165 Kawasaki Disease

Rae S. M. Yeung

Disease Definition

Kawasaki Disease (KD) is one of the most common causes of vasculitis affecting children. Although the inflammatory response is found in medium and small vessels throughout the body, the most common site of damage is the coronary arteries, making KD the leading cause of acquired heart disease in children from the developed world. KD continues to be a diagnostic challenge. There is no single diagnostic test or unique clinical finding to distinguish KD from other acute febrile exanthems of childhood. Although called a disease, KD is truly a syndrome complex characterized by multi-system inflammation. KD presents clinically as prolonged fever, usually greater than 5 days in duration, a polymorphous skin rash, nonexudative bilateral conjunctival injection, oral mucosal inflammation with erythema of the lips and a strawberry tongue, extremity changes which include redness of the palms and soles and swelling of the dorsum of the hands and feet, as well as cervical lymphadenopathy, typically unilateral and greater than 1.5 cm in diameter. Presence of fever plus at least four out of five of these principal features constitutes the diagnosis of typical KD (◉ *Table 165.1*). The absence of a specific diagnostic test for the disease continues to hinder identification of affected children and a lack of predictive markers of this clinically heterogeneous clinical syndrome is an obstacle to the improvement of therapy for affected children.

Epidemiology

The most common age of occurrence is between 12 months and 5 years although younger children and adults can be affected. Since the initial clinical descriptions in Japan and Hawaii, the number of cases of KD has increased dramatically and is currently recognized worldwide. KD is seen in all ethnic groups and in all regions of the world, but the incidence of disease varies dramatically from region to region and between different ethnic groups suggesting a major role for genetics in KD risk and outcome. The annual incidence, reported as number per 1,000,000 children under 5 years of age, ranges from 5 in Denmark, 8 in New Zealand, 26 in Canada, 39 in Hong Kong, 55 in China, 105 in Korea to over 180 in Japan. Siblings of affected children are at tenfold higher risk for KD compared to the general population, and incidence of KD is twofold higher than normal in children of affected individuals.

In Asia and North America, KD is more common during the winter and early spring months and boys outnumber girls by 1.5–1.7 to 1 with greater than three quarters of affected children under the age of 5. The case fatality rate of KD in Japan is about 0.08%. This number appears to be decreasing in the most recent nationwide surveys done in countries that have active surveillance programs for KD. Virtually all deaths of patients with KD result from its cardiac sequelae. The peak mortality has been reported to occur between 15 and 45 days after the onset of fever. During this subacute phase of illness, inflammation continues and is coupled with marked elevation in the platelet count and a hypercoagulable state. Sudden death from myocardial infarctions may also occur years after the acute KD episode in children who had coronary artery aneurysms and stenosis.

Etiology

Despite numerous studies, the etiology of KD remains elusive. KD has been linked with many different etiologic agents ranging from bacteria such as *Staphylococcus*, *Streptococcus*, *Proprionibacterium*, and *Chalmydia* to viruses such as Epstein–Barr virus, parvovirus, coronavirus, and retroviruses, but no one causative agent has been consistently demonstrated. KD fits nicely in the spectrum between an infectious disease, an inflammatory syndrome, and a true autoimmune disease, with an infectious trigger leading to a prolonged self-directed immune response in a genetically susceptible host. The etiology debate has centered around the mechanism of immune activation: conventional antigen versus superantigen. Evidence supporting both hypotheses continues to accumulate. Some investigators have focused their work on identifying

Abdelaziz Y. Elzouki (ed.), *Textbook of Clinical Pediatrics*, DOI 10.1007/978-3-642-02202-9_165,

Table 165.1
Diagnostic features of KD

Prolonged fever (at least 5 days in duration) plus the presence of at least four of the following five principal features:
1. Polymorphous skin rash
2. Bilateral nonexudative conjunctival injection
3. Oral–mucosal changes including:
• Erythema
• Cracked lips
• Strawberry tongue
• Injection of the oral and pharyngeal mucosa
4. Extremity changes including:
• Erythema of the palms and/or soles
• Swelling of the hands and/or feet
• Periungual peeling of the fingers and/or toes in the subacute phase
5. Cervical lymphadenopathy (>1.5 cm in diameter), usually unilateral

one specific pathogen or family of pathogens responsible for disease. One group has identified oligoclonal IgA antibodies present in arterial tissue from fatal cases of KD. Recent interest and debate has centered on a novel human coronavirus found by a group of investigators in the respiratory secretions of some children with KD. Others investigators have not been able to confirm these data, echoing the outbreak-dependent nature of this syndrome.

The longer the search for a single infectious agent, the longer the list of diverse infectious organisms found. The presence of a shared property, common to multiple infectious agents, resulting in the same pathogenic process leading to the clinical syndrome of KD is another explanation. One such common feature of many infectious organisms is the presence of superantigenic activity. Superantigens are a group of proteins which share the ability to stimulate a large proportion of T cells (up to 30% of the T cell repertoire compared to one in a million T cells for conventional antigens) by binding to a portion of the T-cell receptor β chain (TCRVβ) in association with the major histocompatibility complex (MHC) class II molecules with no requirement for antigen processing. Superantigens have been identified in a variety of microorganisms including bacteria (*Staphylococci*, *Streptococci*, *Mycobacterium*, *Mycoplasma*, *Yersinia*), and viruses (rabies, EBV). Evidence from a number of KD outbreaks point to the classic footprint for superantigens specifically TCRVβ skewing in the peripheral blood and in affected cardiac tissue.

Although the debate continues regarding the mechanism of initial immune activation, the more likely scenario is that there is cooperation between different mechanisms and a final common pathway of immune activation responsible for this clinical syndrome. One of the unifying features of KD is a prolonged inflammatory response. It is possible that in many cases the infectious trigger, which started the inflammatory process, has been eliminated, and in those children who develop KD the persistent inflammatory response has become the problem. Containing the inflammatory response is one of the objectives of therapy in acute KD. Inflammation in itself is not worrisome, but prolonged inflammation leads to activation of downstream effectors, which can lead to coronary artery damage.

Pathogenesis

Systemic inflammation is the most striking finding in KD. This is evidenced clinically and biochemically during the acute phase of illness. Like other syndromes characterized by systemic inflammation, TNF-α is markedly elevated in children during the acute phase of KD. TNF-α is a pleiotropic cytokine critical in the regulation of immune cells and plays a critical role in inflammation. The link between the systemic immune response seen in the acute phase of KD and subsequent damage to the coronary arteries is not clearly understood. There is now emerging evidence that TNF-α is critical in the pathogenesis of KD, specifically at the level of the target tissue- the coronary artery. Key downstream effects of TNF-α signaling include leukocyte recruitment to the coronary artery and up-regulation of matrix degrading enzymes and pro-inflammatory cytokines. TNF-α up-regulates expression and activity of many members of the matrix metalloproteinase (MMP) family of enzymes. MMPs are a family of zinc-dependent matrix-degrading proteases that share the ability to degrade molecules of the extracellular matrix. Elastin is an important extracellular matrix component in arterial vessel walls. Breakdown of elastin leads to the loss of structural integrity of the vessel wall and ballooning, the hallmark of aneurysm formation. MMPs play an important role in the degradation of elastin leading to aneurysm formation. Two MMPs in particular, MMP-2 and MMP-9, have been localized to areas of inflammation and internal elastic lamina degradation in aneurysms. In fatal cases of human KD, MMP-9 was expressed in coronary artery aneurysms but not in non-KD control coronary vessels suggesting a role in the development of aneurysms.

Clinical Manifestations

KD has many features suggestive of an infectious trigger. The illness is endemic with seasonal fluctuations and is punctuated with epidemic outbreaks. Many of the clinical features of KD are outbreak dependent with a different spectrum of clinical findings found from one mini outbreak to another, and cases having similar clinical phenotypes clustering temporally. KD can be divided into three phases: acute, subacute, and convalescent. The acute phase is characterized by a multi-system vasculitis, evidenced by the classic signs of inflammation including redness, heat, and swelling. The five principal features plus fever are the distinctive inflammatory changes seen in this illness. There are many associated clinical features, all attributed to the underlying vasculitis. The effects of KD on multiple systems of the body are well recognized. These include: aseptic meningitis, anterior uveitis, myositis, and hydrops of the gall bladder. The pattern of manifestations of many of these associated features has evolved over the past 2 decades mainly due to the changing pattern of clinical treatment. Arthritis can also be a common finding in KD, seen in 7% of children at diagnosis of KD. Which compares favorably to a much higher incidence in the pre-intravenous immunoglobulin (IVIG) treatment era. The arthritis of acute KD is effusive and often noted to be intensely painful, affecting ambulation in many instances. A predominance of large joints are affected regardless of the pattern of joint involvement. The clinical course of symptomatic arthritis is short-lived in the majority of affected children. Most affected children have a dramatic and rapid resolution of their arthritis following combined treatment with IVIG and high dose aspirin, regardless of the number of joints involved or distribution of disease. Despite evidence of increased systemic inflammation in children with arthritis, their response to treatment and coronary outcome are unchanged compared to children without arthritis.

The subacute phase of illness is characterized by resolution of fever, as well as the associated systemic symptoms associated with inflammation. There is often a classic peeling of the skin starting at the periungual region of the fingers and toes. During this phase, coronary artery lesions are most commonly detected. Despite early treatment with high dose IVIG and aspirin, aneurysms continue to develop in approximately 5% of children who are appropriately treated. When adjusted for body surface area, this number increases to 20–30% of affected children who develop coronary artery lesions (CAL). KD is now recognized as the number one cause of acquired heart disease in children in the developed world.

There has been increasing recognition of typical KD (see *Table 165.2* – differential diagnosis). The challenge clinically is recognition of children who present with incomplete or atypical disease. Incomplete KD is the more appropriate term as these children do not present with atypical features but rather they simply do not present with the full clinical picture typical of the disease and have fever with less than four out of five of the principal clinical features of KD. The diagnosis of KD is strictly based on clinical criteria. Having said this, many physicians and experts in the area have recognized that there are supportive criteria which aid in the identification of this group of children at increased risk for development of CAL. The American Heart Association (AHA) has proposed an algorithm to aid in the evaluation and management of children who do not fulfill full diagnostic criteria for KD (*Fig. 165.1*). The proposed supportive criteria include laboratory findings which reflect the underlying multi-system inflammation. These include elevated C-reactive protein (CRP), raised erythrocyte sedimentation rate (ESR), hypoalbuminemia, anemia, elevated serum transaminases, thrombocytosis, and leukocytosis (*Table 165.3*). Incomplete KD presents clinicians with the challenge of correctly identifying and treating patients to prevent the development of coronary artery lesions. The studies investigating the contribution of clinical phenotype to coronary outcome have identified duration of

Table 165.2
Differential diagnosis of KD

• *Staphylococcal* and *Streptococcal* disease
–Scarlet fever
–*Staphylococcal* scalded skin syndrome
–Toxic shock syndrome
• Viral infections
–Measles
–Adenovirus
–Enterovirus
–Epstein–Barr virus
• Cervical adenitis
• Drug hypersensitivity reactions
• Stevens–Johnson syndrome
• Rocky Mountain spotted fever
• Leptospirosis
• Systemic onset juvenile idiopathic arthritis
• Mercury hypersensitivity reaction (acrodynia)

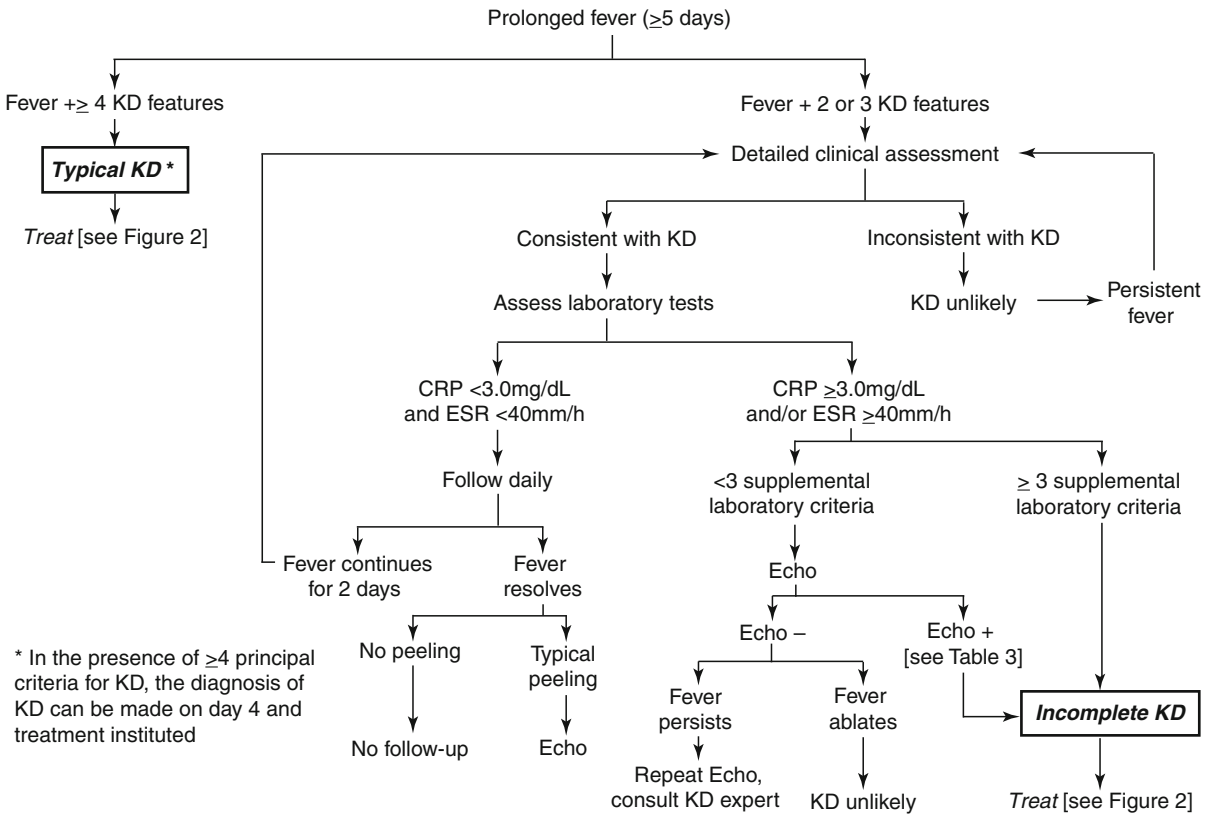

Figure 165.1
Proposed algorithm from the American Heart Association for the evaluation of a child with suspected Kawasaki disease (Adapted from Newburger 2004)

Table 165.3
Supplemental laboratory criteria in the evaluation of suspected incomplete KD[a]

1.	Hypoalbuminemia (Albumin ≤ 3.0 g/dL)
2.	Anemia for age
3.	Liver inflammation (elevated alanine aminotransferase)
4.	Thrombocytosis (platelets ≥ 450,000/mm after day 7)
5.	White blood cell count ≥ 15 000/mm
6.	Sterile pyuria (urine ≥ 10 white blood cells/high-power field)

[a]AHA algorithm 2004

fever as the most powerful predictor of poor coronary outcome. Duration of fever may be an indirect measure of the severity of the underlying vasculitis. Other surrogate markers of inflammation include the platelet count, serum albumin level, and failure to respond to IVIG therapy, all of which are related to fever duration. These clinical and laboratory features have all been identified as high-risk factors for development of coronary artery aneurysms.

The take home message for the evaluation and management of the child with suspected KD is a high index of suspicion for KD in children presenting with prolonged fever. Every young child with prolonged fever and signs or symptoms consistent with KD, with no other disease accounting for these clinical findings, needs close clinical follow-up and appropriate laboratory investigations (*Fig. 165.1*). The AHA algorithm aims to improve identification of at risk children and to initiate appropriate treatment in affected children.

Pathology

The basic pathologic lesion in KD is a necrotizing vasculitis with fibrinoid necrosis of medium-sized muscular arteries (predominantly coronary arteries), but venous involvement is also documented. The initial lesion begins

in the microcirculation in the adventitia. Inflammatory cells are detected by 7–9 days after fever onset with neutrophils rapidly giving way to lymphocytes and large mononuclear cells. Destruction of the external elastic lamina and all layers of the artery accompany this cellular infiltrate resulting in aneurysm formation.

Coronary Artery Lesions

The major long-term sequelae of KD is damage to the coronary vasculature; thus, cardiac imaging is an integral component of the management of children with KD. Two-dimensional echocardiography is the imaging modality of choice due to the noninvasive nature and the high sensitivity and specificity for detection of abnormalities in the proximal segments of the coronary arteries. Echocardiographic evaluation of the coronary anatomy should include assessment of the internal coronary artery diameters. The numbers and locations of aneurysms and the absence or presence of intraluminal thrombus should also be assessed. The criteria used to define coronary artery abnormalities in KD were first proposed by the Japanese Ministry of Health in 1984. These criteria were applicable to either angiographic or echocardiographic measurements, and defined coronary arteries as abnormal if the internal lumen diameter is greater than 3.0 mm in children less than 5 years of age or greater than 4.0 mm in children above 5 years of age, if the internal diameter of a segment measures at least 1.5 times that of an adjacent segment, or if the coronary artery lumen is clearly irregular (◉ *Table 165.4*). The AHA classified aneurysms as small (<5 mm), medium (5–8 mm), or giant (>8 mm). Coronary artery dimensions in normal children increase linearly with body size, as measured by body surface area (BSA). Thus more recently, investigators have recognized the need to correct for BSA and have classified coronary artery lesions as measurements greater than 2.5 standard deviations above the expected mean. Using this corrected BSA definition (Z-scores), there is approximately a 20% incidence of CALs despite appropriate treatment. Although the coronary anatomy is the focus of the attention in KD, cardiac function should be included in the imaging evaluation, as depressed ventricular contractility is common early in acute KD and histologic studies suggests the myocarditis is universal during the acute phase.

Although imaging protocols may vary, most agree that in uncomplicated cases, echocardiographic evaluations are needed at time of diagnosis and in the subacute phase (6–8 weeks). Additional echos between these time points may be needed to guide management of high-risk patients. Some advocate repeat imaging 6 months to 1 year post acute KD, but recent studies have suggested that normal coronary outcome at the subacute echo is unlikely to change at 1 year. There remain limitations to echocardiography, including detection of thrombi and coronary artery stenosis. In addition, the visualization of coronary arteries becomes more difficult as a child grows and body size increases. Angiography, intravascular ultrasound, transesophageal echocardiography, magnetic resonance angiography, and ultrafast computed tomography may be of benefit in the management of certain cases.

The initial size of the aneurysm is an important contributor to the likelihood of resolution/regression of that lesion, with smaller aneurysm more likely to regress. Coronary aneurysms that do not regress may progress to stenosis or occlusion or abnormal tortuosity or show continued aneurysmal morphology. Aneurysmal dilatation can also progress to rupture, but fortunately is extremely rare in KD.

◘ Table 165.4
Echocardiographic results (Echo +) supportive of KD diagnosis[a]

Any of the following three conditions:
1. BSA normalized z-score of ≥ 2.5 for the LAD or RCA
2. Japanese Ministry of Health definitions of coronary artery aneurysm which include:
• Coronary artery internal diameter > 4 mm in those ≥ 5 years old
• Coronary artery internal diameter > 3 mm in those < 5 years old
• Coronary artery internal diameter ≥ 1.5 times that of the adjacent segment
• Coronary artery lumen is clearly irregular
3. ≥3 other suggestive features including:
• Perivascular brightness
• Lack of tapering
• Decreased LV function
• Mitral regurgitation
• Pericardial effusion
• z-scores in LAD or RCA of 2–2.5

[a]AHA guidelines 2004

Treatment of Acute KD

IVIG

High dose IVIG is the accepted therapy in acute KD. Its efficacy in reducing the prevalence of coronary artery

lesions is well documented. Many different doses and administration schedules have been used in North America, Europe, and Japan. The general consensus is that higher doses given in a single infusion have the greatest efficacy. Several meta-analysis have confirmed this dose effect. Dose comparison studies showed a significant reduction of aneurysms with increasing dose, with those receiving 2 g/kg in a single dose showing both a reduction in the number of aneurysms as well as a reduction in the duration of fever compared to those receiving lower doses. Different predictive instruments have been developed to model risk for poor coronary outcome. In Japan, the Harada score was developed to aid in the rational allocation of a limited IVIG supply to those at highest risk for aneurysm formation. In addition to the clinical factors already described, male sex and the very young (<12 months old) were added as demographic features of those at risk.

The AHA recommends that IVIG be administered in a single infusion at a dose of 2 g/kg. Most infusion protocols start with a very slow rate with stepwise increases in infusion rate. The total duration of the IVIG infusion is typically 8–12 h depending on the concentration of IVIG. Multi-system inflammation involving the heart can potentially compromise the heart's ability to handle the fluid challenge associated with the IVIG infusion, thus necessitating the long duration of infusion. IVIG therapy should be instituted during the acute phase of illness, typically within the first 10 days of fever, but IVIG treatment is indicated anytime during the acute phase of illness even in those presenting after day 10 of illness. Early treatment with IVIG before day 5 of illness does not affect coronary outcome, but may increase the need for IVIG retreatment. This observation may be biased for a more severe phenotype in those treated early. When analyzed separately, those treated early ($\leq$ 4 days of fever) had higher risk scores than those treated later suggesting that those treated early in their disease course had more dramatic clinical features implying more intense inflammation and severe vasculitis.

IVIG is made from pooled donor plasma. As such, manufacturing and product differences are present. There are ongoing and conflicting investigations into potential differences in efficacy and side-effect profile between different IVIG preparations. Nonetheless, prescribing practices vary from institution to institution and the use of many different products and concentrations (5% or 10% solutions) of IVIG are employed in the acute therapy of KD and may be dictated by product availability. Although the mechanism of action of IVIG in the treatment of KD is not clearly understood, IVIG does have general immunomodulatory effects. Possible mechanisms of action include general immunosuppression via the modulation of pro-inflammatory cytokine production, and regulation of expression and function of Fc receptors, inhibiting activation of complement, neutralization of bacterial superantigens or other infectious agents, anti-idiotypic antibody effects, and effects on the activation, differentiation, and effector functions of both T cells and B cells and other antigen presenting cells.

Due to the protective effects of receiving pooled immunoglobulin and the general immunomodulatory effects, immunizations may not generate an effective or protective immune response for months after IVIG administration. Although harmless to receive immunizations, both live or killed vaccines, they may not be effective and the child may need to be re-immunized 9–11 months after IVIG administration if there is an inadequate immune response. Typically, live vaccinations are deferred for 9–11 months after a child receives high dose IVIG unless the risk of infectious exposure is high.

Aspirin

A widely debated issue in the acute therapy of KD is the dose of aspirin – high versus low dose. At high doses, aspirin has important anti-inflammatory properties and at low doses, it has anti-platelet activity. At high doses, salicylates inhibit the activity of IKK, thereby preventing NF-κB nuclear translocation. At lower doses, salicylates inhibit the cyclooxygenase enzymes leading to a reduction in prostaglandin and thromboxane synthesis. Despite high dose aspirin having an additional mechanism of immunomodulation compared to low dose aspirin, with inhibition of nuclear translocation of NFκB affecting transcriptional regulation of important pro-inflammatory cytokines as well as inhibition of TNFα signal transduction, administration of aspirin during the acute phase of KD does not appear to alter coronary outcome. During the acute phase of KD, the anti-inflammatory dose of aspirin, 80–100 mg/kg/day given in four divided doses, is typically prescribed in North America. Circulating total salicylate levels have been shown to vary tremendously despite consistent oral dosing at 80–100 mg/kg/day, with serum concentrations ranging from 0.1–0.25 mg/mL.

The duration of high dose aspirin therapy varies from institution to institution. Many centers reduce the aspirin dose to anti-platelet levels (3–5 mg/kg/day) after the affected child has been afebrile for 24–72 h. Others continue anti-inflammatory doses of aspirin until day 14 of illness or longer. In Japan, the dose of aspirin used is lower

(20 mg/kg) and may reflect the different pharmacokinetics of aspirin metabolism in the Oriental population. A Cochrane review of aspirin in the therapeutic management of acute phase of KD concluded that there is insufficient evidence to support or refute the use of aspirin as part of the treatment regimen due to lack of good quality randomized clinical trials. Low dose aspirin is administered for its anti-platelet effect and typically continued until the child shows no evidence of coronary artery damage at 6–8 weeks after fever onset and laboratory measures of inflammation have returned to normal. Children with coronary artery lesions may continue aspirin or other anti-platelet agents indefinitely.

Refractory Disease

One of the major challenges in the current management of KD is the treatment of patients who fail to respond to initial therapy with IVIG. Ten to twenty percent of children will not respond to a single dose of IVIG. The definition of refractory disease or treatment failure varies, but in general is defined as persistent or recrudescent fever $\geq$ 36 h after initial IVIG therapy. Persistent fever is more common than recrudescent fever. Although debate continues regarding the optimal therapy for refractory disease, most investigators agree on a second dose of IVIG. The second dose of IVIG continues to be high dose therapy at 2 g/kg. Treatment of this subgroup of patients with refractory KD has included additional IVIG, corticosteroids, and much less commonly various immunosuppressive agents including cyclophosphamide and cyclosporin, as well as plasma exchange, inhibition of elastase activity (ulinastatin), and more recently the biologic therapy against tumor necrosis factor-alpha (*Fig. 165.2*). The goal of all these therapies is to ameliorate the immune response thus decreasing the chance of ongoing inflammation and damage to the coronary arteries. The order of these therapeutic interventions continues to be controversial.

Although steroids are efficacious and widely used in other forms of vasculitis, their use in KD is very limited.

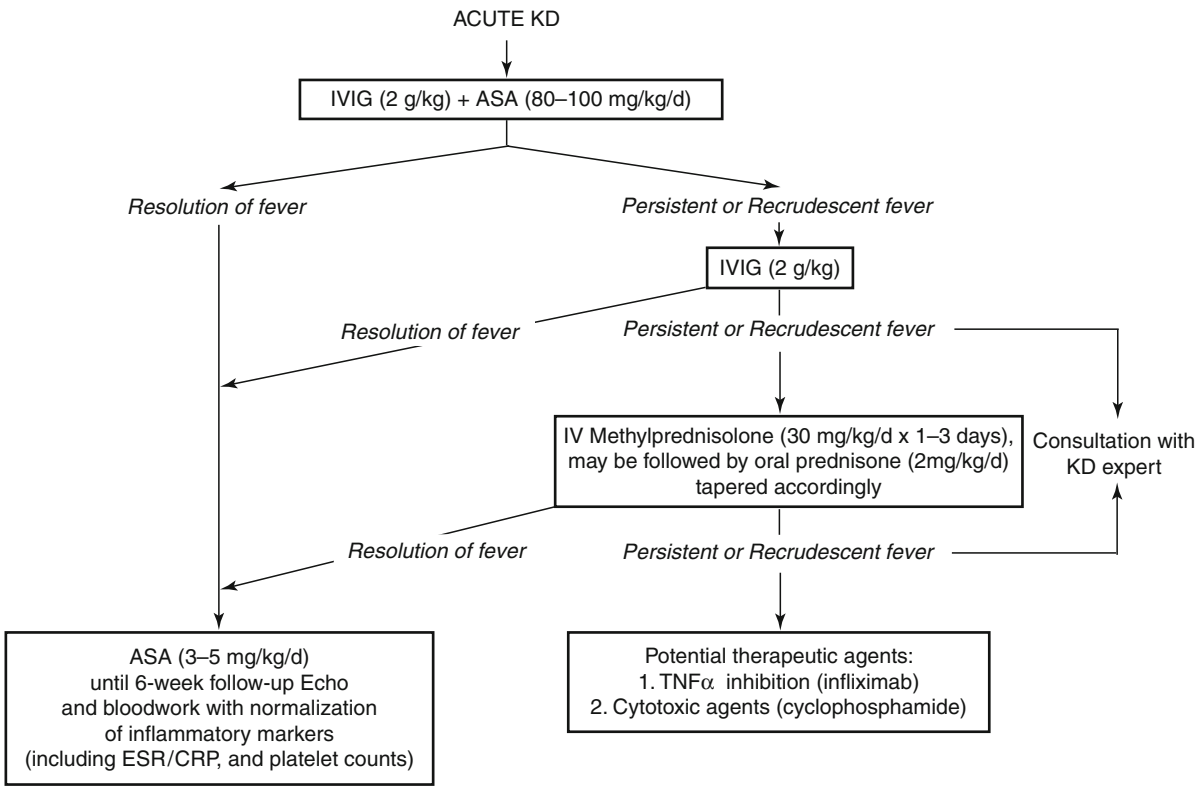

Figure 165.2
Proposed algorithm for the management of acute Kawasaki disease

Use of steroids in acute KD has been controversial, but more recent studies have shown their usefulness in both the acute phase as well as in refractory disease. KD refractory to IVIG was the most common indication for corticosteroid use in patients with KD, and this treatment was found to be effective, with rapid resolution of fever in the majority of patients. The most common dosing regimen of steroids is high dose pulse steroids given as intravenous methylprednisolone 30 mg/kg up to a maximum of 1 g. This is given once per day over 1–3 days. Dosing regimens vary from center to center and little evidence is available to support the dose or schedule of steroid administration. At our institution, high dose IV dosing may be followed by oral prednisone at 2 mg/kg/day which is then rapidly tapered to 0 over the course of 1 to 2 weeks unless resistant fever or fever recrudescence requires a longer taper or alternate therapy (◉ *Fig. 165.2*).

Therapeutic Options in Children with Coronary Artery Aneurysms

No prospective studies are available to guide treatment decisions in children with coronary artery lesions, thus recommendations are based on knowledge of the pathophysiology and lessons learned from adults with coronary disease. The basis of these therapeutic guidelines is prevention of thrombosis, and specific management is dependent on the extent and severity of coronary artery disease. As such, anti-platelet therapy alone or in combination with anti-coagulation is an integral component of the management plan. Thrombocytosis together with platelet activation is a key finding in KD, thus necessitating the use of anti-platelet agents. Low dose aspirin is used even in those with no evidence of coronary damage until the 6-week follow-up echocardiogram and may be continued indefinitely in those with coronary artery damage. In the presence of more severe coronary disease, the addition of another anti-platelet agent targeting non-ASA-dependent pathways of platelet activation (dipyridamole and clopidogrel) may be included. In the presence of large or giant aneurysms, which pose a significant thrombotic risk, anti-coagulation is added. In the acute phase, the usual choice is heparin. Long-term anti-coagulation can be achieved by either warfarin or low-molecular weight heparin in combination with an anti-platelet agent. Little data is available to guide interventions in the presence of intravascular thrombi, but recent trials have targeted the platelet glycoprotein IIb/IIIa receptor involved in the final common pathway of platelet aggregation. Abciximab, a platelet glycoprotein IIb/IIIa receptor inhibitor, has been used acutely in children with intraluminal thrombus to reestablish vessel patency and salvage the myocardium.

Conclusion

In summary, KD is an important cause of acquired heart disease in childhood. There is increasing recognition of typical KD. The challenge clinically is recognition of children who present with an incomplete clinical presentation. A high index of suspicion in every child with prolonged fever and signs or symptoms consistent with KD, coupled with close clinical follow-up and appropriate laboratory investigations and imaging is warranted. Prolonged inflammation leading to coronary artery damage is the underlying pathology in KD. Early identification and treatment of affected children to suppress the inflammatory response is one of the objectives of therapy. High dose IVIG together with aspirin is the mainstay of therapy in acute KD. Disease modeling continues to be imperfect and future studies will need to identify novel biomarkers to enhance the traditional clinical and laboratory measures of inflammation. The ultimate goal for identification of this high-risk phenotype is to guide clinical decisions involving use of therapeutic interventions to improve coronary outcome in affected children.

References

Abe J, Kotzin BL, Jujo K, Melish ME, Glode MP, Kohsaka T, Leung DY (1992) Selective expansion of T cells expressing T-cell receptor variable regions V β 2 and V β 8 in Kawasaki disease. Proc Natl Acad Sci USA 89:4066–4070

American Heart Association (2001) Diagnostic Guidelines for Kawasaki Disease. Circulation 103:335–336

Barbour JR, Spinale FG, Ikonomidis JS (2007) Proteinase systems and thoracic aortic aneurysm progression. J Surg Res 139:292–307

Baumer JH, Love SJ, Gupta A, Haines LC, Maconochie I, Dua JS (2006) Salicylate for the treatment of Kawasaki disease in children. Cochrane Database Syst Rev (4):CD004175

Burns JC, Glode MP, Clarke SH, Wiggins JJ, Hathaway WE (1984) Coagulopathy and platelet activation in Kawasaki syndrome: identification of patients at high risk for development of coronary artery aneurysms. J Pediatr 105:206–211

Burns JC, Mason WH, Hauger SB, Janai H, Bastian JF, Wohrley JD, Balfour I, Shen CA, Michel ED, Shulman ST et al (2005) Infliximab treatment for refractory Kawasaki syndrome. J Pediatr 146:662–667

Dajani AS, Taubert KA, Gerber MA, Shulman ST, Ferrieri P, Freed M, Takahashi M, Bierman FZ, Karchmer AW, Wilson W et al (1993) Diagnosis and therapy of Kawasaki disease in children. Circulation 87:1776–1780

de Zorzi A, Colan SD, Gauvreau K, Baker AL, Sundel RP, Newburger JW (1998) Coronary artery dimensions may be misclassified as normal in Kawasaki disease. J Pediatr 133:254–258

Du ZD, Zhao D, Du J, Zhang YL, Lin Y, Liu C, Zhang T (2007) Epidemiologic study on Kawasaki disease in Beijing from 2000 through 2004. Pediatr Infect Dis J 26:449–451

Durongpisitkul K, Gururaj VJ, Park JM, Martin CF (1995) The prevention of coronary artery aneurysm in Kawasaki disease: a meta-analysis on the efficacy of aspirin and immunoglobulin treatment. Pediatrics 96:1057–1061

Eberhard BA, Andersson U, Laxer RM, Rose V, Silverman ED (1995) Evaluation of the cytokine response in Kawasaki disease. Pediatr Infect Dis J 14:199–203

Elmore JR, Keister BF, Franklin DP, Youkey JR, Carey DJ (1998) Expression of matrix metalloproteinases and TIMPs in human abdominal aortic aneurysms. Ann Vasc Surg 12:221–228

Esper F, Shapiro ED, Weibel C, Ferguson D, Landry ML, Kahn JS (2005) Association between a novel human coronavirus and Kawasaki disease. J Infect Dis 191:499–502

Fischer TK, Holman RC, Yorita KL, Belay ED, Melbye M, Koch A (2007) Kawasaki syndrome in Denmark. Pediatr Infect Dis J 26:411–415

Fujita Y, Nakamura Y, Sakata K, Hara N, Kobayashi M, Nagai M, Yanagawa H, Kawasaki T (1989) Kawasaki disease in families. Pediatrics 84:666–669

Fujiwara H, Hamashima Y (1978) Pathology of the heart in Kawasaki disease. Pediatrics 61:100

Gavin PJ, Crawford SE, Shulman ST, Garcia FL, Rowley AH (2003) Systemic arterial expression of matrix metalloproteinases 2 and 9 in acute Kawasaki disease. Arterioscler Thromb Vasc Biol 23:576–581

Gong GW, McCrindle BW, Ching JC, Yeung RS (2006) Arthritis presenting during the acute phase of Kawasaki disease. J Pediatr 148:800–805

Han RK, Silverman ED, Newman A, McCrindle BW (2000) Management and outcome of persistent or recurrent fever after initial intravenous gamma globulin therapy in acute Kawasaki disease. Arch Pediatr Adolesc Med 154:694–699

Hashino K, Ishii M, Iemura M, Akagi T, Kato H (2001) Re-treatment for immune globulin-resistant Kawasaki disease: a comparative study of additional immune globulin and steroid pulse therapy. Pediatr Int 43:211–217

Heaton P, Wilson N, Nicholson R, Doran J, Parsons A, Aiken G (2006) Kawasaki disease in New Zealand. J Paediatr Child Health 42: 184–190

Holman RC, Belay ED, Curns AT, Schonberger LB, Steiner C (2003) Kawasaki syndrome hospitalizations among children in the United States, 1988–1997. Pediatrics 111:448

Hui-Yuen JS, Duong TT, Yeung RS (2006) TNF-alpha is necessary for induction of coronary artery inflammation and aneurysm formation in an animal model of Kawasaki disease. J Immunol 176:6294–6301

Ikonomidis JS, Barbour JR, Amani Z, Stroud RE, Herron AR, McClister DM Jr, Camens SE, Lindsey ML, Mukherjee R, Spinale FG (2005) Effects of deletion of the matrix metalloproteinase 9 gene on development of murine thoracic aortic aneurysms. Circulation 112:I242–I248

Kato H, Akagi T, Sugimura T, Sato N, Kazue T, Hashino K, Nishiyori A, Sakaguchi M (1995) Kawasaki disease. Coron Artery Dis 6:194–206

Kawasaki T (1967) Acute febrile mucocutaneous syndrome with lymphoid involvement with specific desquamation of the fingers and toes in children (Japanese). Jpn J Allergol 16:178–222

Kawasaki T, Kosaki F, Okawa S (1974) A new infantile acute febrile mucocutaneous lymph node syndrome (MLNS) prevailing in Japan. Pediatrics 54:271–276

Kazatchkine MD, Kaveri SV (2001) Immunomodulation of autoimmune and inflammatory diseases with intravenous immune globulin. N Engl J Med 345:747–755

Kobayashi T, Inoue Y, Takeuchi K, Okada Y, Tamura K, Tomomasa T, Kobayashi T, Morikawa A (2006) Prediction of intravenous immunoglobulin unresponsiveness in patients with Kawasaki disease. Circulation 113:2606–2612

Koren G, MacLeod SM (1984) Difficulty in achieving therapeutic serum concentrations of salicylate in Kawasaki disease. J Pediatr 105: 991–995

Landing BH, Larson EJ (1987) Pathological features of Kawasaki disease (mucocutaneous lymph node syndrome). Am J Cardiovasc Pathol 1:218–229

Lang BA, Silverman ED, Laxer RM, Lau AS (1989) Spontaneous tumor necrosis factor production in Kawasaki disease. J Pediatr 115: 939–943

Lang BA, Yeung RS, Oen KG, Malleson PN, Huber AM, Riley M, Ebbeson R, Ramsey SE, Laxer RM, Silverman ED et al (2006) Corticosteroid treatment of refractory Kawasaki disease. J Rheumatol 33:803–809

Lau AC, Duong TT, Ito S, Yeung RSM (2009) Intravenous immunoglobulin and salicylate differentially modulate pathogenic processes leading to vascular damage in an animal model of Kawasaki disease. Arthritis Rheum 60:2131–2141

Leung DY, Meissner HC, Fulton DR, Quimby F, Schlievert PM (1995a) Superantigens in Kawasaki syndrome. Clin Immunol Immunopathol 77:119–126

Leung DYM, Giorno RC, Kazemi LV, Flynn PA, Busse JB (1995b) Evidence for superantigen involvement in cardiovascular injury due to Kawasaki syndrome. J Immunol 155:5018–5021

Manlhiot C, Yeung RS, Clarizia NA, Chahal N, McCrindle BW (2009) Kawasaki disease at the extremes of the age spectrum. Pediatrics 123(5):e783–e789

McCrindle B, Lobo L, Nagpag S, Fry R, Sinclair B, Dicke F, Yeung R (2003) The epidemiology of Kawasaki disease in Ontario and Canada. Pediatr Res 53:159

McMorrow Tuohy AM, Tani LY, Cetta F, Lewin MB, Eidem BW, Van Buren P, Williams RV, Shaddy RE, Tuohy RP, Minich LL (2001) How many echocardiograms are necessary for follow-up evaluation of patients with Kawasaki disease? Am J Cardiol 88:328–330

Melish ME, Hicks RM, Larson EJ (1976) Mucocutanoeous lymph nodes syndrome in the United States. Am J Dis Child 130:599–607

Ministry of Health and Welfare (1984) Research Committee on Kawasaki disease. Report of subcommittee on standardization of diagnostic criteria and reporting of coronary artery lesions in Kawasaki disease, Tokyo, Japan

Naoe S, Takahashi K, Masuda H, Tanaka N (1987) Coronary findings post Kawasaki disease in children who died of other causes. Prog Clin Biol Res 250:341–346

Newburger JW, Takahashi M, Gerber MA, Gewitz MH, Tani LY, Burns JC, Shulman ST, Bolger AF, Ferrieri P, Baltimore RS et al (2004) 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 110:2747–2771

Ng YM, Sung RY, So LY, Fong NC, Ho MH, Cheng YW, Lee SH, Mak WC, Wong DM, Yam MC et al (2005) Kawasaki disease in Hong Kong, 1994 to 2000. Hong Kong Med J 11:331–335

Park YW, Han JW, Park IS, Kim CH, Cha SH, Ma JS, Lee JS, Kwon TC, Lee SB, Kim CH et al (2007) Kawasaki disease in Korea, 2003–2005. Pediatr Infect Dis J 26:821–823

Pickering LK (2003) Red Book 2003 Report of the committee on Infectious Diseases. American Academy of Pediatrics, Chicago

Rowley AH, Shulman ST, Spike BT, Mask CA, Baker SC (2001) Oligoclonal IgA response in the vascular wall in acute Kawasaki disease. J Immunol 166:1334–1343

Salo E, Pelkonen P, Pettay O (1986) Outbreak of Kawasaki syndrome in Finland. Acta Paediatr Scand 75:75–80

Sasaguri Y, Kato H (1982) Regression of aneurysms in Kawasaki disease: a pathological study. J Pediatr 100:225–231

Stenbog EV, Windelborg B, Horlyck A, Herlin T (2006) The effect of TNFalpha blockade in complicated, refractory Kawasaki disease. Scand J Rheumatol 35:318–321

Taubert KA, Rowley AH, Shulman ST (1991) Nationwide survey of Kawasaki disease and acute rheumatic fever. J Pediatr 119:279–282

Tizard EJ, Suzuki A, Levin M, Dillon MJ (1991) Clinical aspects of 100 patients with Kawasaki disease. Arch Dis Child 66:185–188

Tsai MH, Huang YC, Yen MH, Li CC, Chiu CH, Lin PY, Lin TY, Chang LY (2006) Clinical responses of patients with Kawasaki disease to different brands of intravenous immunoglobulin. J Pediatr 148:38–43

Uehara R, Yashiro M, Nakamura Y, Yanagawa H (2003) Kawasaki disease in parents and children. Acta Paediatr 92:694–697

Vane JR (1971) Inhibition of prostaglandin synthesis as a mechanism of action for aspirin-like drugs. Nat New Biol 231:232–235

Weiss JE, Eberhard BA, Chowdhury D, Gottlieb BS (2004) Infliximab as a novel therapy for refractory Kawasaki disease. J Rheumatol 31:808–810

Williams RV, Wilke VM, Tani LY, Minich LL (2002) Does Abciximab enhance regression of coronary aneurysms resulting from Kawasaki disease? Pediatrics 109:E4

Yanagawa H, Yashiro M, Nakamura Y, Hirose K, Kawasaki T (1995) Nationwide surveillance of Kawasaki disease in Japan, 1984 to 1993. Pediatr Infect Dis J 14:69–71

Yanagawa H, Nakamura Y, Yashiro M, Ojima T, Tanihara S, Oki I, Zhang T (1998) Results of the nationwide epidemiologic survey of Kawasaki disease in 1995 and 1996 in Japan. Pediatrics 102:E65

Yanagawa H, Nakamura Y, Yashiro M, Uehara R, Oki I, Kayaba K (2006) Incidence of Kawasaki disease in Japan: the nationwide surveys of 1999–2002. Pediatr Int 48:356–361

Yeung RSM (2004) The etiology of Kawasaki disease – a superantigen-mediated process. Prog Pediatr Cardiol 19:109–113

Yeung RS (2007) Phenotype and coronary outcome in Kawasaki's disease. Lancet 369:85–87

Yin MJ, Yamamoto Y, Gaynor RB (1998) The anti-inflammatory agents aspirin and salicylate inhibit the activity of I(kappa)B kinase-beta. Nature 396:77–80

Zaitsu M, Hamasaki Y, Tashiro K, Matsuo M, Ichimaru T, Fujita I, Tasaki H, Miyazaki S (2000) Ulinastatin, an elastase inhibitor, inhibits the increased mRNA expression of prostaglandin H2 synthase-type 2 in Kawasaki disease. J Infect Dis 181:1101–1109