Vasculitides

F. Kawasaki's Disease

BARRY L. MYONES, MD

- 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.
- 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.

Kawasaki's disease (KD) is a form of systemic vasculitis that occurs in young children and may be associated with the development of coronary arteritis and aneurysm formation (Figure 21F-1). KD is the leading cause of acquired heart disease of children in the United States. This illness, first recognized to be a new entity by Tomasaku Kawasaki in Japan in 1967 (1,2), was termed for *mucocutaneous lymph node syndrome* (MCLNS) until KD became the accepted designation for this disorder (3). Although the disorder was named after Kawasaki, at least one previous case exists in the medical literature (4). This case, recounted in detail below, is classic in its clinical features of KD.

A 5-year-old girl presented with a sore throat, a fever to 105°F, and an erythematous rash over her trunk, appearing “desperately and acutely ill” (4). Oropharyngeal lesions included an aphthous stomatitis, erythematous lesions of the hard palate, and prominent lingual papillae. On the fifth hospital day the hectic fevers ceased, but low-grade fevers and tachycardia to 140 beats per minute persisted. The skin of her fingers desquamated, but over the ensuing weeks she improved steadily. One month after admission, however, she developed acute chest pain, shortness of breath, and expired. A postmortem examination revealed blood and clots in the pericardial space, and several large aneurysms along the epicardial vessels. One aneurysm, the size of a large ripe cherry in the left coronary artery,

was the site of hemorrhage into the pericardium. Although the microscopic appearance of the disease was typical of periarteritis nodosa (i.e., PAN; see Chapter 21B), no hepatic or renal infarctions were present. Indeed, among the internal organs the heart alone was involved. The child's death was attributed to an atypical case of “infantile periarteritis nodosa,” now recognized as KD.

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

FIGURE 21F-1

Coronary and peripheral aneurysms in Kawasaki's disease (KD). Magnetic resonance angiogram in an infant with KD, revealing irregularities of the subclavian, axillary, and proximal brachial arteries, as well as fusiform dilatation of the right common iliac and right proximal internal iliac arteries. There is also a focal aneurysm of the left internal iliac artery.

FIGURE 21F-2

Coronary artery thrombosis leading to death in Kawasaki's disease. [Reproduced with permission from the American College of Rheumatology collection, slide 124 (#9406010).]

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. *Incom-*

plete 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

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)

^aIllness 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).]

of confusion (and often inappropriate use) surrounding disease terminology, there have been sentiments among KD experts to phase out the term *atypical* and to expand the term *incomplete*. Unusual disease features known to occur in KD include sterile pyuria and urethritis, arthral-

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, $\uparrow$ ALT, platelets after 7 days $\geq 450,000$, WBC $\geq 15,000$, urine microscopic ≥ 10 WBC/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.

gia 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

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

1. LAD^a or RCA^b z score ≥ 2.5
2. Japanese Ministry of Health Criteria (coronary artery diameter >3 mm in children <5 year or >4 mm in children ≥ 5 years, lumen diameter $\geq 1.5\times$ an adjacent segment, coronary lumen is clearly irregular)
3. ≥ 3 suggestive features: (perivascular brightness, lack of tapering, $\downarrow$ 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.

^aLeft anterior descending coronary artery.

^bRight 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 antiplatelet 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*). Molecular biologic techniques have provided support, however, for a *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 toxicity. 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).

Furusko studied the use of aspirin alone versus the combination of aspirin plus IVIG (0.4 mg/kg/day $\times$ 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 $\times$ 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 antiglycoprotein IIb/IIIa monoclonal antibody (abciximab) or with low-molecular-weight heparin have suggested 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).

REFERENCES

1. Kawasaki T. Acute febrile mucocutaneous syndrome with lymphoid involvement with specific desquamation of the fingers and toes in children [in Japanese]. *Arerugi* 1967; 16:178–222.
2. Kawasaki T, Kosaki F, Okawa S, et al. A new infantile acute febrile mucocutaneous lymph node syndrome (MLNS) prevailing in Japan. *Pediatrics* 1974;54:271–276.
3. Takahashi M. Kawasaki syndrome (mucocutaneous lymph node syndrome). In: Emmanouilides GC, ed. *Moss and Adams heart disease in infants, children, and adolescents: including the fetus and young adult*. 5th ed. Baltimore: Williams & Wilkins, 1995:13909.
4. Spector S. Scarlet fever, periarteritis nodosa, aneurysm of the coronary artery with spontaneous rupture, hemopericardium. *Arch Pediatr* 1939;25:319.
5. Kato H, Ichinose E, Yoshioka F, et al. Fate of coronary aneurysms in Kawasaki disease: serial coronary angiography and long-term follow-up study. *Am J Cardiol* 1982; 49:1758–1766.
6. Kato H, Ichinose E, Kawasaki T. Myocardial infarction in Kawasaki disease: clinical analyses in 195 cases. *J Pediatr* 1986;108:923–927.
7. Japan Kawasaki Disease Research Committee. Diagnostic guideline of Kawasaki disease. Tokyo: Japan Kawasaki Disease Research Committee; 1984.
8. American Heart Association Committee on Rheumatic Fever, Endocarditis, and Kawasaki Disease. Diagnostic guidelines for Kawasaki disease. *Am J Dis Child* 1990; 144:1218–1219.
9. Dajani AS, Taubert KA, Gerber MA, et al. Diagnosis and therapy of Kawasaki disease in children. *Circulation* 1993;87:1776–1780.
10. Rowley AH, Gonzalez-Crussi F, Gidding SS, et al. Incomplete Kawasaki disease with coronary artery involvement. *J Pediatr* 1987;110:409–413.
11. Rosenfeld EA, Corydon KE, Shulman ST. Kawasaki disease in infants less than one year of age. *J Pediatr* 1995; 126:524–529.
12. Newburger JW, Takahashi M, Gerber MA, 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. *Circulation* 2004;110:2747–2771.
13. Newburger JW, Takahashi M, Gerber MA, 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* 2004;114: 1708–1733.
14. Taubert KA. Epidemiology of Kawasaki disease in the United States and worldwide. *Prog Pediatr Cardiol* 1997;6:181–185.
15. Mason WH, Takahashi M, Schneider T. Recurrence of Kawasaki disease in a large urban cohort in the United States. In: Takahashi M, Taubert K, eds. *Proceedings of the Fourth International Symposium on Kawasaki Disease*. Dallas: American Heart Association; 1993:21–26.
16. Taubert KA, Rowley AH, Shulman ST. A 10 year (1984–1993) United States hospital survey of Kawasaki disease. In: Kato H, ed. *Kawasaki disease: proceedings of the 5th International Kawasaki Disease Symposium*. New York: Elsevier; 1995:34–38.
17. Yanagawa H, Yashiro M, Nakamura Y, et al. Results of 12 nationwide epidemiological incidence surveys of Kawasaki disease in Japan. *Arch Pediatr Adolesc Med* 1995;149:779–783.
18. Barron KS, Shulman ST, Rowley A, et al. Report of the National Institutes of Health workshop on Kawasaki disease. *J Rheumatol* 1999;26:170–190.
19. Leung DY, Meissner HC, Shulman ST, et al. Prevalence of superantigen-secreting bacteria in patients with Kawasaki disease. *J Pediatr* 2002;140:742–746.
20. Leung DYM, Giorno RC, Kazemi LV, et al. Evidence for superantigen involvement in cardiovascular injury due to Kawasaki disease. *J Immunol* 1995;155:5018–5021.
21. Leung DY, Meissner HC, Fulton DR, et al. Toxic shock syndrome toxin-secreting *Staphylococcus aureus* in Kawasaki syndrome. *Lancet* 1993;342:1385–1388.

22. Abe J, Kotzin BL, Jujo K, et al. Selective expansion of T cells expressing T-cell receptor variable regions V beta 2 and V beta 8 in Kawasaki disease. *Proc Natl Acad Sci USA* 1992;89:4066–4070.
23. Tomita S, Myones BL, Shulman ST. In vitro correlates of *L. casei* animal model of Kawasaki Disease. *J Rheumatol* 1993;20:362–367.
24. Duong TT, Silverman ED, Bissessar MV, et al. Superantigenic activity is responsible for induction of coronary arteritis in mice: and animal model for Kawasaki disease. *Int Immunol* 2003;15:79–89.
25. Rowley AH, Eckerley CA, Jack HM, et al. IgA plasma cells in vascular tissue of patients with Kawasaki syndrome. *J Immunol* 1997;159:5946–5955.
26. Rowley AH, Shulman ST, Spike BT, et al. Oligoclonal IgA response in the vascular wall in acute Kawasaki disease. *J Immunol* 2001;166:1334–1343.
27. Laxer RM, Schaffer FM, Myones BL, et al. Lymphocyte abnormalities and complement activation in Kawasaki disease. *Prog Clin Biol Res* 1987;250:175–184.
28. Myones BL, Bathori JM, Tomita S, et al. Intravenous IgG infusions are associated with the in vitro inhibition of classical pathway-mediated lysis of sheep red blood cells and a decrease in C4d levels in Kawasaki disease. In: Takahashi M, Taubert K, eds. *Proceedings of the Fourth International Kawasaki Disease Symposium*. Dallas: American Heart Association; 1993:412–418.
29. Terai M, Shulman ST. Prevalence of coronary artery abnormalities in Kawasaki disease is highly dependent on gamma globulin dose but independent of salicylate dose. *J Pediatr* 1997;131:888–893.
30. Furusho K, Kamiya T, Nakano H, et al. High-dose intravenous gammaglobulin for Kawasaki disease. *Lancet* 1984; 2:1055–1058.
31. Newburger JW, Takahashi M, Burns JC, et al. The treatment of Kawasaki syndrome with intravenous gamma globulin. *N Engl J Med* 1986;315:341–347.
32. Newburger JW, Takahashi M, Beiser AS, et al. A single intravenous infusion of gamma globulin as compared with four infusions in the treatment of acute Kawasaki syndrome. *N Engl J Med* 1991;324:1633–1639.
33. Dajani AS, Taubert KA, Takahashi M, et al. Guidelines for long-term management of patients with Kawasaki disease. *Circulation* 1994;89:916–922.
34. Kato H, Koike S, Yokoyama T. Kawasaki disease: effect of treatment on coronary artery involvement. *Pediatrics* 1979;63:175–179.
35. Wright DA, Newburger JW, Baker A, et al. Treatment of immune globulin-resistant Kawasaki disease with pulsed doses of corticosteroids. *J Pediatr* 1996;128: 146–149.
36. Shinohara M, Sone K, Tomomasa T, et al. Corticosteroids in the treatment of the acute phase of Kawasaki disease. *J Pediatr* 1999;135:465–469.
37. Hashino K, Ishii M, Iemura M, et al. Re-treatment of immunoglobulin-resistant Kawasaki disease: a comparative study of additional immune globulin and steroid pulse therapy. *Pediatr Int* 2001;43:211–217.
38. Sundel RP, Baker AL, Fulton DR, et al. Corticosteroids in the initial treatment of Kawasaki disease: report of a randomized trial. *J Pediatr* 2003;142:611–616.
39. Myones BL, Altman CA, Ayres N, et al. Imaging of coronary and peripheral arteries with magnetic resonance angiography (MRA) in infants with Kawasaki disease: a new utilization to guide therapy. *Arthritis Rheum* 2002;46: S309.
40. Furukawa S, Matusubara T, Umezawa Y, et al. Pentoxifylline and intravenous gamma globulin combination therapy for acute Kawasaki disease. *Eur J Pediatr* 1994;153: 664–667.
41. Best BM, Burns JC, DeVincenzo J, et al. Pharmacokinetics and tolerability assessment of a pediatric oral formulation of pentoxifylline in Kawasaki disease. *Curr Ther Res* 2003;64:96–115.
42. Burns JC, Mason WH, Hauger SB, et al. Infliximab treatment for refractory Kawasaki Syndrome. *J Pediatr* 2005; 146:662–667.
43. Weiss JE, Eberhard BA, Chowdhury D, et al. Infliximab as a novel therapy for refractory Kawasaki disease. *J Rheumatol* 2004;31:808–810.