteria, and unfortunately they also have the highest risk of developing coronary artery abnormalities.[16] Rosenfeld et al. found that up to 60% of children younger than 12 months old developed aneurysms in one series.[17] For this reason, the diagnosis of KD should be considered in any infant with prolonged, unexplained fever, and there should be a low threshold for performing echocardiography in this age group. Conversely, in older children, treating KD is seldom an emergency, especially when patients present symptoms after only 5 or 6 days of fever. Observation of children older than 6 months who do not fulfill criteria may be the best course of action. The mean duration of fever in children with untreated KD is 12 days,[18] much longer than typical viral illnesses, so the persistence of fever or development of additional signs of KD can be an indicator for treatment.

EPIDEMIOLOGY

Although worldwide in distribution, the incidence of KD is highest in Japan and is steadily increasing over time, although the reasons behind this increase are unclear. In 2010, the annual incidence rate recorded in Japan was 239.6 per 100,000 children aged up to 4 years, which is higher than during any of the three epidemics of KD in Japan in 1979, 1982, and 1986. Children of Japanese descent who reside outside Japan also face a higher risk of KD than do Caucasian children.[19] The incidence is increasing in South Korea as well, with the second highest worldwide incidence of 134.4/100,000 children younger than 5 years of age in 2011.[20] Rates in Taiwan[21] and China[22] are also high.

The epidemiology of KD in the United States differs from countries in Asia in that there are fewer cases (20.8/100,000 children <5 years in

BOX 35-1 Criteria for the Diagnosis of Kawasaki Disease

Fever for more than 5 days (4 days if treatment with intravenous immunoglobulin eradicates fever) plus at least four of the following clinical signs not explained by another disease process:

- Bilateral conjunctival injection (80% to 90%)*
- Changes in the oropharyngeal mucous membranes, including one or more of injected and/or fissured lips, strawberry tongue, injected pharynx (80% to 90%)
- Changes in the peripheral extremities, including erythema and/or edema of the hands and feet (acute phase) or periungual desquamation (convalescent phase) (80%)
- Polymorphous rash, primarily truncal; nonvesicular (>90%)
- Cervical lymphadenopathy with at least one node >1.5 cm (50%)

*Numbers in parentheses indicate the approximate percentage of children with Kawasaki disease who demonstrate the criterion.

2006) and the incidence does not seem to be rising over time.[23] As assessed by hospital admissions in the U.S., children of Asian or Pacific Island ancestry have the highest incidence (30.3/100,000 <5 years). The incidence was intermediate for African Americans (17.5/100,00 <5 years) or children of Hispanic origin (15.7/100,000 <5 years), and lowest for whites (12/100,000 <5 years).[23] In one large area of Great Britain, the annual incidence rate was 5.5 cases per 100,000 for children younger than 5 years old; the incidence for children of Asian ancestry was more than double that for Caucasian and African or Afro-Caribbean children.[24]

KD is an illness of early childhood. Seventy-seven percent of affected patients are younger than 5 years old, with an average age of approximately 3 years,[23] although there are reports of KD occurring in older children[25] and adults.[26-28] KD is more common in boys than in girls (male-to-female ratio of 1.36:1 to 1.62:1).[29,30]

In Japan, the highest incidence occurs between 6 and 11 months old.[31] In North America, the peak age at onset of KD is between 2 and 3 years old. In a recent Australian study of the years 2000 through 2009, the mean age of diagnosis was 4.2 years.[32] The reasons for the geographic differences in age at onset are unclear.[33]

Several reports document a seasonal incidence of KD.[33-35] Burns et al. established a global seasonal pattern of KD with a peak in disease in January through March in the extratropical Northern Hemisphere.[35] In Japan, the disease occurs most frequently in winter and spring months, with a nadir in October.[31] In a study from Taiwan, the highest incidence was in the summer.[36] In North America, cases have tended to occur between November and May.[37] There were no seasonal variations in the incidence of KD in a study from western Australia.[32] Although epidemics of KD were documented in Japan up to 1987, none has occurred since then.[38]

In Japan, siblings of affected children have a risk of contracting KD that is approximately 10 times higher than the risk in the general population,[39] but cases among children sharing the same home in other countries are uncommon.[34] Dergun and colleagues[40] reported 18 families in the United States with 24 affected members, including 9 sibling pairs. Second and even third attacks have been reported in a range of 1.5% to 3% of cases.[31,36]

ETIOLOGY AND PATHOGENESIS

The cause of KD remains unknown. Many of its epidemiological and clinical manifestations suggest an infectious origin. If an infectious agent does indeed cause KD, the putative organism would appear to be of very low communicability, or predominantly responsible for subclinical infections. Repeated attempts to identify a particular infectious trigger have been unsuccessful.[41]

A predominance of immunoglobulin A (IgA)-secreting plasma cells in the blood vessel walls of children with fatal KD has suggested to Rowley and colleagues that an organism that gained entry through mucosal surfaces underlies the disease.[42] No single pathogen is regularly demonstrable, although associations with Epstein–Barr virus (EBV),[43] rotavirus,[44] other viruses,[45,46] and with bacteria[47,48] have been reported. An association with a coronavirus[49] was not confirmed.[50] It is nonetheless a possibility that the vascular injury in KD may be the result of a direct cell-mediated attack on endothelial cells that are infected with an unidentified pathogen.[51]

Other investigators have proposed that the vasculitis in KD is caused by either conventional antigens or superantigens that trigger an immune response to endothelial cells, rather than by direct infection of the vessels.[52] Superantigens are produced by several bacteria, notably certain strains of *Staphylococcus* and *Streptococcus,* and are capable of stimulating large numbers of T cells in an antigen-nonspecific manner by interaction with the β chain of the T-cell receptor. Overrepresentation of T cells bearing Vβ2 among lymphocytes in coronary artery aneurysms, intestinal mucosa,[53,54] and peripheral blood[55] from patients with KD supports the hypothesized role of superantigens in the pathogenesis. A variety of additional circumstantial evidence[52,56-58] and a murine model of *Lactobacillus casei*–induced vasculitis lend credence to this theory.[59] Further, children with KD have unique reactions to mycobacterial antigens,[60-62] which may also function as superantigens, including recall reactions at the site of a previous bacillus Calmette–Guérin immunization.[61] Nonetheless, the only human illness definitively ascribed to superantigens is toxic shock syndrome, and different groups have published conflicting evidence regarding the isolation of superantigen-producing organisms, the detection of superantigen proteins, and the presence of an immunological signature of superantigen activity in patients with KD.[55,63,64]

Additional clues to the cause of KD may come from humoral factors, including antiendothelial cell antibodies, circulating immune complexes,[65] and antineutrophil cytoplasm antibodies (ANCAs) that are demonstrated by some researchers in a proportion of patients,[65,66] but not by others.[67,68] For example, findings from a murine model indicated that B cells may not be necessary for coronary arteritis.[69] However, genome-wide association studies have implicated single nucleotide polymorphisms (SNPs) in the B lymphoid tyrosine kinase and CD40 genes as evidence that B cells may play a pathogenic role in KD.[70,71]

Recent studies have demonstrated that regulation of T-cell activation may determine susceptibility to and severity of KD.[59] Onouchi et al. identified a functional SNP in the inositol 1,4,5-triphosphate 3-kinase C *(IPTKC)* gene on chromosome 19 through linkage disequilibrium mapping. *ITPKC* acts as a negative regulator for T-cell activation, and the SNP was associated with risk for developing KD and coronary artery lesions.[72] Supportive evidence for the role of T cells in KD has recently been provided via an animal model of KD, in which mice are injected intraperitoneally with *Lactobacillus casei* cell wall extract. T-cell costimulation was identified as a critical regulator of susceptibility to and severity of coronary arteritis in this model.[59]

In the absence of confirmed evidence of a single etiological agent, a reasonable working hypothesis is that KD represents a stereotyped, pathological immune response to one or a variety of environmental and/or infectious triggers. It may be a form of reactive vasculopathy, like polyarteritis nodosa or Henoch–Schönlein purpura, with an

inflammatory response developing in sterile tissues as a result of immune activation.[73] Presumably, certain individuals are predisposed by virtue of their genetic constitution. The strong predilection for childhood onset may reflect the presence of developmental antigens that are targets for the inflammatory response only early in life, subtle maturational defects in immune responsiveness,[74] or the timing of exposure to environmental triggers.

GENETIC BACKGROUND

In Japan, approximately 1% of patients with KD have a history of an affected sibling,[75] and concordance for KD was 13.3% in dizygotic twins and 14.1% in monozygotic twins.[76] Similarly, in Japan there is a significantly increased frequency of a history of KD in the parents of children with the disease.[77] These observations indicate that there is a genetic predisposition to this disease, although the fact that affected twin pairs became ill within 2 weeks of each other also suggests an important role for an environmental agents.

The exact genetic factors that may underlie the disorder are unknown. Reported genetic associations have been reviewed by Hata and Onouchi.[78] Candidate genes include those at the histocompatibility locus and those for other proteins involved in immunoregulation. Human leukocyte antigen (HLA) genes for B5, B44, Bw51, DR3, and DRB3*0301 have been associated with KD in Caucasians; Bw54, Bw15, and Bw35 in the Japanese; and Bw51 in Israelis.[79] Onouchi and colleagues[80] concluded that HLA polymorphisms contributed little to the pathogenesis of KD. However, a recent study identified an SNP that achieved genome-wide significance in the HLA-DQB2-HLA-DOB locus.[81] There has been no reported association of any HLA antigen with the risk of coronary artery disease.[82]

Polymorphisms of the tumor necrosis factor (TNF)-α gene *(TNF),*[83] the *IL 18* gene,[84] the *HLA E* gene,[85] and the gene for angiotensin-converting enzyme[86,87] have also been associated with KD, but their pathogenic significance is disputed. A separate report implicated polymorphisms of the mannose-binding lectin (MBL) in the pathogenesis of KD.[88] MBL binds to n-acetyl glucosamine and mannose present on the surface of many microbes. This interaction results in activation of complement (C3) independent of antibody. Levels of MBL are determined by polymorphisms of the MBL 2 gene and its promoters. Higher expression of MBL is associated with lower incidence of coronary artery lesions in patients under 1 year old, but it has the opposite effect in older patients. This apparent paradox is congruent with the belief that MBL is important in protecting the very young child from infectious diseases.[88]

The gene controlling expression of inositol 1,4,5-triphosphate 3-kinase (*ITPKC*) has been identified as a susceptibility gene not only for KD, but also for coronary artery disease.[72] This enzyme is strongly expressed by peripheral blood mononuclear cells and has an important role in inflammation by decreasing interleukin (IL)-2 expression. The functional polymorphism ITPKC 3 is significantly increased in patients with KD and coronary artery disease in Japanese and American populations.[89] An SNP in the *caspase-3* gene on chromosome 4 has also been associated with risk for IVIG resistance and coronary artery abnormalities,[90] which may be due to its role in apoptosis. An SNP in the *FAM167A-BLK* gene is a recently identified locus that is significantly associated with a risk for KD.[70,81] It is of interest, as previous studies have reported an association between SNPs in this region and autoimmune diseases, including rheumatoid arthritis[91] and systemic lupus erythematosus.[92,93] There have also been reports of associations of functional SNPs in immunoglobulin receptor pathways[81,94] and in the gene for *CD40*.[71,81]

CLINICAL MANIFESTATIONS

Disease Course

The course of untreated KD may be divided into three phases (Fig. 35-1): An acute, febrile period lasting for 10 to 14 days is followed by a subacute phase of approximately 2 to 4 weeks. This ends with a return to normal of the platelet count and erythrocyte sedimentation rate (ESR). The subsequent convalescent or recovery period lasts months to years, during which time vessels undergo healing, remodeling, and scarring.

Acute Febrile Phase

The onset of fever in KD is characteristically abrupt, sometimes preceded by symptoms of an upper respiratory or gastrointestinal illness. Baker and colleagues[95] studied the symptoms in the 10 days prior to diagnosis of KD in 198 patients. They reported that irritability occurred in 50%, vomiting in 44%, decreased food intake in 37%, diarrhea in 26%, and abdominal pain in 18%. Cough was reported in 28%, and 19% had rhinorrhea. In addition, 19% reported weakness, and 15% reported arthralgia or arthritis. Perineal desquamation may be another early sign of KD.[96] Over the next 3 to 4 days, cervical adenitis, conjunctivitis, changes in the buccal and oral mucosa, a pleomorphic rash, and erythema and edema in the hands and feet develop. The manifestations occur in no particular order and can fluctuate in the first 7 to 10 days of illness. Accordingly, a thorough medical history is important for identifying subtle or transient manifestations of KD. Untreated, the clinical signs of KD subside after an average of 12 days. If myocarditis occurs, it often does so early and may be manifested by tachycardia, an S3 gallop, and perhaps signs of congestive heart failure.[97] Pericarditis, abdominal pain, ascites, and hydrops of the gallbladder also may occur at this time.

Subacute Phase

After the acute phase, the child may be entirely asymptomatic if given IVIG. During this period, desquamation of the skin and specifically, periungual desquamation of the digits,[98] may be the only clinically apparent residual feature. One in 13 children may develop arthritis of one or several joints during the late acute and subacute phases.[99] Coronary artery aneurysms most commonly first develop during the subacute phase or occasionally earlier, but rarely later in children treated with IVIG. The irritability that can be quite prominent in the acute phase diminishes and resolves completely during the subacute phase.

Convalescent Phase

Most children are asymptomatic during the convalescent phase. The acute phase response has usually returned to normal, unless there are complications. Horizontal ridging of the nails (Beau lines), characteristic of many acute inflammatory conditions, may appear during this period.

Clinical Characteristics of the Classification Criteria

Fever

Fever, often exceeding 40°C (104°F), is the hallmark of KD. The fever is typically persistent and minimally responsive to antipyretic agents, tending to remain above 38.5°C (101.3°F) during most of the acute phase of the illness. It reflects elevated levels of TNF-α and IL-1, which are thought to mediate the underlying vascular inflammation.[100] The diagnosis must be suspect in the absence of fever, though brief temperature spikes may be missed by fatigued or inexperienced parents.

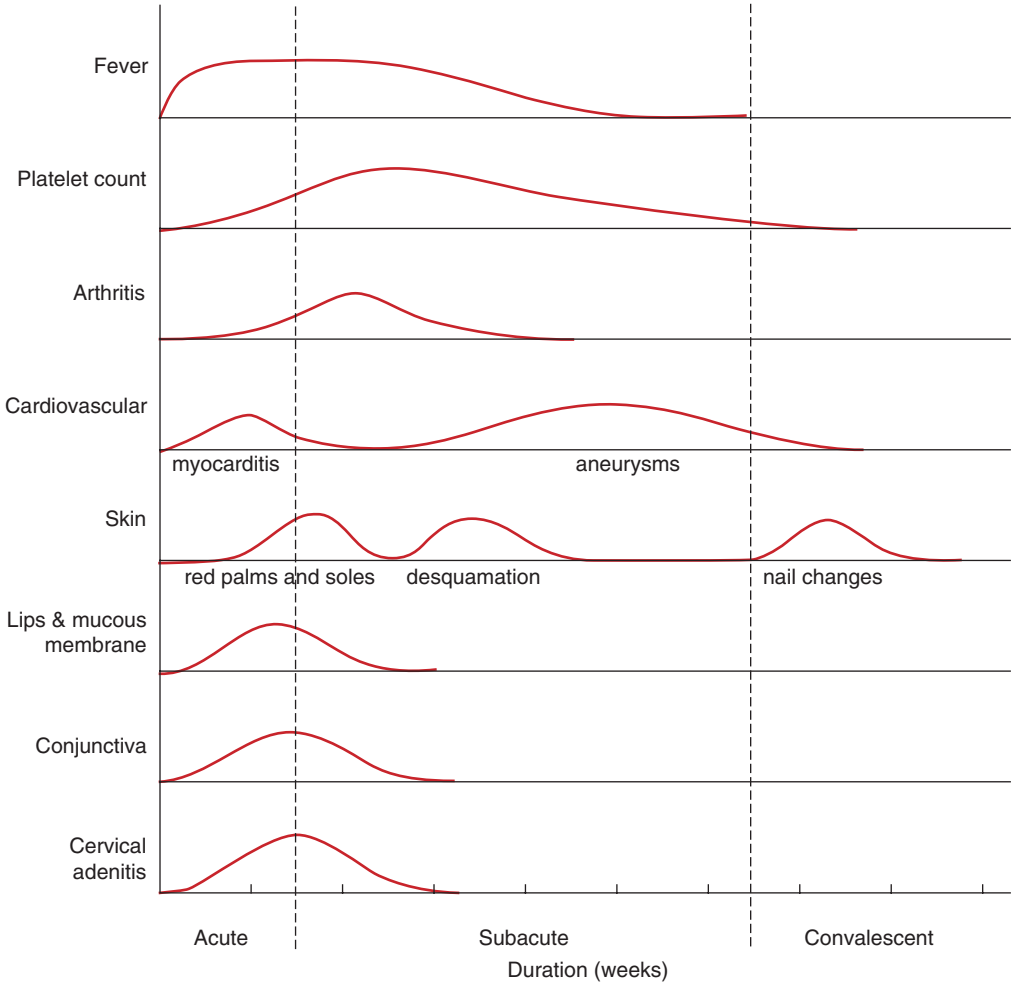

FIGURE 35-1 Kawasaki disease can be viewed as an illness with acute, subacute, and recovery phases. The temporal characteristics outlined here are typical of the course of the disease. (Adapted from Kawasaki T, Acute febrile mucocutaneous syndrome with lymphoid involvement with specific desquamation of the fingers and toes in children, *Arerugi* 16 (3) (1967) 178–222. [Article in Japanese].)

Conjunctivitis

Bilateral, nonexudative bulbar conjunctivitis occurs in more than 85% of patients with KD. Conjunctival injection typically spares the limbus, which is the zone immediately around the cornea. However, the characteristic of limbal sparing is not required for conjunctival erythema to qualify as a diagnostic criterion. Inflammation of the palpebral conjunctiva is not prominent. Purulent discharge is especially unusual[101] and suggests an alternative diagnosis.

Other ocular abnormalities also may occur, although they are not part of the diagnostic criteria. During the first week of illness, about three fourths of children are photophobic, a consequence of anterior uveitis,[102] which peaks between 5 and 8 days of illness and is more common in children over 2 years old. Ocular inflammation usually resolves without specific therapy or sequelae. In exceptional instances, there may be posterior synechiae, scleral[100] or conjunctival[103] scarring, changes in the retina and vitreous,[104] or even blindness.[105]

Changes in the Lips and Oral Mucosa

Swollen, vertically cracked red lips and a strawberry tongue are characteristic of KD; the latter is caused by sloughing of filiform papillae and prominence of the large hyperemic fungiform papillae (Fig. 35-2). Diffuse erythema of the oropharynx is also seen. Vesicles, ulcers, or tonsillar exudate suggest a viral or bacterial infection rather than KD.

Exanthem

The cutaneous manifestations of KD are protean. Although the rash usually begins on the trunk, there is often a perineal confluence during the first days of the illness, followed by desquamation in the diaper area by day 6 in many cases.[96] Macular, morbilliform, or targetoid lesions of the trunk and extremities are most characteristic. The rash is seldom pruritic, and vesicular or bullous lesions are rare (Fig. 35-3). Psoriasis has been reported in several children with KD.[106]

Lymphadenopathy

Anterior cervical lymphadenopathy occurs during the acute phase of the disease, is usually unilateral, and may appear to involve only a single node. However, ultrasonography or computed tomographic imaging of the neck typically reveals grapelike clusters of enlarged nodes similar to those seen in EBV infections rather than the isolated adenopathy typical of bacterial adenitis.[107] Occasionally, a node enlarges rapidly and may be mistaken for infectious lymphadenitis. After 3 or 4 days, it usually shrinks with or without specific therapy.

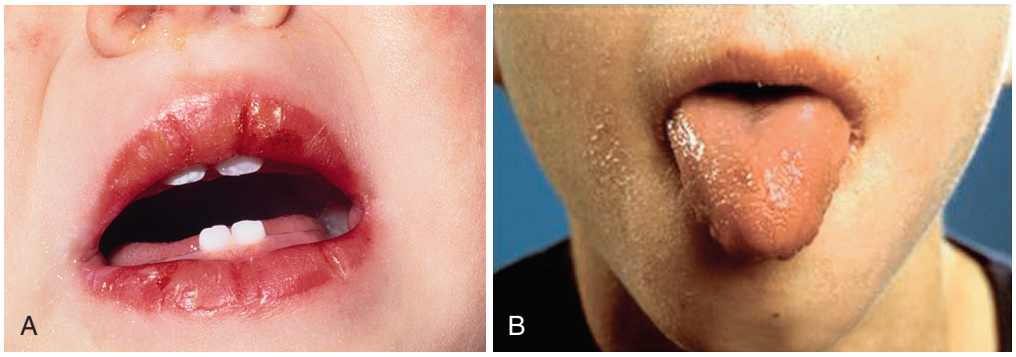

FIGURE 35-2 **A,** The intense reddening, swelling, and vertical cracking of the lips are characteristic of Kawasaki disease (KD). **B,** The strawberry tongue of acute KD with hypertrophied papillae on an erythematous base and the peeling of the facial skin.

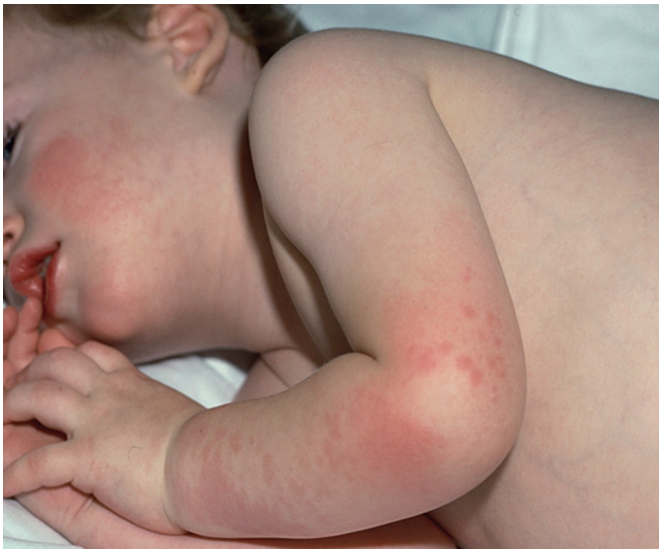

FIGURE 35-3 The nonspecific polymorphous rash is seen on the face arms and chest of this 2-year-old boy with acute Kawasaki disease.

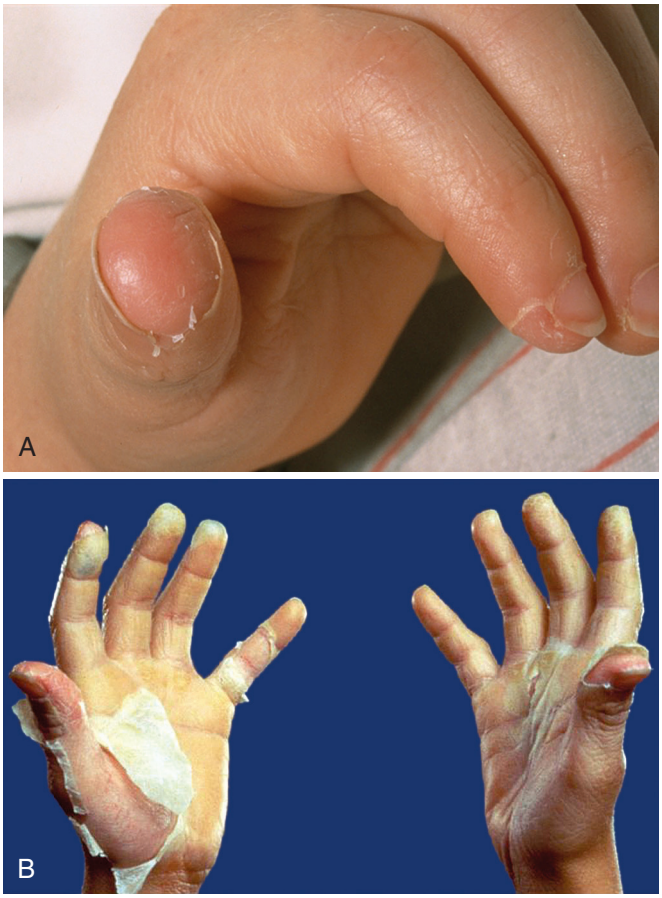

FIGURE 35-4 **A**, Desquamation of the skin of the tips of the thumb and finger seen during the subacute phase of Kawasaki disease. **B,** Desquamation of the skin of the hand occurs later in the subacute and early recovery phase of the disease. In many children, the degree of desquamation is much less than is depicted here.

Diffuse lymphadenopathy and splenomegaly are not typical of KD and should raise suspicions of a viral illness.

Extremity Changes

Indurated edema of the dorsum of the hands and feet and a diffuse red-purple erythema of the palms and soles occur early and last for 1 to 3 days. Sheetlike desquamation typically occurs 10 days or more after the start of the fever. It characteristically begins at the tips of the fingers followed by the toes, just below the distal edge of the nails (Fig. 35-4). Flaky desquamation may occur elsewhere, but acral skin peeling usually occurs late in the course of KD and may be absent or inapparent.[98] Consequently, it is more useful for retrospective confirmation of the diagnosis rather than for making therapeutic decisions.

Incomplete Kawasaki Disease

Signs and symptoms in children who do not meet criteria for KD tend to parallel those of children who fulfill the diagnostic criteria.[108] Incomplete KD is seen more frequently in young infants and older children, which is a critical observation as these groups of children are also at higher risk for coronary artery lesions.[25,31,109,110] A particularly high level of suspicion is needed in infants younger than 1 year old. In a retrospective review of 45 cases of KD, 5 (45%) of 11 infants had incomplete disease, compared with 4 (12%) of 33 older children.[111] In this study, coronary artery complications occurred in three older children (9%) but in seven infants (64%), including all five with incomplete disease.[111] In view of these data, the American Heart Association (AHA) has suggested additional markers for identification of children who do not meet the classic criteria for KD but who might nonetheless be at increased risk for developing coronary artery aneurysms (Fig. 35-5).[7] Reports suggest that the algorithm recommended by the AHA

committee performs well in reducing the number of children who are not treated for KD but who ultimately develop aneurysms.[112]

Other Clinical Manifestations of Kawasaki Disease

Table 35-1 shows other clinical manifestations of KD.

Cardiovascular Disease

At onset, there is nearly always tachycardia, typically commensurate with the degree of fever. Early myocarditis occurs in at least one third[113] to half[114] of patients, and pericarditis also may occur.[115] Myocardial involvement often leads to decreased contractility, commonly manifested by an S3 gallop that may become more prominent with hydration. Tachycardia out of proportion to the fever is also found in children with significant myocarditis. Such children may be misdiagnosed with viral myocarditis. In more severe cases, myocardial involvement may progress to dysrhythmias and signs of congestive heart failure.[116] Children with prominent KD-associated myocarditis tend to respond briskly to treatment with IVIG, and long-term

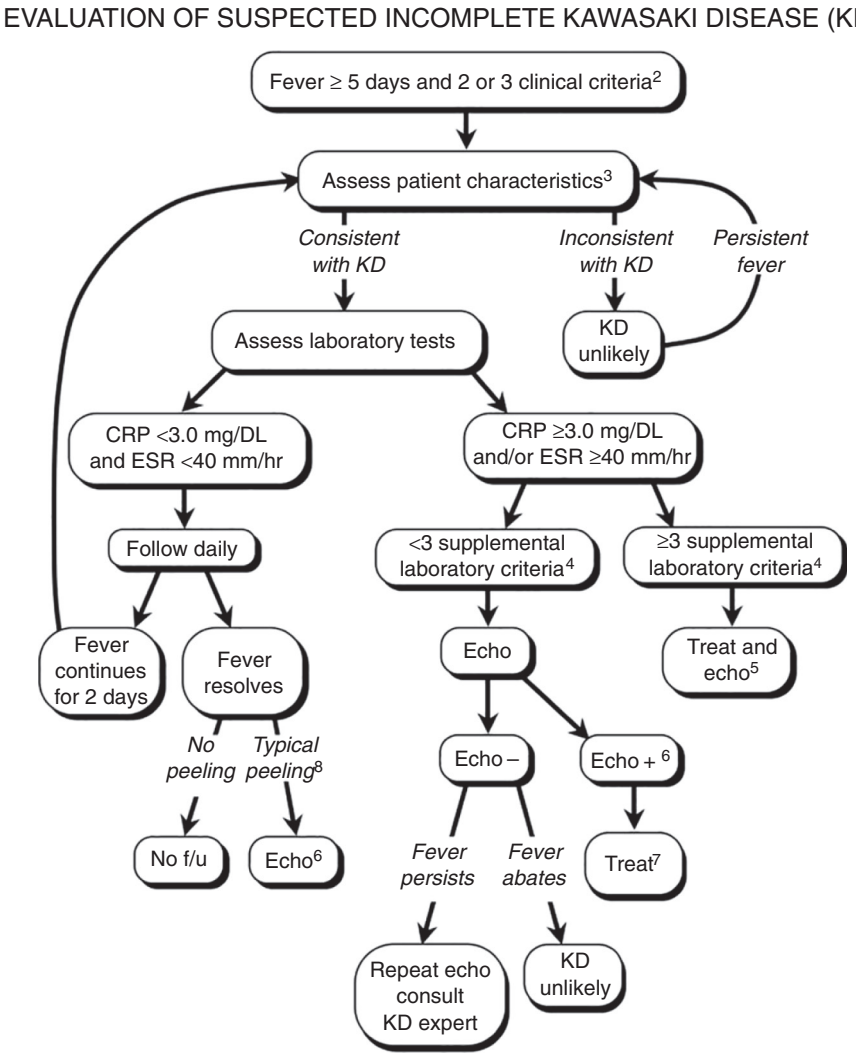

FIGURE 35-5 Evaluation of suspected incomplete Kawasaki disease. [1]In the absence of gold standard for diagnosis, this algorithm cannot be evidence based but rather represents the informed opinion of the expert committee. Consultation with an expert should be sought anytime assistance is needed. [2]Infants 6 months old on day 7 of fever without other explanation should undergo laboratory testing and, if evidence of systemic inflammation is found, an echocardiogram, even if the infants have no clinical criteria. [3]Characteristics suggesting disease other than Kawasaki disease include exudative conjunctivitis, exudative pharyngitis, discrete intraoral lesions, bullous or vesicular rash, or generalized adenopathy. Consider alternative diagnoses. [4]Supplemental laboratory criteria include albumin 3.0 g/dL, anemia for age, elevation of alanine aminotransferase, platelets after 7 d 450 000/mm^3, white blood cell count 15 000/mm^3, and urine 10 white blood cells/high-power field. [5]Can treat before performing echocardiogram. [6]Echocardiogram is considered positive for purposes of this algorithm if any of 3 conditions are met: z score of LAD or RCA 2.5, coronary arteries meet Japanese Ministry of Health criteria for aneurysms, or 3 other suggestive features exist, including perivascular brightness, lack of tapering, decreased LV function, mitral regurgitation, pericardial effusion, or z scores in LAD or RCA of 2–2.5. [7]If the echocardiogram is positive, treatment should be given to children within 10 d of fever onset and those beyond day 10 with clinical and laboratory signs (CRP, ESR) of ongoing inflammation. [8]Typical peeling begins under nail bed of fingers and then toes. (American Heart Association, Diagnosis, treatment, and long-term management of Kawasaki disease. Circulation 110 (2004) 2747–2771.)

TABLE 35-1 Manifestations of Kawasaki Disease

ORGAN SYSTEM	COMMON	UNCOMMON	FINDING SUGGESTS ALTERNATE DIAGNOSIS
Skin	Targetoid, urticarial, morbilliform rashes, livedo reticularis	Psoriasiform rash	Pustular, vesicular rashes
Lungs	Pleural effusion	Nodules, interstitial infiltrates	
Urinary tract	Urethritis, pyuria	Hematuria, proteinuria, orchitis	
Nervous system	Irritability, lethargy, anterior uveitis, sensorineural hearing loss	Seizure, stroke, cranial nerve palsy	
Gastrointestinal system	Diarrhea, vomiting, hydrops of gallbladder, hepatomegaly	Intestinal hemorrhage, ruptured viscus	
Hematological system	Anemia, thrombocytosis, leukocytosis	Thrombocytopenia, consumptive coagulopathy, hemophagocytic syndrome	Lymphocytosis*
Reticuloendothelial system	Anterior cervical lymphadenopathy	Posterior cervical, axillary lymphadenopathy	Diffuse lymphadenopathy, splenomegaly
Mucosa	Mucositis, glossitis, conjunctivitis		Discrete oral lesions, exudative conjunctivitis
Musculoskeletal system	Extremity edema, arthritis	Raynaud phenomenon	
Cardiac system	Tachycardia, gallop rhythm, myocarditis, pericarditis	Coronary artery aneurysm, aortic root dilation, valvulitis	

*Except during the convalescent phase.

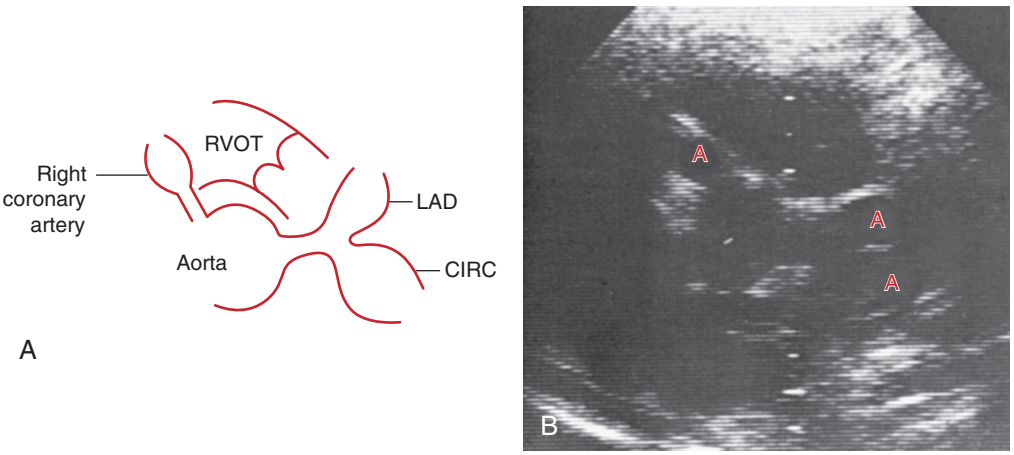

FIGURE 35-6 Echocardiographic demonstration of aneurysms of three coronary arteries in a child with Kawasaki disease. *A*, Aneurysms; *CIRC*, circumflex; *LAD*, left anterior descending coronary artery; *RVOT*, right ventricular outflow tract. (Courtesy Dr. Dennis Crowley.)

abnormalities of cardiac contractility are very uncommon in children treated appropriately during the acute phase of KD.[117] Tacke et al. performed cardiac magnetic resonance (MR) imaging in patients and controls at a median of 11.6 years following diagnosis of KD and found that only those with severe coronary artery pathology had evidence of cardiac dysfunction.[118]

Recently, there has been increasing awareness of a shocklike syndrome that can occur with KD (KD shock syndrome [KDSS]).[119] Kanegaye and colleagues identified 13 children with systolic hypotension, which is a 20% or greater decrease in baseline systolic blood pressure, or clinical signs of poor perfusion from a cohort of 187 consecutive patients with KD at a single center.[119] They found that a third of the children with KDSS had impaired left ventricular systolic function and nearly two thirds had coronary artery abnormalities. IVIG resistance was also seen more commonly in the patients with KDSS. A Taiwanese group performed a case control study of 9 patients with KDSS compared with 27 season-matched controls and also found that the cases had a higher risk for coronary artery dilation.[120]

The most significant and characteristic complication of KD, the development of coronary artery aneurysms in up to 25% of untreated patients, makes KD the leading cause of acquired heart disease among children in the developed world (Figs. 35-6 and 35-7). Frank aneurysms are unusual early in the course of disease, but the lack of tapering seen on echocardiograms is typical, and coronary artery dimensions may be increased in the first 5 weeks after the disease first manifests. Interestingly, Muniz et al. compared coronary artery dimensions of febrile patients with non-KD illnesses to KD patients, and found that the non-KD febrile controls exhibited enlarged coronary artery dimensions, although not to the same degree as the KD cases.[121] Similarly, Bratincsak found that no febrile controls had coronary artery diameters more than 2.5 standard deviations above the mean for age, size,

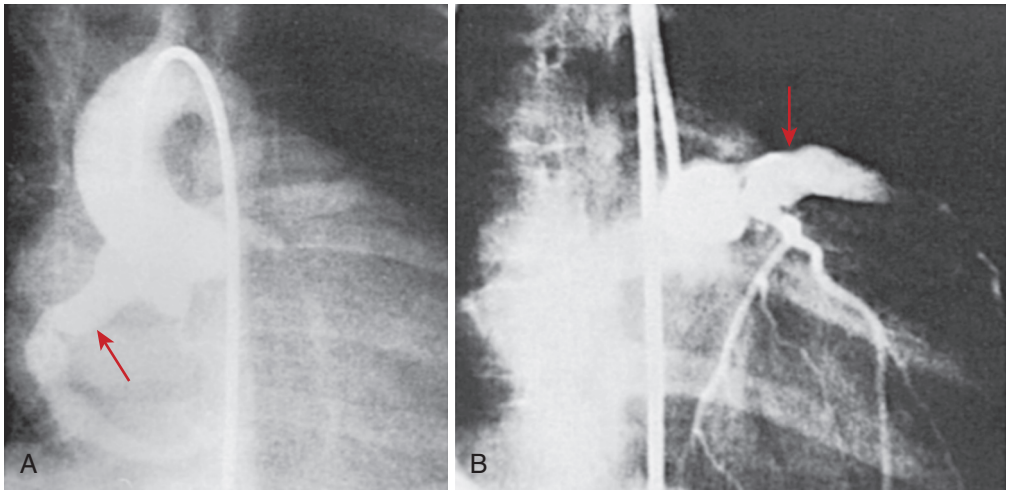

FIGURE 35-7 **A,** Angiography of the coronary vessels in a 7-month-old boy with Kawasaki disease shows a huge aneurysmal dilation of the right coronary artery (*arrow*). **B,** Aneurysm of the left coronary artery in a 3-year-old girl with Kawasaki disease (*arrow*). (Courtesy Dr. Zuidi Lababidi.)

and gender, a diameter typically reached by more than 10% of children with KD.[122]

The Japanese Ministry of Health (JPH) criteria[123,124] use angiography or echocardiography to define coronary arteries as abnormal if the internal lumen diameter is greater than 3 mm in children younger than 5 years old or greater than 4 mm in children at least 5 years old. In addition, vessels are considered aneurysmal if the internal diameter of a segment measures at least 1.5 times that of an adjacent segment or the coronary artery lumen is clearly irregular. Aneurysms can be defined as small (an internal diameter of <5 mm), medium (an internal diameter of 5 to 8 mm) or giant (an internal diameter >8 mm) per the JPH.

Although coronary artery dimensions in normal children have been shown to increase linearly with body surface area (BSA) or length,[125] the JPH criteria are not based on body size. Evaluation of coronary arteries in KD using age-, size-, and sex-adjusted indices (z scores) suggests that the incidence of abnormalities is higher than was generally recognized.[126] Among patients classified as having normal coronary arteries by the JPH criteria, 27% had at least one BSA-adjusted coronary artery dimension more than 2 standard deviations above the mean. Of note, z scores are available only for the left main coronary artery, the left anterior descending artery, and the right coronary artery. Other coronary vessels can be assessed using the JPH criteria. Even children whose vessel dimensions are within the "normal" range may demonstrate a decrease in coronary artery diameter as they convalesce from KD.[127] Some experts think that a z-score-based system of classifying aneurysms may be more discriminating, with a giant aneurysm defined as a z score of 10 or higher.

Coronary aneurysms may cause morbidity early in the course due to rupture or thrombosis, resulting in sudden death or myocardial infarction.[128] Development of *de novo* coronary artery abnormalities more than 2 weeks after the end of the acute illness is unusual.

Although involvement of the coronary arteries is the most characteristic manifestation of the vasculitis of KD, other medium-sized muscular arteries also may be involved. Aneurysms of brachial and femoral arteries may be palpable clinically or demonstrable angiographically (Fig. 35-8). In severe cases, peripheral arterial obstruction may lead to ischemia and gangrene. Visceral arteries are usually spared, although there are reports of gastrointestinal obstruction[129] and acute abdominal catastrophe[130] occurring because of vasculitis. Such complications generally arise in children with other signs of severe vasculitis, including aneurysms in coronary and peripheral arteries.

Central Nervous System Complications

One of the most consistent clinical observations of children with KD, particularly in infants and very young children, is their extreme irritability. This probably represents the effect of aseptic meningitis and associated headache.[131] Cerebrovascular accident[132,133] and facial nerve paralysis[134] have also been reported.

Musculoskeletal Disease

Arthritis was observed by Gong and colleagues[99] in 7.5% of 414 children with KD. Arthritis was oligoarticular in 55% and polyarticular in 45%. Joints most commonly affected were (in order of decreasing frequency) knee, ankle, wrist, elbow, and hip. Joint pain was often severe, but responded to IVIG and high-dose aspirin in most instances. It may occur at any time during the disease course but has been described most commonly during the recovery phase. Arthritis in KD ultimately resolves, leaving no residua.

Respiratory Tract Disease

Cough, coryza, hoarseness, and otitis media frequently occur early in the course of the disease, and suggest a viral upper respiratory tract infection. Approximately one third of children have some degree of sensorineural hearing loss when tested within 30 days of fever onset. Salicylate toxicity may be responsible for transient cases, but sensorineural hearing loss of unclear etiology rarely may persist after aspirin is discontinued.[135-137]

Gastrointestinal Tract Disease and Other Abnormalities

Abdominal pain is common, and approximately one fourth of children with KD have profuse, watery diarrhea during the acute febrile period. Abdominal distention may mimic mesenteric vasculitis or intussusception, and children with KD can present with an acute surgical abdomen, although this is rare.[130] Segmental bowel wall thickening has been described in children with KD and abdominal pain, presumably reflecting visceral arteritis.[138] The relatively common occurrence of hydrops of the gallbladder demonstrated by ultrasonography[139] may aid in the diagnosis of incomplete KD. Occasionally, the gallbladder becomes large enough to be seen as a bulge in the anterior abdominal

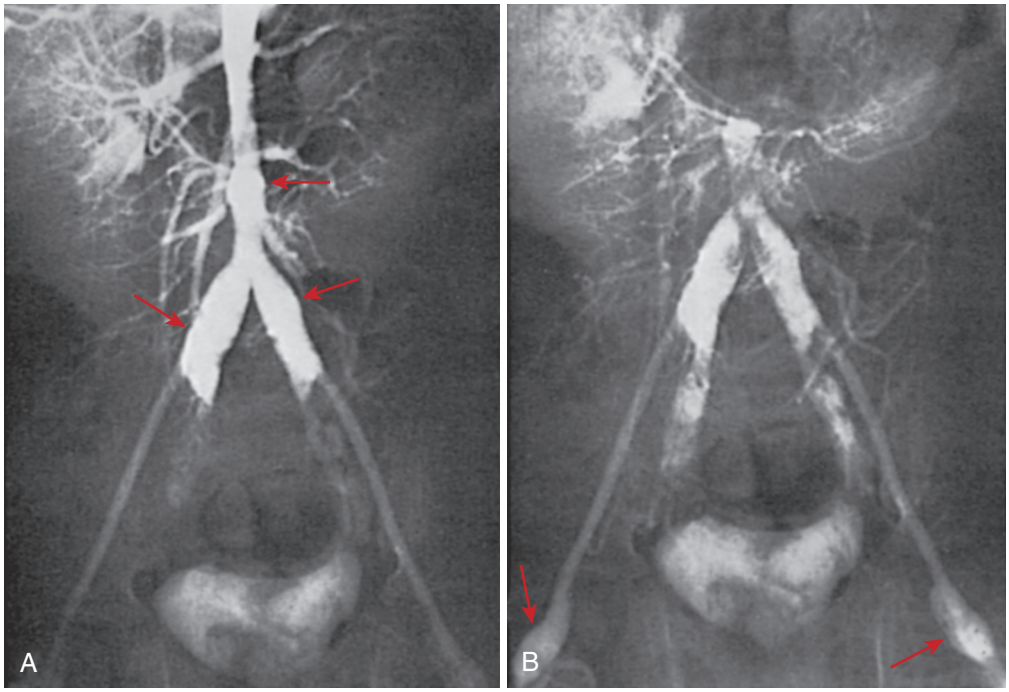

FIGURE 35-8 Angiographic study of a 2-year-old boy with severe Kawasaki disease resulting in multiple aneurysms of the coronary, axillary, iliac, and femoral arteries. The study revealed large aneurysms of the aorta and iliac arteries **(A)** and the femoral arteries (**B;** *arrows*). Aneurysms that were palpable in the axilla and groin in this patient later resolved. (Courtesy Dr. G. Culham.)

wall. The specificity of gallbladder distension is limited, however, and a dilated, engorged gallbladder may be seen in cases of streptococcal and staphylococcal infections, among other mimics of KD. Hepatosplenomegaly may occur in the absence of heart disease, or it may reflect cardiac failure.

Genitourinary Tract Involvement

Kidney and genitourinary tract involvement is uncommon but reported in KD.[140] A study of 50 children with KD from Taiwan[141] revealed hematuria (>5 red blood cells per high-power field [RBC/HPF]) in 6 patients, proteinuria (>100 mg/dL) in 5, and leukocyturia (>10 white blood cells per high-power field [WBC/HPF]) in 19. Renal ultrasonography was abnormal in five patients, and dimercaptosuccinic acid single photon emission computed tomography (DMSA SPECT) revealed inflammatory lesions in 26 children. Although renal function remained normal, scarring was demonstrated in 46% on repeated DMSA SPECT. Sterile pyuria is one of the supplemental laboratory criteria in the algorithm for suspected incomplete KD. Burns et al. compared pyuria in KD cases versus febrile controls without urinary tract infections. They found that pyuria was neither sensitive nor specific for KD, but that the magnitude of pyuria in KD was significantly higher than in febrile controls (42 WBC/μL vs. 12 WBC/μL).[142]

Scrotal pain and swelling due to testicular inflammation are characteristic of pediatric vasculitides, including Henoch–Schönlein purpura, polyarteritis nodosa, and KD.[143] Meatitis and dysuria also occur frequently during the acute phase of KD, and priapism has been described.[144] Hemolytic-uremic syndrome, immune complex–mediated glomerulonephritis, and acute interstitial nephritis have each been reported in a few cases.[145,146] Acute renal failure is a rare complication most commonly ascribed to complications of treatment with certain preparations of IVIG.[147]

BOX 35-2 Differential Diagnosis of Kawasaki Disease

Infectious Conditions
Adenovirus
Measles
Parvovirus
Human herpesviruses (HHV) (e.g., herpes simplex virus, cytomegalovirus, HHV-6, HHV-7)
Rocky Mountain spotted fever
Leptospirosis
Streptococci
Staphylococci

Immune System Reactions
Stevens–Johnson syndrome
Toxin-mediated diseases (toxic shock syndrome)
Serum sickness

Rheumatic Diseases
Systemic-onset juvenile idiopathic arthritis
Polyarteritis nodosa

DIFFERENTIAL DIAGNOSIS

The differential diagnosis of KD includes viral and bacterial infections, toxin-mediated diseases, systemic-onset juvenile idiopathic arthritis and Stevens–Johnson syndrome (Box 35-2). Viral illnesses such as measles (especially when atypical or occurring after vaccination), EBV, and adenovirus infections share many of the signs of mucocutaneous involvement, but they typically have less evidence of systemic

inflammation and generally lack the extremity changes of KD. Toxin-mediated illnesses, especially scarlet fever, staphylococcal scalded skin syndrome, and toxic shock syndrome lack the ocular and articular involvement typical of KD. Drug reactions, such as those in Stevens–Johnson syndrome or serum sickness, may mimic KD but have subtle differences in the ocular and mucosal manifestations. In particularly severe or prolonged KD, the possibility of a chronic vasculitis such as polyarteritis nodosa[148] must be considered carefully. A lack of renal involvement and presence of mucocutaneous changes favor the diagnosis of KD over polyarteritis nodosa.

PATHOLOGY

The signs and symptoms of KD are due to a systemic necrotizing vasculitis with fibrinoid necrosis of the medium-sized muscular arteries; the coronary arteries are the predominant sites of involvement.[149] Disruption of the lamina elastica is characteristic of the aneurysms. Fujiwara documented early neutrophilic infiltrate in all layers of the heart, including the valves. Inflammation begins in the microvasculature (i.e., arterioles, capillaries, vasa vasorum, and venules) and subsequently spreads to larger vessels, especially the coronary arteries.[150] In these lesions, infiltrating cells are mostly macrophages and IgA-secreting plasma cells,[42] findings that may be unique to KD.[151] Endothelial cells express a variety of markers of activation, presumably as a result of the high levels of proinflammatory cytokines that characterize the acute phase of disease.[152] Some children have a lymphocytic myocarditis, with endomyocardial biopsy demonstrating cellular infiltrates or myofibrosis that may persist for years in untreated cases.[153]

Evolution of the cardiac lesions was detailed in the study by Fujiwara and Hamashima.[150] Pericarditis, myocarditis, and endocarditis were universal findings early in the disease, but diminished as fibrosis of the myocardium became the predominant lesion in children whose death occurred 40 days or more after onset. Coronary artery vasculitis predominated early in the disease but was absent in those who died after 28 days of illness. Aneurysms, thrombosis, and stenosis did not appear until 12 days of disease or later.

In a study of 262 children, Suzuki and colleagues[154] documented an equal frequency of aneurysms in the right and left coronary arteries, but a higher propensity for development of segmental stenosis and occlusions in the right coronary artery.

Using light and electron microscopy, Orenstein et al. reviewed autopsy and cardiac transplant tissues from KD patients, and described three phases to the arteriopathy of KD that differ in some ways from prior descriptions.[155] The first phase is characterized by a neutrophilic necrotizing arteritis that begins in the endothelium and can cause saccular aneurysms as the process moves through the walls of the arteries to the adventitia in the first 2 weeks of illness. This is followed by a subacute or chronic vasculitis driven by lymphocytes, plasma cells, and eosinophils that may last weeks to years and results in fusiform aneurysms. During the subacute or chronic vasculitis, smooth muscle cells may be converted to myofibroblasts that cause progressive stenosing lesions, leading to thrombosis.[155]

LABORATORY EXAMINATION

There are no specific diagnostic tests for KD, but at onset, evidence of inflammation is manifested by elevation of C-reactive protein (CRP) and ESR, leukocytosis, and a left shift in the white blood cell (WBC) differential count. Toxic granulation of neutrophils is more frequent in children with KD than in those with other febrile illnesses.[156] Occasionally, significant neutropenia occurs early[157]; this may be a marker for particularly severe disease. Thrombocytopenia and anemia may herald the onset of macrophage activation syndrome (see Chapter 49).[158] Although platelet counts may be normal at the onset of disease, by the second week of illness they characteristically rise and may reach 1,000,000/mm^3 (reactive thrombocytosis) in the most severe cases. Children with KD often present with a normocytic, normochromic anemia; hemoglobin concentrations greater than 2 standard deviations below the mean for age are found in half of patients within the first 2 weeks of illness.[11]

Sterile pyuria is of urethral origin and therefore is missed on urinalyses obtained by bladder aspiration or catheterization. The WBCs are mononuclear and are not detected by dipstick tests for leukocyte esterase. Measurement of liver enzymes often reveals elevated transaminase levels or mild hyperbilirubinemia due to intrahepatic congestion. A few children develop obstructive jaundice from hydrops of the gallbladder or hepatic vasculitis.

Cerebrospinal fluid (CSF) analysis typically displays a mononuclear pleocytosis with normal glucose and protein. In a chart review of 46 children with KD, 39% were documented to have elevated CSF WBC counts.[131] The median count was 22.5 cells/mm^3 with 6% neutrophils and 91.5% mononuclear cells, although cell counts as high as 320/mm^3 with up to 79% neutrophils were reported. Arthrocentesis of involved joints typically demonstrates synovial fluid WBC counts of 50 to 300,000 WBC/mm^3 consisting primarily of neutrophils.

Children with KD develop significant perturbations in serum lipid profiles beginning during the subacute phase of illness. These abnormalities include elevated concentrations of triglycerides and low-density lipoproteins, and depressed levels of high-density lipoproteins.[159] They are most likely caused by widespread endothelial injury, and persistent abnormalities in lipid profiles are more likely in those children with coronary artery abnormalities. Ou et al. found that 1 year after the onset of KD, children with coronary artery aneurysms were more likely to have depressed high-density lipoprotein cholesterol levels and elevated high-sensitivity CRP levels than those KD patients who had normal coronary arteries.[160] As with other sequelae of KD, normalization may take years in untreated children but typically occurs within weeks or months after IVIG therapy.

ANCAs[161] and antibodies to endothelial cells[162] may be present late but not early in the disease.[67] Consequently, they have unclear pathological significance and are of little diagnostic value. Other autoantibodies are usually absent. Elevated levels of von Willebrand factor antigen indicate the presence of damaged endothelium.[163] Activation products of C3 and C4 have been demonstrated on erythrocytes (C3g) and in the plasma (C4d),[164] suggesting the participation of complement in at least some of the manifestations of the disease.

TREATMENT

General Approach

The child with suspected or definite KD should be admitted to the hospital for observation, monitoring of cardiac status, and management of systemic manifestations (Box 35-3). Initial evaluation of the heart should include an electrocardiogram to identify dysrhythmias, signs of ischemia, or myocarditis. A baseline echocardiogram should be performed to detect coronary artery vasculitis, ectasia, or aneurysms and to document biventricular function. If the diagnosis is relatively certain (even if diagnostic criteria are not met), and other diagnoses have been considered and excluded, treatment should be initiated with aspirin and IVIG without further delay.

Goals of Therapy

In addition to control of the acute inflammation and its symptoms, the goal of therapy is to prevent long-term sequelae and, most

BOX 35-3 Initial Evaluation and Management of Kawasaki Disease

Evaluation

- General physical exam
- Cardiac status (ECHO, ECG)
- CNS status
- Hematological and inflammatory parameters (CBC, differential, platelet count, ESR, CRP)
- Fluid and electrolyte status (AST, ALT, bilirubin, electrolytes, BUN, creatinine); urinalysis
- Ophthalmological status
- Monitor cardiac status
- Monitor CRP (ESR) and platelet count at 2-week intervals until stable, then 1-month intervals until normal
- Repeat echocardiogram at 6 to 8 weeks

Treatment

- Aspirin:
  - If patient is febrile: 80 to 100 mg/kg/day in four doses
  - If patient is afebrile: 3 to 5 mg/kg/day in one dose
- IVIG: 2 g/kg administered over 8 to 12 hours with premedications
- Keep in hospital until afebrile for 24 hours or if there are complications
- If fever persists, repeat IVIG once
- If inadequate clinical response, consider corticosteroids (2 mg/kg/day, or 30 mg/kg/dose, or infliximab 5 mg/kg [see discussion in this chapter])
- Maintain low-dose aspirin until ESR and platelet count are normal if there have been no coronary artery abnormalities; for 2 years if coronary abnormalities have resolved; "forever" if coronary artery disease persists

ALT, Alanine transaminase; *AST*, aspartate transaminase; *BUN*, blood urea nitrogen; *CNS*, central nervous system; *CRP*, C-reactive protein; *ECG*, electrocardiogram; *ECHO*, echocardiogram; *ESR*, erythrocyte sedimentation rate; *IVIG*, intravenous immunoglobulin.

importantly, coronary artery abnormalities. The consequences of failure to appropriately treat a child with KD are so important that, within reason and after very careful evaluation, error on the side of premature or unnecessary therapy is preferable to delayed or missed therapy for a child for whom the diagnosis is uncertain. The American Academy of Pediatrics and the AHA recommend that children with KD should be treated with aspirin and IVIG during the first 10 days of the illness.[7,165]

Treatment strategies also depend on the presence of coronary artery dilation, given the long-term morbidity associated with this complication. Approximately half of coronary artery aneurysms demonstrated by echocardiogram regress to normal lumen diameter via myointimal proliferation in 1 to 2 years after illness onset, usually in aneurysms smaller than 6 mm in diameter.[166] However, persistent vasodilatory abnormalities have been observed in arteries where aneurysms resolved.[167] Giant coronary artery aneurysms, with an internal diameter larger than 8 mm, are associated with the highest risk of morbidity and mortality. Up to one third of such aneurysms become obstructed, leading to myocardial infarction, dysrhythmias, or sudden death.[168] Treatment with IVIG decreases the incidence of giant aneurysms by more than 98% and the overall incidence of aneurysms by 85%.[18,169]

Acute phase reactants and platelet counts do not return to normal for up to 2 months after apparently successful treatment with IVIG, suggesting that vasculitis and endothelial inflammation may not fully resolve, even when fever is controlled. IVIG-resistant KD requires additional therapy, and questions remain whether initial treatment should be more robust than IVIG alone, at least for some children at high risk of responding incompletely to IVIG, aiming for anatomically and functionally normal vessels in everyone.

Aspirin

Aspirin was the first medication to be used for treatment of KD because of its antiinflammatory and antithrombotic effects.[170] Antiinflammatory regimens using high-dose (>80 mg/kg/day)[7] or lower-dose (30 to 50 mg/kg/day)[170] aspirin have been recommended during the acute phase of the illness. After the fever resolves, the dose is usually reduced to an antiplatelet range of 3 to 5 mg/kg/day. These doses, well below the antiinflammatory level, have the effect of inhibiting platelet adhesion to endothelium by curtailing platelet release of thromboxane A_2 without suppressing prostacyclin production by endothelial cells.[171] This effect is thought to be beneficial in preventing thrombosis when platelet counts are elevated, although no studies have demonstrated such a benefit clinically. In the event of aspirin sensitivity, another antiplatelet agent, such as dipyridamole, should be considered in patients at particular risk of developing thromboses. Unless coronary artery abnormalities are detected by echocardiogram, aspirin is discontinued after results of laboratory studies return to normal, usually within 2 months of disease onset.

A meta-analysis found that high-dose and lower-dose aspirin regimens were associated with a similar incidence of coronary artery abnormalities at 30 and 60 days after disease onset.[172] Lee et al. enrolled 51 children with KD and treated them with standard doses of IVIG but without concomitant use of acetylsalicylic acid (ASA) in the acute phase, and compared them to a historical control group treated with IVIG plus high-dose ASA. The ASA-treated group had shorter duration of fever as compared to the no-ASA group, but there was no difference in IVIG resistance (17.1% vs. 15.7%, $P = 1.000$) or the development of coronary artery lesions (7.8% vs. 3.9%, $P = 0.514$).[173] A retrospective study by Hsieh et al. had similar findings, although the duration of fever was not different in the no-ASA group.[174] Although the necessity of using high-dose aspirin might be questioned because of the rapid response to IVIG, all of the trials showing the benefit of IVIG were conducted with children who also were receiving antiinflammatory doses of aspirin. There have been no published comparisons of aspirin with other antiinflammatory agents, and it is unclear whether salicylates are uniquely efficacious for this condition. For other complications, such as treatment of prolonged arthritis, alternative antiinflammatory agents may be used. The AHA warns against prescribing ibuprofen in children, as they require protection from thrombosis because ibuprofen antagonizes the antiplatelet effects of low-dose aspirin.[7,175]

The risks of aspirin appear to be similar to those reported in other settings: chemical hepatitis, transient hearing loss, and, rarely, Reye syndrome.[176] These risks may be increased in KD. Aspirin-binding studies have suggested that the hypoalbuminemia of children with KD predisposes them to toxic levels of free salicylate, despite measured (bound) values within the therapeutic range.[177]

Intravenous Immunoglobulin

Furusho and co-workers[178] first reported that high-dose IVIG appeared to decrease the incidence of coronary artery abnormalities. Newburger and colleagues[18] verified these findings in a 19-month, randomized, controlled clinical trial in 168 children with KD. Half of the children received IVIG (400 mg/kg/day on 4 consecutive days) plus high-dose aspirin (100 mg/kg/day), and half of the children received aspirin alone. IVIG reduced the incidence of coronary artery abnormalities by 78%, and no child suffered serious adverse effects from the therapy, thereby confirming the remarkable therapeutic potential of IVIG.

BOX 35-4 Potential Effects of Intravenous Immunoglobulin in Kawasaki Disease

Specific Effects

- Provides antibodies against infectious agent
- Provides antibodies against circulating toxin
- Provides antiidiotypic antibodies

Nonspecific Effects

- Blockades Fc receptors
- Accelerates clearance of activated complement fragments
- Alters solubility characteristics of circulating immune complexes
- Decreases soluble adhesion molecules (e.g., E-selectin, ICAM-1)
- Upregulates activity of natural killer cells
- Reverses immunoregulatory abnormalities by increasing suppressor T cells and decreasing helper T cells and circulating B cells
- Downregulates transcription of cytokine genes
- Neutralizes activity of proinflammatory cytokines
- Causes feedback inhibition of autoantibody synthesis
- Reverses inhibited lymphocyte apoptosis
- Induces neutrophil apoptosis

The initial IVIG treatment regimen was based on then-current protocols for treating immune thrombocytopenic purpura. The question of whether this protocol was optimal for KD was addressed in 1991.[179] Children were randomized to receive the traditional four-dose regimen or a single dose of 2 g/kg of IVIG infused over 8 to 12 hours. Children receiving the larger, single dose fared better. Meta-analyses have documented a dose-response benefit of IVIG therapy in the range of 200 mg/kg to 2 g/kg.[180]

IVIG is most effective in reducing the risk of coronary artery disease when administered within 10 days of the onset of fever. Unfortunately, the diagnosis may remain in doubt as this deadline approaches. In ambiguous cases, the physician may be guided by the epidemiology of the disease. More than 50% of infants with KD present atypically (i.e., do not fulfill diagnostic criteria), and they have a very high incidence of aneurysms. Thus, empiric treatment in very young children warrants serious consideration.[6]

The mechanism of action of IVIG is uncertain, with studies adding induction of neutrophil apoptosis[181] and reversal of inhibited lymphocyte apoptosis[182] to a long list of immunomodulatory effects of IVIG (Box 35-4). The response is generally prompt, and temperature returns to normal in many children even before the end of the IVIG infusion, with rapid clearing of the rash, mucositis, and conjunctivitis. Irritability and emotional lability, however, may persist for up to several weeks before resolving.

The greatest long-term concern about IVIG use is potential transmission of blood-borne pathogens. Technical deficiencies in production led to more than 100 cases of hepatitis C in recipients of a single brand of IVIG in 1994, although none was a child with KD.[183] No cases of IVIG-transmitted infections have been reported since the institution, in 1995, of current purification and processing practices, and no cases of IVIG-transmitted human immunodeficiency virus (HIV) have ever been reported. Overall, the cost-benefit analysis documents that IVIG treatment of KD is one of the most cost-effective medical therapies available, leading to impressive short- and long-term savings.[184]

Infusion reactions (fever, rash, nausea, and hypotension) occasionally accompany IVIG administration and are best managed by slowing the rate of infusion and administering diphenhydramine. With no viable alternative therapies, aggressive premedication with corticosteroids, or even use of a different brand of IVIG, is preferable to foregoing immunoglobulin. Rarely, a child might develop congestive heart failure during or after infusion of the IVIG because of the high solute load and subsequent increase in intravascular volume. Slowing the infusion rate and administration of furosemide are usually the only treatments required. Treatment with IVIG leads to improvement in myocardial contractility and is almost invariably adequate therapy.[7] Hemolysis is uncommon, but occasionally it may be severe, requiring transfusion.[185] Headache up to 72 hours after the infusion is common, especially in older patients. Such children may require low-dose opiates for relief.[186]

Virtually all data concerning the role of IVIG are limited to treatment during the first 10 days of illness. This is not to say that treatment after 10 days of illness is ineffective or contraindicated; it is merely inadequately studied. In a report of 16 children with coronary artery aneurysms treated a mean of 17 days after the onset of fever, echocardiogram showed there was a trend toward resolution of abnormalities.[187] The American Academy of Pediatrics cautiously recommends IVIG for children beyond the tenth day of illness with "manifestations of continuing inflammation," and such an approach appears prudent.[165] Questions have arisen concerning very early treatment of KD.[188] Tse and colleagues,[189] on the other hand, reported that IVIG given on or before the fifth day of illness resulted in fewer coronary artery abnormalities at the 1-year follow-up assessment. Thus, decisions about the optimal date for treating with IVIG are best made based on a patient's clinical status and the certainty of the diagnosis of KD rather than anticipated advantages of administration on a particular day of disease.

Prediction of IVIG Resistance

The clinical importance of predicting which children will suffer from cardiac sequelae from KD has led to the creation of several risk scores for IVIG resistance. In a retrospective series from Japan, Fukunishi and colleagues[190] found higher serum levels of CRP, lactate dehydrogenase, and bilirubin to be predictive of failure to respond to IVIG. More recently, Kobayashi and colleagues reported on several factors that were associated with decreased responsiveness to IVIG, and therefore increased risk of coronary artery abnormalities: hyponatremia; elevated hepatic transaminase and CRP; a high percentage of bands on the WBC count differential; a platelet count of 300,000 or less; short duration between fever onset and diagnosis (4 days or less); and being younger than 12 months of age at onset.[191] Egami et al.[192] and Sano et al.[193] have also constructed risk scores for IVIG resistance utilizing similar parameters. Unfortunately, application of these risk scores did not accurately identify all children at risk for IVIG resistance and coronary artery abnormalities in a North American cohort.[194] In a Canadian study, Han and colleagues[188] could not identify any difference in laboratory parameters between responders and nonresponders. Confirming the importance of controlling inflammation in KD, Mori and co-workers[195] reported that a rise in the WBC count and CRP level after IVIG infusion are independent predictors of coronary artery abnormalities.

Glucocorticoids

Glucocorticoids, the preferred initial treatment for other forms of vasculitis, were considered unsafe in KD for many years following the early descriptions of the disease. This is based primarily on a study[196] that demonstrated an extraordinarily high incidence of coronary artery aneurysms (11 of 17 patients) in a group that received oral prednisolone at a dose of 2 to 3 mg/kg/day for at least 2 weeks, followed by 1.5 mg/kg/day for an additional 2 weeks. Interestingly, seven patients in the same study received prednisolone plus aspirin, and none

developed aneurysms. In fact, no subsequent study has indicated that corticosteroids are harmful when used either with IVIG or as an alternative to IVIG therapy. Corticosteroids in KD have been studied both as primary therapy and "rescue" therapy, and doses have ranged from pulse doses of 30 mg/kg (maximum of 1 g) to conventional antiinflammatory doses (2 mg/kg/day).

Potential benefits of corticosteroids as rescue therapy in KD have been reported. Initially, two retrospective analyzes supported the use of corticosteroids in children who were unresponsive to two doses of IVIG or who relapsed after such therapy.[197,198] Hashino and colleagues[199] also found a beneficial effect of glucocorticoids in KD in a prospective trial. Children who had failed to respond to two doses of IVIG were randomized to receive a third dose of IVIG or pulse-dose methylprednisolone. Patients who received methylprednisolone had a significantly shorter duration of fever, and although transient coronary artery dilation was associated with glucocorticoid therapy, there was no overall difference in the incidence of coronary artery abnormalities between groups. Recently, Kobayashi et al.[200] retrospectively reviewed 359 consecutive KD patients over 12 years who failed to respond to first-line therapy of IVIG. They compared outcomes of children who received a second dose of IVIG versus a second dose of IVIG plus prednisolone versus prednisolone as monotherapy (maximum dose of 2 mg/kg/day for all children receiving steroids). They found that outcomes were better in the IVIG + prednisolone group with decreased need for subsequent treatments (aOR 0.16, 95% confidence interval [CI] 0.09-0.31), and fewer coronary artery abnormalities at 1 month (aOR 0.40, 95% CI 0.18-0.91) than the IVIG group. However, the treatment regimens were selected arbitrarily in this retrospective study. A prospective study is likely needed to assess the role of corticosteroids as rescue therapy.

Might steroids be more effective if administered earlier in the course of KD? Shinohara and colleagues[201] retrospectively reviewed the results in almost 300 patients with acute KD seen between 1982 and 1998 who were treated before the tenth day of illness. All patients received aspirin, dipyridamole, and propranolol. The addition of prednisolone therapy, either alone or with IVIG, was associated with a significantly shorter duration of fever and a lower prevalence of coronary artery aneurysms. No adverse reactions were recorded for any therapy. A prospective study suggested benefit as well: Inoue[202] reported that the frequency of coronary artery abnormalities in children treated with IVIG plus prednisolone at a dose of 2 mg/kg/d was lower than in those treated with IVIG alone. Three other studies[197,203,204] have shown that children treated with intravenous methylprednisolone (IVMP) (or dexamethasone) plus IVIG had a faster resolution of fever, more rapid improvement in the markers of inflammation, and a shorter length of hospitalization than those who received IVIG alone. Two of these studies had insufficient statistical power to detect a potential benefit of glucocorticoid therapy on coronary artery outcomes. The third trial, by Newburger and colleagues, found no significant difference in the frequency or severity of coronary artery lesions between treatment groups at the 1- or 5-week follow-up. Interestingly, however, post hoc analysis suggested that children who ultimately failed to respond to an initial dose of IVIG were less likely to develop coronary artery aneurysms if their initial therapy had included IVMP.

Following up on this finding, the Osaka Kawasaki Disease Study Group[205] conducted a comparative trial of IVIG versus IVIG + IVMP in children with KD who were regarded as being at high risk to be nonresponse to IVIG.[193] Patients were given heparin (10 U/kg/hour) for 48 hours beginning 2 hours before receiving IVMP (30 mg/kg), followed by IVIG (2 g/kg). Aspirin (30 mg/kg/d) was started at the end of the heparin infusion and reduced to 10 mg/kg/day after resolution of fever. Therapy was effective in 44% of those given IVIG alone compared with 66% of those receiving both IVIG and IVMP. Coronary artery abnormalities, including aneurysms, were significantly less frequent in the IVIG + IVMP group (24%) compared with the IVIG-alone group (46%).

In a meta-analysis of eight studies, Wooditch and Aronson concluded that the incidence of coronary artery aneurysms was reduced by the addition of corticosteroids to therapeutic regimens that included aspirin.[198] However, a subsequent meta-analysis of four studies that evaluated primary treatment of KD with corticosteroids found that IVIG resistance was less common in those treated with steroids as primary therapy (OR 0.48, 95% CI 0.24-0.95), but coronary outcomes did not differ.[206]

The most definitive trial to date regarding corticosteroids in combined primary therapy with IVIG was the RAISE trial by Kobayashi et al. in 2012.[207] There were 248 patients were enrolled in this multicenter, prospective, randomized, open label, blinded end points trial. All patients enrolled had a Kobayashi score or 5 or greater,[191] and therefore were considered to be at high risk for IVIG resistance. Of note, patients on day 9 or later of illness were excluded, as were patients with coronary artery abnormalities on baseline echocardiogram. Patients were randomized to standard therapy with IVIG and ASA versus IVIG plus prednisolone at a dose of 2 mg/kg/day. The corticosteroid was initially given intravenously for 5 days, which was changed to oral dosing if the patient's fever abated, and then tapered following normalization of the CRP. The primary end point of the trial was defined as coronary artery abnormalities per JPH criteria seen on two-dimensional (2D) echocardiography in the steroid versus IVIG alone groups at weeks 1, 2, or 4. A significant difference in coronary artery abnormalities between the groups at the interim analysis, favoring administration of steroids with IVIG (3% [n = 4] vs. 23% [n = 28], $P < 0.0001$), led to early termination of the study. Secondary end points included incidence of coronary artery abnormalities at week 4, z scores of coronary arteries, incidence of need for rescue therapy, duration of fever after enrollment, and serum CRP concentrations at weeks 1 and 2. All secondary end points were also met, a remarkable achievement. Of note, although the overall incidence of coronary artery abnormalities in the IVIG group was high at 23% during the study period, as would be expected in this group of high-risk patients, the maximum z scores were relatively low, between 2.26 and 2.32.[207]

Challenges in determining the optimal use of corticosteroid treatment in KD remain. An accurate, easily applicable risk score has not been constructed to effectively stratify children with KD in North America and Europe who are at increased risk of developing coronary artery abnormalities. Furthermore, it remains unclear whether corticosteroids are best used as intensification of primary therapy for all KD patients at a time when the vascular walls of the arteries may be particularly vulnerable, or as rescue therapy for children who fail conventional therapy and are at higher risk for coronary artery abnormalities.

Anti-TNF Agents

Levels of TNF-α are markedly increased in children with KD, especially in those who develop coronary artery lesions.[208,209] As such, infliximab, a monoclonal antibody to TNF-α, has been the subject of trials in children with KD, both as rescue therapy as well as primary therapy.

A prospective randomized multicenter comparison of the effectiveness of IVIG (2 g/kg) and infliximab (5 mg/kg) in children who had not responded to an initial infusion of IVIG[210] showed that both agents were equally safe and well tolerated. Hirono and colleagues[211] also found that infliximab was effective in controlling fever but did

not completely prevent coronary artery changes, although single case reports document resolution of aneurysms following infliximab therapy in some patients.[212,213] A retrospective two-center comparison of KD patients resistant to initial therapy with IVIG who were treated with either methylprednisolone (30 mg/kg) or infliximab (5 mg/kg) found that infliximab-treated patients had less fever and fewer days in the hospital, but there were no differences in coronary artery outcomes between the treatment groups.[214]

Recently, Tremoulet et al. explored the utility of administering infliximab (5 mg/kg) as primary therapy with IVIG.[215] There were 196 patients enrolled in a phase 3, randomized, double-blind, placebo-controlled trial at two centers. The primary end point of a difference in IVIG resistance between patients receiving combined therapy with IVIG and infliximab, and those receiving IVIG alone, was not met (11.2% vs. 11.3%, $P = 0.81$). Patients treated with infliximab had fewer days of fever and reduced inflammatory markers. The z score of the left anterior descending artery was significantly decreased in the infliximab group as compared with the placebo group at week 2 ($P = 0.45$). However, coronary outcomes at week 5 did not differ between treatment groups. There were no serious adverse events attributed to infliximab during the trial. At this time, the use of infliximab in the treatment of patients with KD remains essentially center-dependent, though convincing evidence of a beneficial effect on coronary artery outcomes is lacking.

Other Therapeutic Approaches

Therapies that are effective in other forms of vasculitis have been used in KD. Pentoxifylline was alleged to be effective in preventing coronary artery aneurysms,[216] but demonstration of flaws in the analysis of the data in this study[217] led to the conclusion that it is ineffective. Similarly, the human trypsin inhibitor, Ulinastatin, has been the subject of studies from Japan. Its efficacy in preventing coronary artery disease in KD is not convincing.[218]

The recent data regarding the potential role of T cells in KD[59,72] have led researchers to prescribe cyclosporine, a potent suppressor of T-cell activity through the nuclear factor of activated T-cells (NFAT) pathway. Suzuki et al.[219] studied 28 patients treated with cyclosporine A (CyA, 4 to 8 mg/kg/day) for refractory KD, defined as persistent fever after two doses of IVIG. The fevers of 18 of 28 patients subsided within 3 days of starting CyA. Four patients developed aneurysms, one of which was a giant aneurysm. Hyperkalemia occurred in nine patients, but no serious adverse events were reported. Tremoulet et al. also evaluated the use of calcineurin inhibitors in IVIG-resistant KD.[220] All 10 patients had already received rescue therapy in the form of an additional dose of IVIG (10 patients), pulsed methylprednisolone (3 patients), and infliximab (4 patients). Following treatment with a calcineurin inhibitor, all 10 patients reported the subsidence of fever. Seven of the patients experienced rapid resolution of the fever within 24 hours of starting treatment. Four of the patients had developed coronary artery aneurysms prior to therapy with a calcineurin inhibitor; all improved thereafter.

The use of statins has been explored in patients with significant cardiovascular sequelae from KD, given their potential beneficial effects on vascular reactivity and remodeling as well as their antiinflammatory effects.[221,222] A very small study of 11 KD patients with coronary artery aneurysms treated with simvastatin for 3 months reported a significant reduction in the high-sensitivity (hs)-CRP level and improvement in flow-mediated dilation.[223] Niedra et al. evaluated the safety of atorvastatin by following 20 patients with coronary artery aneurysms for a median of 2.5 years while treated with atorvastatin (5 to 10 mg daily).[224] Almost half of the patients had at least one episode of hypocholesterolemia, and two required a lowered dose. Mild transaminitis occurred in seven of the patients; only one patient had increased creatine phosphokinase level. They concluded that use of atorvastatin was safe with close monitoring.[224]

The potential role for cyclophosphamide[225] in KD is extremely limited, but it may be useful in cases with persistent active disease that is unresponsive to conventional therapy. In fact, children with prolonged inflammation ascribed to KD may be similar to children with polyarteritis nodosa, in which longer-term immunosuppression with cyclophosphamide is standard therapy.[226] A dramatic response to plasmapheresis in refractory cases of KD also has been reported,[227] but the technical limitations and potential hazards of this therapy are considerable. It should be reserved for children with active inflammation who have failed all available medical interventions, including multiple doses of IVIG, intravenous methylprednisolone, and TNF inhibition. There have been conflicting reports of the efficacy of abciximab, a monoclonal antibody that inhibits platelet glycoprotein IIb/IIIa receptor. In one study,[228] there was an increased resolution of aneurysms in patients with KD who received abciximab compared with those who received conventional treatment. However, a second study[229] could not duplicate these findings.

TREATMENT OF RELAPSES

Fever returns within 48 hours of treatment with IVIG in 10% to 20% of children, indicating failure to suppress the underlying inflammatory process. Because prolonged fever is an independent risk factor for the development of coronary artery aneurysms, current treatment protocols generally recommend retreatment with a second dose of IVIG (2 g/kg).[6] Those who fail to respond to a second dose—up to one third of patients in some studies[230]—are at extremely high risk of developing coronary artery aneurysms.[199] As noted above, use of corticosteroids appears to have the most convincing evidence of benefit in children resistant to IVIG, although definitive evidence for preference of one regimen over another is lacking. Therapeutic strategies include intravenous methylprednisolone (30 mg/kg/day for 1 to 3 days)[188] prednisolone at 2 mg/kg/day,[200] or infliximab (5 mg/kg).[231] Regardless of which approach is selected, treatment should continue until fever resolves and the CRP is normal. Frequent monitoring of the coronary arteries should be pursued until children have fully recovered.

PREVENTION AND MANAGEMENT OF THROMBOSES

The risk of thrombosis of coronary or other arteries depends on the degree of vascular damage. In all patients with KD, irrespective of the demonstration of coronary artery abnormalities, low-dose (3 to 5 mg/kg/day) aspirin should be continued until the ESR and platelet counts have normalized. Children with coronary artery abnormalities demonstrated by echocardiography are often treated with antithrombotic agents, such as low-dose aspirin, for as long as the abnormalities persist (Table 35-2). Children with large aneurysms are given warfarin or low-molecular-weight heparin to induce anticoagulation.

When injured coronary arteries become obstructed (risk level V), in addition to anticoagulation, various therapies have been attempted to restore circulation. Should the obstruction occur within 6 weeks of the onset of illness, control of vascular inflammation with IVIG and other agents is an essential prerequisite to arterial reperfusion. Thereafter, treatments may include thrombolytic therapy for arterial thrombosis or vasodilators if tissue viability is primarily threatened by vasospasm. Urokinase, streptokinase, and tissue-type plasminogen have all been used for the lysis of coronary artery thromboses. Similarly, peripheral arterial obstruction may be corrected by thrombolysis,

TABLE 35-2 Recommendations for Long-Term Follow-Up

RISK LEVEL	PHARMACOLOGICAL THERAPY	PHYSICAL ACTIVITY	FOLLOW-UP AND DIAGNOSTIC TESTING	INVASIVE TESTING
I (no coronary artery changes at any stage of illness)	None beyond first 6-8 weeks	No restrictions beyond first 6-8 weeks	Cardiovascular risk assessment counseling at 5-year intervals	None recommended
II (transient coronary artery ectasia disappears within first 6-8 weeks)	None beyond first 6-8 weeks	No restrictions beyond first 6-8 weeks	Cardiovascular risk assessment counseling at 3- to 5-year intervals	None recommended
III (1 small to medium coronary artery aneurysm/major coronary artery)	Low-dose aspirin (3-5 mg/kg aspirin/day), at least until aneurysm regression documented	For patients <11 years old, no restriction beyond first 6-8 weeks; patients 11-20 years old, physical activity guided by biennial stress test, evaluation of myocardial perfusion scan; contact or high-impact sports discouraged for patients taking antiplatelet agents	Annual cardiology follow-up with echocardiogram + electrocardiogram, combined with cardiovascular risk assessment, counseling; biennial stress test/ evaluation of myocardial perfusion scan	Angiography, if noninvasive test suggests ischemia
IV (≥1 large or giant coronary artery aneurysm, or multiple or complex aneurysms in same coronary artery, without obstruction)	Long-term antiplatelet therapy and warfarin (target international normalized ratio 2.0-2.5) or low-molecular-weight heparin (target: antifactor Xa level 0.5-1.0 U/mL) should be combined in giant aneurysms	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	Biannual follow-up with echocardiogram + electrocardiogram; annual stress test/evaluation of myocardial perfusion scan	First angiography at 6-12 months or sooner if clinically indicated; repeated angiography if noninvasive test, clinical, or laboratory findings suggest ischemia; elective repeat angiography under some circumstances
V (coronary artery obstruction)	Long-term low-dose aspirin; warfarin or low-molecular-weight heparin if giant aneurysm persists; consider use of β-blockers to reduce myocardial O_2 consumption	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	Biannual follow-up with echocardiogram and electrocardiogram; annual stress test/evaluation of myocardial perfusion scan	Angiography recommended to address therapeutic options

From Newburger, Takahashi, Gerber, et al., Diagnosis, treatment and long-term management of Kawasaki disease: a statement for health professionals from the committee on rheumatic fever, endocarditis and Kawasaki disease. Council on Cardiovascular Disease in the Young: American Heart Association, Pediatrics 114 (2004) 1708–1733.

after which perfusion is maintained with heparin followed by a chronic oral anticoagulant regimen. If these treatments fail, a variety of invasive approaches have been suggested, including percutaneous transluminal coronary angioplasty[232] and coronary artery bypass grafting.[233] A small number of children with particularly severe coronary artery disease due to KD have required cardiac transplantation.[234]

MONITORING CARDIAC STATUS

There is no universal agreement about the timing and frequency of echocardiographic monitoring of patients with KD. Most protocols take into account the development of coronary artery aneurysms, which occur most frequently between the second and the eighth weeks after the onset of fever. It is recommended that the initial echocardiogram be obtained at the time a diagnosis of KD is suspected, and that each child with KD have a repeat echocardiography at 2 weeks and 6 weeks following illness.[235] Patients should also have repeated clinical examinations during the first 2 months to detect dysrhythmias, congestive heart failure, valvular insufficiency, or myocarditis.[236] Further follow-up is individualized, with more frequent studies performed in children with demonstrated coronary artery abnormalities (see Table 35-2).

Children whose coronary arteries have always been normal (risk level I) or are normal by echocardiographic criteria 1 to 2 months after the acute illness (risk level II) are regarded as healthy, and no further intervention is recommended after the 8-week follow-up assessment. In view of possible chronic abnormalities in endothelial function, however, many physicians consider a history of KD to be a risk factor for the development of coronary artery disease later in life.[237] They counsel modification of other atherosclerotic risk factors and continue to monitor children once every 5 years.

Single small- to medium-sized aneurysms (risk level III) usually resolve as determined by echocardiographic criteria, although this is not always the case. Healing occurs by fibrointimal proliferation, often accompanied by calcification, and vascular reactivity does not return to normal despite a grossly normal appearance.[238] This point is highlighted by a report of the sudden death of a 3½-year-old child 3 months after the child's dilated coronary arteries had regained a

normal echocardiographic appearance.[239] Autopsy revealed obliteration of the lumen of the left anterior descending coronary artery due to fibrosis, with evidence of ongoing active inflammation in the epicardial arteries. Such reports emphasize the need for confirmation of complete response to therapy in children who have had KD.

Giant aneurysms with an internal diameter of at least 8 mm represent a significant risk for morbidity and mortality, including a 35% chance of infarction (risk level IV).[168] These children are followed more closely and are treated with more aggressive antithrombotic and anticoagulation regimens.

DISEASE COURSE AND PROGNOSIS

Although standard therapy with IVIG and aspirin given within the first 10 days of illness greatly improves outcomes, approximately 5% of children still develop coronary artery aneurysms, and more children demonstrate coronary artery ectasia.[7]

The mortality rate has dropped steadily as the diagnosis and treatment have improved. Currently, the rate is about 0.1% in the United States and Japan.[239,240] Recurrent disease after full recovery from a first episode of KD is rare, but it does occur. In Japan, the recurrence rate is 3.6%,[31] with a higher incidence of cardiac complications during the second episode.[241] In the United States, the rate of recurrence is lower.

There have been two recent studies from Japan of long-term outcomes in KD cases complicated by giant coronary artery aneurysms. Suda et al. reviewed the case records of 76 patients with giant coronary artery aneurysms and found that the 30-year survival rate was 88%. However, there was a nearly 60% cumulative coronary intervention rate at 25 years from onset, indicating that these patients carry significant morbidity in terms of multiple procedures.[242] Tsuda reported similar survival rates in patients with giant coronary artery aneurysms followed for up to 3 decades, and noted that the long-term outcomes were worse for those patients with involvement of both the right coronary and the left coronary arteries.[243]

As mentioned previously, whether children with normal coronary artery dimensions throughout their illness are at higher risk for atherosclerotic disease later in life remains an area of ongoing research. Studies to date have been conflicting.[244-248] However, when standardized mortality ratios were calculated in 2009 for individuals in Japan who were diagnosed with KD during the years 1982–1992 and who had no cardiac sequelae, the mortality ratios of the KD patients showed no increases as compared to the general population.[249] Definitive data regarding long-term outcomes in KD patients who always have normal coronary arteries will likely be established as the KD cohorts in Japan reach middle age.

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