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The Complexities of the Diagnosis and Management of Kawasaki Disease

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Abstract

It is critical for pediatricians, especially infectious diseases specialists, to consider Kawasaki Disease (KD) in the differential diagnosis of any child with fever for 4–5 days and compatible clinical and laboratory features. The diagnosis should also be considered in any infant with prolonged fever and compatible laboratory features, even in the absence of the classic clinical signs. Prompt therapy is required, because delayed or unrecognized KD can lead to lifelong heart disease or death in previously healthy children. Most children with KD respond to a single 2 gram/kg dose of intravenous gammaglobulin with oral aspirin, but a small subset require additional therapies to resolve the clinical illness. The goal of therapy is to prevent or reduce coronary artery inflammation and subsequent coronary artery stenoses from thromboses and/or luminal myofibroblastic proliferation.

Keywords

Coronary artery aneurysms; prolonged fever; systemic inflammation; myocardial infarction; acquired pediatric heart disease

Introduction

Although KD has been recognized in Japan and the United States for decades, the etiology and pathogenesis of the illness remain major pediatric mysteries. The abrupt onset of clinical signs such as fever, exanthem and enanthem in previously healthy children, the rarity of recurrence, the very young age group affected, and the well-documented epidemics and outbreaks of illness are strongly suggestive of an infectious etiology, as well-described in a classic epidemiologic study from the 1980s [1]. The very high incidence of the illness in Japan, where about 1 in 90 children develop KD by age 5 years [2], is highly suggestive of a ubiquitous infectious agent affecting young susceptible children who are genetically

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predisposed. Key features of KD are presented in Table 1. It is important to understand the major pathologic features of KD arteriopathy, briefly summarized in Table 1, because these features predict the adverse clinical outcomes observed in KD patients who develop coronary artery abnormalities [3]. Moreover, knowledge of the many organs and tissues involved in the systemic inflammation of KD assists in understanding the many possible clinical manifestations of the illness (Table 2 [4]). Risk factors for KD and for the development of coronary artery abnormalities are summarized in Table 3.

Incidence and Mortality Rates

The incidence of KD varies in different countries throughout the world (Table 4) and remains unknown in many regions, especially in those that continue to have a high prevalence of measles, which shares many clinical features with KD. In Japan, there is high recognition and early treatment of the condition, and mortality rates have fallen from 1.4% in 1970 to 0.01% in recent years; fatality rates began to fall markedly after the introduction of intravenous gammaglobulin therapy in the late 1980s [8]. In the U.S., fatality rates are also very low; fatal cases are often associated with delayed or missed diagnoses [3]. Peak months of KD incidence vary somewhat by country, but a consistent theme appears to be a peak during the winter in non-temperate climates [9].

Patient History

The history is particularly important in KD, as some clinical features of the illness may begin and abate prior to the patient's presentation. It is recommended to ask the parent or guardian non-leading questions about symptoms to avoid introducing recall bias. Table 5 lists common features in the history of children with KD. Excessive irritability, refusal to bear weight, redness and swelling of the hands and feet, and an erythematous peeling groin rash may be very helpful in establishing the diagnosis, as these are not common features of most other diseases in the differential diagnosis. In a child who has received Bacillus Calmette-Guérin (BCG) vaccine, redness at the site should prompt consideration of KD [21]; the mechanism of this response is unknown.

Physical Examination

Physical findings in KD can be very striking in classic cases (Table 6, Figures 1 and 2). However, young infants in particular can present with incomplete clinical signs (fever with fewer than 4 of the other findings) or signs that are rather mild. The findings of classic KD are listed in Table 6. Although some clinicians refer to incomplete KD as "atypical" KD, it is important to recognize that these terms indicate a lack of full clinical features, not to the presence of unexpected signs not listed in Table 6. An alternative diagnosis should be strongly considered in a child who has signs or symptoms not generally associated with KD. Because hydrops of the gallbladder occurs commonly in KD, right upper quadrant pain may be present on abdominal examination. Marked irritability, greater than that observed in other routine childhood febrile illnesses, is also characteristic and commonly observed during physical examination.

Other clinical manifestations of KD

KD children can present with shock syndrome; such patients are at higher risk of IGIV resistance and of developing coronary artery abnormalities [22–26]. Although cervical lymphadenopathy is the least commonly observed clinical feature among the classic diagnostic criteria for KD, it can be the dominant clinical feature, and some of these patients also have retropharyngeal phlegmon (without abscess) documented by neck imaging studies [27–29]. KD should be considered in the differential diagnosis of any infant with prolonged fever and aseptic meningitis [30].

Imaging and Additional Testing

Laboratory findings in KD are non-diagnostic, but can support the diagnosis (Table 7). In particular, a child with a low or normal peripheral white blood cell count with a lymphocyte predominance does not have a compatible laboratory profile of KD. KD is most prevalent in the winter in non-temperate climates, during the time that many respiratory viruses are circulating. Therefore, some children with KD will concurrently have infection with one of these viruses; this should not preclude the diagnosis in cases with clinical and laboratory features of KD. Echocardiography can be very useful in assessing a child for possible KD, as a right or left anterior descending coronary artery Z score >2.5 is highly supportive of the diagnosis [31, 32], and 30% of KD patients have abnormal coronary artery Z scores at the time of initial diagnosis, in the first 10 days of illness [33, 34]. The presence of three of the following echocardiographic findings: pericardial effusion, lack of tapering of the coronary arteries, a coronary artery Z score of 2–2.5 of the right or left anterior descending coronary arteries, decreased left ventricular function, and mitral regurgitation should also increase clinical suspicion of KD [7].

Diagnosis of Incomplete (Atypical) KD

Although the classic diagnostic criteria are the mainstay of diagnosis, some KD children, particularly infants, manifest fever with fewer than four of the five clinical signs described in Table 6; these children are considered to have incomplete KD. In some infants, the clinical findings are mild, and may not be noted unless there is a high index of suspicion for KD. Unfortunately, coronary artery abnormalities in incomplete cases can be as severe as in classic cases. Because incomplete KD can be difficult to diagnose and has potentially severe consequences that may be prevented by early treatment, the American Heart Association Committee on Endocarditis, Rheumatic Fever, and Kawasaki Disease developed a treatment algorithm combining laboratory and echocardiographic findings with clinical signs and symptoms to identify patients who may benefit from therapy for incomplete KD [7] (Figure 4).

Primary Therapy

All patients diagnosed with KD should be treated with 2 gm/kg intravenous gammaglobulin (IGIV) with oral high-dose aspirin (80–100 mg/kg/day divided every 6 hours) as soon as possible after diagnosis [35]. IGIV significantly reduces the prevalence of coronary artery abnormalities when given within the first 10 days of illness [35, 36] and improves

myocardial function [37]. However, improved echocardiographic imaging and use of body surface area-adjusted Z scores to identify coronary artery dilation has led to the realization that coronary artery injury likely occurs in many patients in the first week of illness [33, 34], and that coronary artery Z scores >2 can be observed in 18% of KD children at about 6 weeks after onset even with treatment within the first 10 days [34]. This emphasizes the need for early diagnosis and treatment. At least 80% of KD patients respond to initial therapy with IGIV and aspirin with resolution of fever, improvement in clinical signs and symptoms, and decreased laboratory markers of inflammation. Aspirin is maintained at high doses for anti-inflammatory effect until the patient is afebrile for 2–3 days; at some centers, it is continued until the 14th illness day. Aspirin is then reduced to anti-platelet doses of 3–5 mg/kg/day in a single daily dose, and continued until echocardiography at 6–8 weeks after the onset remains normal and acute phase reactants have normalized. In patients who develop coronary artery abnormalities, low-dose aspirin is continued indefinitely. In patients with severe coronary artery abnormalities, clopidogrel and/or anticoagulation therapy with warfarin or low molecular weight heparin may be indicated, and consultation with a pediatric cardiologist is advised [7].

Research Studies on Adjunctive Primary Therapy

Unfortunately, ~15–20% of KD children do not respond to initial IGIV therapy, with persistence of fever 36 hours after completion of IGIV infusion, and these patients are at increased risk of developing coronary artery abnormalities. Some KD patients, especially infants, can develop coronary artery abnormalities despite apparent clinical response to IGIV treatment given in the first 10 days of illness. Therefore, recent research has focused on the study of combination immunomodulatory therapies given with IGIV for primary therapy of KD. A randomized study of a single 30 mg/kg dose of methylprednisolone administered with IGIV did not reveal a significant improvement in outcomes [38]. A randomized, double-blind, placebo-controlled trial of infliximab (a tumor necrosis factor α inhibitor) for intensification of primary therapy for KD did not show a reduction in treatment resistance nor a reduction in the overall prevalence of coronary artery abnormalities when infliximab was administered with IGIV, although the addition of infliximab did result in lower C-reactive protein levels and absolute neutrophil counts 24 hours after the infusion [39]. More promising was the Randomized controlled trial to Assess Immunoglobulin plus Steroid Efficacy for Kawasaki disease (RAISE study), which demonstrated improvement in coronary artery outcomes in Japanese patients with high-risk KD when prednisolone was given with IGIV and continued for 15 days after normalization of the C-reactive protein level [40]. A randomized trial of cyclosporin with IGIV for Japanese children with high-risk KD is presently ongoing in Japan and the results of this study will also be of interest. Because the identification of risk scoring systems with high sensitivity for the prediction of coronary artery abnormalities in mixed ethnic populations has proven elusive, application of the RAISE study protocol or other high-risk protocols to KD children in countries such as the U.S. and Canada is not presently feasible [41].

Refractory KD

Refractory KD generally refers to the persistence of fever 36 hours after completion of initial IGIV infusion. Patients with IGIV resistance have a higher prevalence of coronary artery abnormalities [42]. Most of these patients respond to a second 2 gm/kg dose of IGIV. For those patients who do not respond to a second dose of IGIV, several options for treatment exist, but controlled data are lacking (Table 8).

Clinical Outcomes and Complications

Most children with KD respond to IGIV, and those who do not develop coronary artery abnormalities by 4–6 weeks after the onset of fever have no known adverse outcomes. In patients who develop coronary artery dilation or aneurysm formation, outcomes are dependent upon the severity of coronary artery disease. In very severe cases, giant coronary artery aneurysms can form, which can rarely rupture, and virtually always thrombose to a varying extent. Patients with this severe complication of KD are generally maintained on anti-platelet and anti-coagulation therapy, and they are at the highest risk for thrombotic occlusion and myocardial infarction, in some cases requiring catheter interventions or coronary artery bypass surgery. However, coronary artery stenosis in KD patients can also be caused by luminal myofibroblastic proliferation (LMP) with or without thromboses. LMP is an active proliferative process of smooth muscle cell-derived myofibroblasts and their matrix products that can result in progressive arterial stenosis [3]. In rare cases, LMP and/or thrombosis can result in such significant stenoses of multiple coronary arteries that heart transplantation is required [3, 49]. KD can affect all medium-sized muscular arteries outside of the central nervous system, but it appears that peripheral arterial aneurysms occur only in children with severe coronary artery disease. The most commonly affected arteries are the axillary, brachial, and inguinal arteries; aneurysms in these arteries can rarely result in morbidity or mortality [3, 50].

References

1. Yanagawa H, Nakamura Y, Yashiro M, Fujita Y, Nagai M, Kawasaki T, et al. A nationwide incidence survey of kawasaki disease in 1985–1986 in japan. *J. Infect. Dis.* 1988; 158(6):1296–1301. [PubMed: 3198940]
2. Nakamura Y, Yashiro M, Uehara R, Sadakane A, Tsuboi S, Aoyama Y, et al. Epidemiologic features of kawasaki disease in japan: Results of the 2009–2010 nationwide survey. *J. Epidemiol.* 2012; 22(3):216–221. [PubMed: 22447211]
3. Orenstein JM, Shulman ST, Fox LM, Baker SC, Takahashi M, Bhatti TR, et al. Three linked vasculopathic processes characterize kawasaki disease: A light and transmission electron microscopic study. *PLoS ONE.* 2012; 7(6):e38998. [PubMed: 22723916]
4. Amano S, Hazama F, Kubagawa H, Tasaka K, Haebara H, Hamashima Y. General pathology of kawasaki disease. On the morphological alterations corresponding to the clinical manifestations. *Acta Pathol. Jpn.* 1980; 30(5):681–694. [PubMed: 7446109]
5. Fujita Y, Nakamura Y, Sakata K, Hara N, Kobayashi M, Nagai M, et al. Kawasaki disease in families. *Pediatrics.* 1989; 84(4):666–669. [PubMed: 2780128]
6. Uehara R, Yashiro M, Nakamura Y, Yanagawa H. Kawasaki disease in parents and children. *Acta Paediatr.* 2003; 92(6):694–697. [PubMed: 12856980]
7. Newburger JW, Takahashi M, Gerber MA, Gewitz MH, Tani LY, Burns JC, 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(17):2747–2771. [PubMed: 15505111]

8. Takahashi K, Oharaseki T, Yokouchi Y, Yamada H, Shibuya K, Naoe S. A half-century of autopsy results—incidence of pediatric vasculitis syndromes, especially kawasaki disease. *Circulation journal : official journal of the Japanese Circulation Society*. 2012; 76(4):964–970. [PubMed: 22313802]
9. Uehara R, Belay ED. Epidemiology of kawasaki disease in asia, europe, and the united states. *J. Epidemiol*. 2012; 22(2):79–85. [PubMed: 22307434]
10. Kim GB, Han JW, Park YW, Song MS, Hong YM, Cha SH, et al. Epidemiologic features of kawasaki disease in south korea: Data from nationwide survey: 2009–2011. *Pediatr. Infect. Dis. J*. 2014; 33(1):24–27. [PubMed: 24064559]
11. Du ZD, Zhao D, Du J, Zhang YL, Lin Y, Liu C, et al. Epidemiologic study on kawasaki disease in beijing from 2000 through 2004. *Pediatr. Infect. Dis. J*. 2007; 26(5):449–451. [PubMed: 17468660]
12. Huang SK, Lin MT, Chen HC, Huang SC, Wu MH. Epidemiology of kawasaki disease: Prevalence from national database and future trends projection by system dynamics modeling. *J. Pediatr*. 2013; 163(1):126–131. e1. [PubMed: 23312687]
13. Holman RC, Belay ED, Christensen KY, Folkema AM, Steiner CA, Schonberger LB. Hospitalizations for kawasaki syndrome among children in the united states: 1997–2007. *Pediatr. Infect. Dis. J*. 2010; 29(6):483–488. [PubMed: 20104198]
14. Holman RC, Christensen KY, Belay ED, Steiner CA, Effler PV, Miyamura J, et al. Racial/ethnic differences in the incidence of kawasaki syndrome among children in hawaii. *Hawaii Med. J*. 2010; 69(8):194–197. [PubMed: 20845285]
15. Lin YT, Manlhiot C, Ching JC, Han RK, Nield LE, Dillenburg R, et al. Repeated systematic surveillance of kawasaki disease in ontario from 1995 to 2006. *Pediatr. Int*. 2010; 52(5):699–706. [PubMed: 20113416]
16. Heuclin T, Dubos F, Hue V, Godart F, Francart C, Vincent P, et al. Increased detection rate of kawasaki disease using new diagnostic algorithm, including early use of echocardiography. *J. Pediatr*. 2009; 155(5):695–699. e1. [PubMed: 19595368]
17. Saundankar J, Yim D, Itotoh B, Payne R, Maslin K, Jape G, et al. The epidemiology and clinical features of kawasaki disease in australia. *Pediatrics*. 2014; 133(4):e1009–e1014. [PubMed: 24685950]
18. Salo E, Griffiths EP, Farstad T, Schiller B, Nakamura Y, Yashiro M, et al. Incidence of kawasaki disease in northern european countries. *Pediatr. Int*. 2012; 54(6):770–772. [PubMed: 22726311]
19. Borzutzky A, Hoyos-Bachiloglu R, Cerda J, Talesnik E. Rising hospitalization rates of kawasaki disease in chile between 2001 and 2007. *Rheumatol. Int*. 2012; 32(8):2491–2495. [PubMed: 21785955]
20. Bar-Meir M, Haklai Z, Dor M. Kawasaki disease in israel. *Pediatr. Infect. Dis. J*. 2011; 30(7):589–592. [PubMed: 21343843]
21. Lai CC, Lee PC, Wang CC, Hwang BT, Meng CC, Tsai MC. Reaction at the bacillus calmette--guerin inoculation site in patients with kawasaki disease. *Pediatrics and neonatology*. 2013; 54(1):43–48. [PubMed: 23445742]
22. Gatterre P, Oualha M, Dupic L, Iserin F, Bodemer C, Lesage F, et al. Kawasaki disease: An unexpected etiology of shock and multiple organ dysfunction syndrome. *Intensive Care Med*. 2012; 38(5):872–878. [PubMed: 22273753]
23. Gamez-Gonzalez LB, Murata C, Munoz-Ramirez M, Yamazaki-Nakashimada M. Clinical manifestations associated with kawasaki disease shock syndrome in mexican children. *Eur. J. Pediatr*. 2013; 172(3):337–342. [PubMed: 23152158]
24. Kanegaye JT, Wilder MS, Molkara D, Frazer JR, Pancheri J, Tremoulet AH, et al. Recognition of a kawasaki disease shock syndrome. *Pediatrics*. 2009; 123(5):e783–e789. [PubMed: 19403470]
25. Lin MT, Fu CM, Huang SK, Huang SC, Wu MH. Population-based study of kawasaki disease shock syndrome in taiwan. *Pediatr. Infect. Dis. J*. 2013; 32(12):1384–1386. [PubMed: 23748909]

26. Dominguez SR, Friedman K, Seewald R, Anderson MS, Willis L, Glode MP. Kawasaki disease in a pediatric intensive care unit: A case-control study. *Pediatrics*. 2008; 122(4):e786–e790. [PubMed: 18809597]
27. Kanegaye JT, Van Cott E, Tremoulet AH, Salgado A, Shimizu C, Kruk P, et al. Lymph-node-first presentation of kawasaki disease compared with bacterial cervical adenitis and typical kawasaki disease. *J. Pediatr*. 2013; 162(6):1259–1263. 63, e1–e2. [PubMed: 23305955]
28. Stamos JK, Corydon K, Donaldson J, Shulman ST. Lymphadenitis as the dominant manifestation of kawasaki disease. *Pediatrics*. 1994; 93(3):525–528. [PubMed: 8115224]
29. Nomura O, Hashimoto N, Ishiguro A, Miyasaka M, Nosaka S, Oana S, et al. Comparison of patients with kawasaki disease with retropharyngeal edema and patients with retropharyngeal abscess. *Eur. J. Pediatr*. 2014; 173(3):381–386. [PubMed: 24146166]
30. Yeom JS, Park JS, Seo JH, Park ES, Lim JY, Park CH, et al. Initial characteristics of kawasaki disease with cerebrospinal fluid pleocytosis in febrile infants. *Pediatr. Neurol*. 2012; 47(4):259–262. [PubMed: 22964439]
31. Bratincsak A, Reddy VD, Purohit PJ, Tremoulet AH, Molkara DP, Frazer JR, et al. Coronary artery dilation in acute kawasaki disease and acute illnesses associated with fever. *Pediatr. Infect. Dis. J*. 2012; 31(9):924–926. [PubMed: 22673140]
32. Muniz JC, Dummer K, Gauvreau K, Colan SD, Fulton DR, Newburger JW. Coronary artery dimensions in febrile children without kawasaki disease. *Circulation. Cardiovascular imaging*. 2013; 6(2):239–244. [PubMed: 23357243]
33. Dominguez SR, Anderson MS, Eladawy M, Glode MP. Preventing coronary artery abnormalities: A need for earlier diagnosis and treatment of kawasaki disease. *Pediatr. Infect. Dis. J*. 2012
34. Printz BF, Sleeper LA, Newburger JW, Minich LL, Bradley T, Cohen MS, et al. Noncoronary cardiac abnormalities are associated with coronary artery dilation and with laboratory inflammatory markers in acute kawasaki disease. *J. Am. Coll. Cardiol*. 2011; 57(1):86–92. [PubMed: 21185506]
35. Newburger JW, Takahashi M, Beiser AS, Burns JC, Bastian J, Chung KJ, 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(23):1633–1639. [PubMed: 1709446]
36. Newburger JW, Takahashi M, Burns JC, Beiser AS, Chung KJ, Duffy CE, et al. The treatment of kawasaki syndrome with intravenous gamma globulin. *N. Engl. J. Med*. 1986; 315(6):341–347. [PubMed: 2426590]
37. Newburger JW, Sanders SP, Burns JC, Parness IA, Beiser AS, Colan SD. Left ventricular contractility and function in kawasaki syndrome. Effect of intravenous gamma-globulin. *Circulation*. 1989; 79(6):1237–1246. [PubMed: 2720925]
38. Newburger JW, Sleeper LA, McCrindle BW, Minich LL, Gersony W, Vetter VL, et al. Randomized trial of pulsed corticosteroid therapy for primary treatment of kawasaki disease. *N. Engl. J. Med*. 2007; 356(7):663–675. [PubMed: 17301297]
39. Tremoulet AH, Jain S, Jaggi P, Jimenez-Fernandez S, Pancheri JM, Sun X, et al. Infliximab for intensification of primary therapy for kawasaki disease: A phase 3 randomised, double-blind, placebo-controlled trial. *Lancet*. 2014; 383(9930):1731–1738. [PubMed: 24572997]
40. Kobayashi T, Saji T, Otani T, Takeuchi K, Nakamura T, Arakawa H, et al. Efficacy of immunoglobulin plus prednisolone for prevention of coronary artery abnormalities in severe kawasaki disease (raise study): A randomised, open-label, blinded-endpoints trial. *Lancet*. 2012; 379(9826):1613–1620. [PubMed: 22405251]
41. Son MB, Newburger JW. Management of kawasaki disease: Corticosteroids revisited. *Lancet*. 2012; 379(9826):1571–1572. [PubMed: 22405252]
42. Wallace CA, French JW, Kahn SJ, Sherry DD. Initial intravenous gammaglobulin treatment failure in kawasaki disease. *Pediatrics*. 2000; 105(6):E78. [PubMed: 10835091]
43. Sundel RP, Burns JC, Baker A, Beiser AS, Newburger JW. Gamma globulin re-treatment in kawasaki disease. *J. Pediatr*. 1993; 123(4):657–659. [PubMed: 8410524]
44. Wright DA, Newburger JW, Baker A, Sundel RP. Treatment of immune globulin-resistant kawasaki disease with pulsed doses of corticosteroids. *J. Pediatr*. 1996; 128(1):146–149. [PubMed: 8551407]

45. Burns JC, Best BM, Mejias A, Mahony L, Fixler DE, Jafri HS, et al. Infliximab treatment of intravenous immunoglobulin-resistant kawasaki disease. *J. Pediatr.* 2008; 153(6):833–838. [PubMed: 18672254]
46. Tremoulet AH, Pancoast P, Franco A, Bujold M, Shimizu C, Onouchi Y, et al. Calcineurin inhibitor treatment of intravenous immunoglobulin-resistant kawasaki disease. *J. Pediatr.* 2012; 161(3):506–512. e1. [PubMed: 22484354]
47. Suzuki H, Terai M, Hamada H, Honda T, Suenaga T, Takeuchi T, et al. Cyclosporin a treatment for kawasaki disease refractory to initial and additional intravenous immunoglobulin. *Pediatr. Infect. Dis. J.* 2011; 30(10):871–876. [PubMed: 21587094]
48. Lee TJ, Kim KH, Chun JK, Kim DS. Low-dose methotrexate therapy for intravenous immunoglobulin-resistant kawasaki disease. *Yonsei Med. J.* 2008; 49(5):714–718. [PubMed: 18972590]
49. Checchia PA, Pahl E, Shaddy RE, Shulman ST. Cardiac transplantation for kawasaki disease. *Pediatrics.* 1997; 100(4):695–699. [PubMed: 9310527]
50. Suda K, Tahara N, Honda A, Iemura M, Yoshimoto H, Kudo Y, et al. Persistent peripheral arteritis long after kawasaki disease - another documentation of ongoing vascular inflammation. *Int. J. Cardiol.* 2015; 180(88):90.

Key Points

- The diagnosis of KD requires a high index of suspicion. Infants and children may present with “soft” or incomplete clinical features, yet still develop significant coronary artery abnormalities.
- Asian children have the highest incidence of KD of all ethnic/racial groups. Siblings and children of KD patients are at increased risk.
- Laboratory and echocardiographic findings can help establish the diagnosis in nonclassic cases. In particular, a child with prolonged fever, laboratory evidence of systemic inflammation, and a coronary artery Z score ≥ 2.5 has a very high probability of having KD.
- Prompt treatment with intravenous gammaglobulin and aspirin can be life-saving. Children who do not have resolution of fever with this primary therapy are at increased risk of developing coronary artery abnormalities, and additional anti-inflammatory therapies should be administered.

Figure 1.
Conjunctival injection and red lips in a child with acute KD.

Figure 2.
Maculopapular rash on the extremities in a child with acute KD.

Figure 3.
Periungual desquamation of the fingers two weeks after fever onset in a child with KD.

Treatment algorithm for children with suspected incomplete Kawasaki Disease*

- Child with fever for ≥ 5 days and 2 or 3 other clinical features of KD
- Infant with fever for 7 days without explanation, even in absence of other KD features

CRP ≥ 3 mg/dl and/or ESR ≥ 40 mm/hr

CRP < 3 mg/dl and ESR ≤ 40 mm/hr

Three or more laboratory abnormalities:

- Albumin ≤ 3 g/dl
- Anemia for age
- Elevated ALT level
- Platelet count $\geq 450,000/\text{mm}^3$ after day 7
- WBC $> 15,000/\text{mm}^3$
- Urine > 10 WBC/hpf

OR

One of these echocardiography findings:

- CA Z score of LAD or RCA ≥ 2.5
- At least 3 of the following: decreased LV function, mitral regurgitation, pericardial effusion, lack of CA tapering, CA Z score of LAD or RCA 2-2.5

Follow closely; serial clinical and laboratory evaluation if fever persists

Treat with IVIG and aspirin therapy

*Adapted from Reference 7

Figure 4.

Treatment algorithm for children with suspected incomplete KD, adapted from [7].

Table 1

Key features of KD

<p>An acute onset of prolonged febrile illness in previously healthy children.</p> <p>The leading cause of acquired heart disease in children in developed nations.</p> <p>A systemic inflammatory illness affecting many organs and tissues, but leading to long-term consequences almost exclusively confined to medium-sized muscular arteries, particularly the coronary arteries.</p> <p>KD arteriopathy is characterized by three linked pathologic processes: necrotizing arteritis, subacute/chronic arteritis, and luminal myofibroblastic proliferation. Necrotizing arteritis occurs in the first two weeks after onset and can result in necrosis of the coronary arteries; if the necrosis is extensive, giant coronary artery aneurysms can form, which are associated with severe outcomes. Subacute/chronic arteritis begins in the first two weeks and can continue for months to years after onset. It is closely associated with luminal myofibroblastic proliferation, an active proliferative process of smooth muscle cell-derived myofibroblasts and their matrix products, which can lead to progressive arterial stenosis.</p> <p>The etiology remains unknown but clinical and epidemiologic features support an infectious cause.</p> <p>Genetic factors play a role in susceptibility, with Asian children at highest risk. However, children of all racial and ethnic groups can develop KD.</p>

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Table 2**Systemic Pathological Abnormalities Reported in KD [4]**

<ul style="list-style-type: none">• Cardiovascular: vasculitis, endocarditis, myocarditis, pericarditis• Gastrointestinal: sialoductitis, enteritis, hepatitis, cholangitis, pancreatitis and pancreatic ductitis• Respiratory: bronchitis, segmental interstitial pneumonia• Genitourinary: Cystitis, focal interstitial nephritis, prostatitis• Nervous system: Aseptic leptomeningitis, choriomeningitis, ganglionitis, neuritis• Hematopoeitic: Lymphadenitis, splenitis, thymitis

Table 3**Risk Factors for KD**

Factors associated with an increased risk of KD	
<ul style="list-style-type: none">• Asian ethnicity• Age < 5 years• Parent or sibling with prior history of KD [5, 6]	
Factors associated with higher risk of coronary artery abnormalities in children with KD [7]	
<ul style="list-style-type: none">• Age < 1 year or > 8 years• Male gender• Longer interval from disease onset to treatment with intravenous gammaglobulin• Failure to respond to initial intravenous gammaglobulin therapy• Laboratory features (albumin < 3.0 mg/dl, anemia for age, elevated alanine aminotransferase, hyponatremia, thrombocytopenia)	

Table 4

Incidence of KD in various countries, as reported in the last decade

Country	Approximate risk of child developing KD by age 5 years*	Reference
Japan	1 in 90	Nakamura et al [2]
Korea	1 in 150	Kim et al [10]
China	1 in 400	Du et al [11]
Taiwan	1 in 300	Huang et al[12]
Continental United States	1 in 1000	Holman et al [13]
Hawaii-Japanese American	1 in 95	Holman et al [14]
Hawaii-Native Hawaiian	1 in 230	Holman et al [14]
Hawaii-Chinese American	1 in 240	Holman et al [14]
Hawaii-Other Asian	1 in 235	Holman et al [14]
Hawaii-Caucasian	1 in 1000	Holman et al [14]
Canada	1 in 770	Lin et al [15]
France	1 in 2200	Heuckin et al [16]
Australia	1 in 2200	Saundankar et al[17]
Finland	1 in 1750	Salo et al [18]
Norway	1 in 3700	Salo et al [18]
Sweden	1 in 2700	Salo et al [18]
Chile	1 in 2600	Borzutzky et al [19]
Israel	1 in 1680	Bar-Meir et al [20]

* Based upon yearly incidence per 100,000 children <5 years in each country.

Table 5

Common features in the history of children with KD

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- Prolonged intermittent high-spiking fevers (ask parent how temperatures are taken; oral or rectal temperatures are most accurate)
 - Excessive irritability when compared with other previous febrile illnesses
 - Refusal to bear weight or to hold objects in hands
 - Redness and swelling of hands and feet
 - Redness and peeling of the skin in the groin area
 - Red eyes
 - Red lips and tongue
 - Red rash on body, primarily on trunk, arms and legs
 - Swollen glands in neck
 - Vomiting
 - Diarrhea
 - Cough
 - Redness at BCG site (children born in countries where this vaccine is routinely administered)
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Table 6**Physical examination findings (Classic Diagnostic Criteria)**

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- Intermittent high fever
 - Plus 4 of the following 5 features:
 - Bulbar conjunctival injection, generally without exudate and often with limbal sparing (Figure 1)
 - Oral changes: Redness of the throat, strawberry tongue, redness of the lips, sometimes with bleeding or peeling of the lips (Figure 1)
 - Rash: erythematous maculopapular (Figure 2), scarlatiniform, or erythema multiforme, sometimes with marked groin erythema and desquamation
 - Extremity changes: redness and swelling of the hands and feet during the first week; typical periungual desquamation occurs in the second or third week (Figure 3)
 - Cervical lymphadenopathy 1.5 cm in diameter
 - Illness not explained by other known disease process
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Table 7**Laboratory findings**

Normal peripheral white blood cell count with left shift, or elevated white blood cell count with predominance of neutrophils
Elevated erythrocyte sedimentation rate (40 mm/hr) and/or C-reactive protein (3.0 mg/dl)
Anemia for age
Albumin <3.0 mg/dl
Hyponatremia
Thrombocytosis in second to third week
Sterile pyuria (10 white blood cells/high powered field)
Elevated serum transaminases with or without elevated serum gamma glutamyl transpeptidase or bilirubin
Cerebrospinal fluid pleocytosis, usually with normal glucose and protein levels
Leukocytosis in synovial fluid

Table 8**Options for Therapy of Refractory KD**

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- Additional dose(s) of 2 gm/kg of IGIV [43]
 - Intravenous methylprednisolone 30 mg/kg/day for 1–3 days [44]
 - Infliximab 5 mg/kg x1 [45]
 - Other possible therapies: cyclosporine [46,47], methotrexate [48]
 - Therapies sometimes used in Japan: plasmaphoresis, neutrophil elastase inhibitor
 - Possible future therapies: statins, IL-1 inhibitors
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