Kawasaki’s disease (KD), once known as mucocutaneous lymph node syndrome, is a systemic inflammatory disorder occurring in children that is accompanied by vasculitis and a risk of coronary artery aneurysms.

Other typical features of KD include spiking fevers, cervical lymphadenopathy, conjunctivitis, erythematous changes on the lips and in the oral cavity, dryness and cracking of the lips, a strawberry appearance to the tongue, and a polymorphous rash.

Eighty percent of KD cases occur in children less than 5 years of age.

Kawasaki’s disease strikes quickly, runs a furious course over a few weeks, and then apparently resolves. In all 50 of the patients described initially by Kawasaki, the symptoms resolved without sequelae within 1 month. In subsequent years, however, mortality from cardiac complications (usually coronary artery thrombosis) was reported (5,6). Cardiac complications of KD result from a severe panvasculitis, leading to narrowing of the coronary lumina by the migration of myointimal cells from the media through the fragmented internal elastic lamina. Although catastrophic heart complications occur in only a small minority of patients (<5%), the preponderance of patients with KD appear to have at least some cardiac involvement. Heart lesions may include myocarditis, pericarditis, aneurysmal dilatation...

Attempts to link KD definitively to some types of infection, particularly ones associated with superantigens, have thus far been unsuccessful.

High dose aspirin and intravenous immune globulin (IVIG) are the cornerstones of therapy in KD. IVIG is essential to the prevention of coronary aneurysms.

Years after KD has occurred during childhood years, some cases of myocardial infarction caused by thrombosis of coronary aneurysms have been reported.

CLINICAL FEATURES

Kawasaki’s disease strikes quickly, runs a furious course over a few weeks, and then apparently resolves. In all 50 of the patients described initially by Kawasaki, the symptoms resolved without sequelae within 1 month. In subsequent years, however, mortality from cardiac complications (usually coronary artery thrombosis) was reported (5,6). Cardiac complications of KD result from a severe panvasculitis, leading to narrowing of the coronary lumina by the migration of myointimal cells from the media through the fragmented internal elastic lamina. Although catastrophic heart complications occur in only a small minority of patients (<5%), the preponderance of patients with KD appear to have at least some cardiac involvement. Heart lesions may include myocarditis, pericarditis, aneurysmal dilatation...
and thrombosis of the coronary arteries (Figure 21F-2), and myocardial infarction. The tropism of the vascular inflammation for coronary arteries and its unusual propensity to cause aneurysm formation remain unexplained.

In addition to the cardiac findings, KD is associated with a number of other dramatic clinical findings (Table 21F-1). Spiking fevers may last for 5 days or more. The conjunctivae, generally inflamed in a nonpurulent manner, are accompanied by erythematous changes on the lips and in the oral cavity [Figure 21F-3(A)]. The lips become dry and cracked [Figure 21F-3(B)], with a diffuse reddening of the oropharyngeal area and a strawberry appearance to the tongue (Figure 21F-4). A polymorphous rash typically involves the trunk [Figure 21F-3(A)], and there may be extensive lymphadenopathy in the neck region. The palms and soles become erythematous and indurated, followed by desquamation in the skin of these areas during the healing phase (7–9).

The term atypical KD has been used to describe both older children and young infants presenting outside the typical age range of 2 to 5 years, as well as those presenting with features other than the classical criteria. Incomplete KD has been applied to any patient felt to have KD but who did not fulfill classical criteria. These are often diagnosed by echocardiogram findings of coronary aneurysms and often occur in the older children or young infants (10,11). Coronary aneurysms, in fact, are most likely to occur in infants <6 months of age. Because

### Table 21F-1. Principal Criteria for the Diagnosis of Kawasaki’s Disease (5 Out of 6 Criteria Met).^a^

| Criteria                                                                 | Description |
|--------------------------------------------------------------------------|-------------|
| Fever lasting 4 days or more                                             |             |
| Bilateral nonpurulent conjunctival injection                             |             |
| Changes of the lips and oral cavity (including dry, fissured lips, strawberry tongue, diffuse reddening of the oropharyngeal mucosa) |             |
| Polymorphous rash primarily on the trunk                                 |             |
| Acute nonpurulent swelling of a cervical lymph node to >1.5 cm           |             |
| Changes of the peripheral extremities (including reddening of palms and soles, indurative edema of hands and feet, membranous desquamation from the fingertips) |             |

^a^Illness not explained by any other known disease process.
FIGURE 21F-3
Oral and cutaneous manifestations of Kawasaki’s disease. (A) Erythema of the lips and an erythematous, annular rash on the skin. (B) Cracking and desquamation of the lips in a patient with Kawasaki’s disease. [Reproduced with permission pending from the American College of Rheumatology slide collection. (A) Slide 93 (#9106110). (B) Slide 92 (#9106131).]

FIGURE 21F-4
Strawberry tongue in Kawasaki’s disease. [Reproduced with permission pending from the American College of Rheumatology slide collection, Slide 95 (#9106120).]

TABLE 21F-2. REVISED GUIDELINES FOR THE DIAGNOSIS AND TREATMENT OF KAWASAKI’S DISEASE.

Expanded epidemiologic case definition includes fever of at least 4 days and ≥4 principal criteria (Table 21F-1) without other explanation OR fever and <4 principal criteria if coronary artery abnormalities are detected by echocardiogram or coronary angiography

An echocardiogram should be performed in any patient ≤6 months of age if fever persists ≥7 days without other explanation and with laboratory measures of inflammation, even in the absence of any principal clinical criteria

The following laboratory parameters may be used to help with diagnosis and determine disease severity: CRP ≥3.0 mg/dL, ESR ≥40 mm/h, albumin ≤3.0 g/dL, anemia for age, ↑ ALT, platelets after 7 days ≥450,000, WBC ≥15,000, urine microscopic ≥10WBC/high-powered field

SOURCE: From the scientific statement by the American Heart Association (AHA) Committee on Rheumatic Fever, Endocarditis, and Kawasaki Disease. Circulation 2004;110:2747–2771 and Pediatrics 2004;114:1708–1733.

ABBREVIATIONS: ALT, alanine aminotransferase; CRP, C-reactive protein; ESR, erythrocyte sedimentation rate; WBC, white blood cell count.
Epidermolysis and arthritis, aseptic meningitis, diarrhea, abdominal pain, pericardial effusion, obstructive jaundice, and hydrops of the gallbladder.

Intravenous immune globulin (IVIG), a critical medication in the treatment of KD, is a limited resource in many parts of the world because of its expense. The American Heart Association (AHA), concerned about both the potential for overuse of IVIG as well as the failure to employ this medication in a timely manner in appropriate patients, issued guidelines on the diagnosis and treatment of KD (Tables 21F-2 through 21F-4) (12,13). In these guidelines, the epidemiologic case definition of KD included fever of at least 4 days and four or more principal criteria (Table 21F-1) without other explanation; or fever and less than four principal criteria if coronary artery abnormalities are detected by echocardiogram or coronary angiography.

**Epidemiology**

In Japan, the illness appears in late winter and spring. The peak age is 6 to 12 months, with 80% of cases occurring in patients younger than 5 years of age. The male: female ratio is 1.5:1. Except for three major pandemics (1979, 1982, 1985/6), the cases have reached a plateau of 5000 to 6000 per year. The endemic annual incidence is 67/100,000 children <5 years old, with a recurrence rate of 6%.

In the United States, there is also a seasonal variation in most places. The peak age is 18 to 24 months, and the illness accounts for 3000 hospitalizations/year. The recurrence rate is 1% to 3%. Data from Hawaii from 1971–1980 show ethnic incidence rate/100,000 children <8 years old per year of 33.6 in Japanese, 11.1 in Chinese, 9.2 in Hawaiians, 2.9 in Filipinos, 2.8 in Caucasians. In Los Angeles from 1980–1983, rates per 100,000 children 9.2 in Hawaiians, 2.9 in Filipinos, 2.8 in Caucasians. In 1979, 1982, 1985/6, the cases have reached a plateau of 5000 to 6000 per year. The endemic annual incidence is 67/100,000 children <5 years old, with a recurrence rate of 6%.

*Source*: From the scientific statement by the American Heart Association (AHA) Committee on Rheumatic Fever, Endocarditis, and Kawasaki Disease. Circulation 1993;87:1776–1780 and Pediatrics 1979;63:175–179.

### TABLE 21F-3. ECHOCARDIOGRAM CRITERIA INCLUDE ANY OF THE FOLLOWING THREE.

1. LAD$^a$ or RCA$^b$ z score $\geq 2.5$

2. Japanese Ministry of Health Criteria (coronary artery diameter $>3$ mm in children $<5$ year or $>4$ mm in children $\geq 5$ years, lumen diameter $\pm 1.5x$ an adjacent segment, coronary lumen is clearly irregular)

3. $\geq 3$ suggestive features: (perivascular brightness, lack of tapering, ↓ left ventricular function, mitral regurgitation, pericardial effusion, LAD or RCA z scores $= 2–2.5$)

*Source*: From the scientific statement by the American Heart Association (AHA) Committee on Rheumatic Fever, Endocarditis, and Kawasaki Disease. Circulation 2004;110:2747–2771 and Pediatrics 2004;114:1708–1733.

$^a$Left anterior descending coronary artery.

$^b$Right coronary artery.

### TABLE 21F-4. KAWASAKI’S DISEASE: RECOMMENDED THERAPY.

| Acute Stage | Aspirin 80–100 mg/kg/day in 4 divided doses until the 14th day of illness + IVIG 2 g/kg in 1 dose over 10–12 hours |
| Convalescent Stage (>14th illness day; afebrile patient) | ASA at 3–5 mg/kg/day in a single dose Discontinue 6–8 weeks after onset of illness after verifying that no coronary abnormalities are present by echocardiography |
| Acute Coronary Thrombosis | Prompt fibrinolytic therapy with streptokinase, urokinase, or tissue plasminogen activator by a tertiary care center under the supervision of a cardiologist |
| Chronic Treatment for Patients with Coronary Aneurysms | ASA 3–5 mg/kg/day in a single dose Some physicians add dipyridamole in selected patients deemed at high risk Some physicians use warfarin or heparin in combination with antplatelet therapy in patients with severe coronary findings or past evidence of coronary thrombosis |

*Source*: From the scientific statement by the American Heart Association (AHA) Committee on Rheumatic Fever, Endocarditis, and Kawasaki Disease. Circulation 1993;87:1776–1780 and Pediatrics 1979;63:175–179.

<14 years old per year include 23.0 in Asians, 2.3 in African Americans, and 1.6 in Caucasians and Hispanics (14–17).

### Etiology

The epidemiology of KD is consistent with an infectious cause: clinical features that resemble infection (fever, lymphadenopathy), time-space clusters, epidemic occurrences, and alleged proximity of case foci to bodies of water. To date, however, no infectious etiology has been proven. There has been no culture or serologic evidence for conventional viral agents, Mycoplasmae, Rickettsiae, or bacterial agents (*Streptococcus*, *Staphylococcus*, or *Propionibacterium acnes* variant, retroviruses, Rickettsiae, parvovirus B19, Epstein–Barr virus, and coronavirus, as well as for the participation of the *S. aureus* toxin TSST-1 and other superantigens (e.g., *Yersinia pseudotuberculosis*).

Support exists for a superantigen-mediated process both from clinical studies (18–22) and from a murine model for coronary arteritis stimulated by *Lactobacillus casei* cell wall extracts (23). This hypothesis proposes that the etiologic agents—which may differ across geographic sites throughout the world—are capable of evoking immunologic responses via T-cell receptor V beta restriction. An oligoclonal response is supported by the discovery of IgA-secreting plasma cells within...
the walls of the affected arteries. This finding lends credence to the hypothesis that the respiratory or gastrointestinal tract may be the portal of entry for the inciting organism, and that the process is antigen-driven (24,25).

**PATHOGENESIS**

The pathogenesis is characterized by immune activation. A host of immunologic irregularities have been described in KD, not all of which have been confirmed consistently: endothelial cell activation [particularly human leukocyte antigen (HLA)-DR expression on coronary endothelial cells]; autoantibody formation (e.g., anti-endothelial cell antibodies); complement activation and immune complex formation; abnormalities of immunoregulation (lymphocyte infiltration, activated CD4+ and B cells, activated monocyte/macrophages, T lymphopenia, polyclonal B-cell activation); adhesion molecule upregulation (soluble P-, E-, and L-selectins); increased vascular endothelial growth factor; and marked cytokine production with high levels of interferon-gamma, interleukins-1, -4, -6, and -10, and tumor necrosis factor (TNF)-alpha (18,26–28). In severe cases, this “cytokine storm” results in a macrophage activation syndrome (MAS).

**TREATMENT**

Following the initial recognition of KD, this illness was treated with salicylates, using the same doses of aspirin employed in the treatment of rheumatic fever. Because of the potential for impedance of aspirin absorption caused by vasculitic involvement of the gastrointestinal tract, however, the use of aspirin must be monitored carefully in this setting. If aspirin doses are too high (e.g., 100–150 mg/kg/day), improvement of intestinal absorption with therapy may lead to symptoms of toxic-ity. In Japan, doses of 30 to 50 mg/kg/day have been employed because of the high incidence of the slow-acetylator gene in the Japanese population. A combined US and Japanese multicenter study demonstrated that 30 to 50 mg/kg of aspirin plus IVIG (see below) was effective at preventing aneurysm formation in most cases (29). Current AHA guidelines, however, endorse aspirin doses of 80 to 100 mg/kg/day, in four divided doses (Table 21F-4).

Furusho studied the use of aspirin alone versus the combination of aspirin plus IVIG (0.4 mg/kg/day × 4 days), using a protocol then in use for immune thrombocytopenic purpura (30). A multicenter study demonstrated a decrease in the incidence of coronary artery abnormalities: only 4% (3 of 68) in the IVIG group, compared with 33% (38 of 119) in the aspirin-only arm (31). No patients in the IVIG arm developed giant coronary artery aneurysms. In contrast, 6% of the aspirin-only group suffered this occurrence. This study established IVIG as the standard of care. Several years later, a follow-up trial compared a single dose of IVIG (2 g/kg) to the traditional 0.4 mg/kg/day × 4 schedule, confirming the superiority (a further lowering of the coronary aneurysm rate) of the single-dose regimen (32). Thereafter, the single-dose regimen became the standard of care recommendation by the AHA (Table 21F-4) (9,33).

The use of glucocorticoids in KD is, surprisingly, controversial. One retrospective study assessed the outcomes of five different treatment regimens, including aspirin alone, aspirin plus prednisolone, prednisolone alone, prednisolone plus warfarin, and no treatment aside from background antibiotic therapy (which all other treatment groups received, as well). Although aspirin alone reduced the aneurysm rate from 20% to 11% compared with the no-treatment group, treatment with prednisolone was associated with an increase in the percentages of patients who developed aneurysm to 67% (34). Of note, the seven patients treated with aspirin plus prednisolone—none of whom developed aneurysm—were not emphasized in the discussion. In addition, the patients in the prednisolone-only group were perhaps the most ill at baseline (and hence were treated with glucocorticoids, presumed empirically to be the most powerful therapy).

After the publication of this study’s results, glucocorticoids for the treatment of KD fell into disfavor among pediatricians and in fact were viewed as contraindicated for this disease. More recent case series, evaluating the use of pulse methylprednisolone as rescue therapy for IVIG nonresponders, have been more encouraging with regard to the potential for a beneficial effect of glucocorticoids (35–37). Initial results from a multicenter trial (38) indicate no worsening in the coronary aneurysm rate among patients treated with glucocorticoids, and a decrease in fever, inflammatory markers, length of hospital stay, and IVIG side effects.

A consensus conference at the National Institutes of Health (18) was prompted by the recognition of an ongoing immune activation at microvascular levels in patients treated adequately by the current therapies. Outcome data from Japan with long-term (10–15 year) follow-up demonstrated persistence of disease in some cases, with intravascular ultrasound and ultrafast computed tomography studies demonstrating lingering coronary aneurysms and/or wall fibrosis. Of greatest alarm was the finding of such abnormalities in areas of the vasculature previously documented as normal by echocardiogram and even coronary angiography. Electron microscopy studies of endomyocardial biopsies up to 23 years after the KD episode showed ongoing microaneurysms and small vessel coagulopathy. In a small number
of young adults who have experienced myocardial infarctions in the absence of known cardiac risk factors, angiograms have revealed giant coronary artery aneurysms compatible with old KD. The extent of active KD in such patients, if any, as opposed to the clinical sequelae occurring in arteries damaged years before, is not clear.

Newer treatment modalities have been utilized in selected patients and patient populations. Small studies and anecdotal reports of treatment with the antilipocytic protein IIb/IIIa monoclonal antibody (abiximab) or with low-molecular-weight heparin have suggested a more rapid regression of aneurysms and perhaps endothelial cell remodeling. Noninvasive imaging modalities, such as magnetic resonance imaging studies of the chest and abdomen, have identified the extracardiac arterial aneurysms and dilatation (Figure 21F-1). The knowledge of the more widespread nature of the vasculitic involvement has prompted more aggressive and combination therapies (39).

Pentoxifylline, a phosphodiesterase inhibitor, has antiplatelet activity, vasodilatory effects, effects on red blood cell rheology, and the ability to inhibit TNF synthesis. A regimen of 20 mg/kg/day of pentoxifylline in three divided doses demonstrated an improvement in clinical features and the rate of aneurysm formation in KD (40). Further pharmacokinetic studies of a commercial liquid preparation of pentoxifylline demonstrated safety and a reduction in TNF levels in KD patients of 28% with doses up to 25 mg/kg/day (41). Anecdotal reports indicate tolerability of doses of 40 to 60 mg/kg/day in infants with KD. A multicenter trial of infliximab in KD is currently under way (42,43).

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