LEARNING OBJECTIVE FR1

Kawasaki Disease

Featured reading: 2021 American College of Rheumatology/Vasculitis Foundation Guideline for the Management of Kawasaki Disease.

Quick Points

Know

- Kawasaki disease (KD; a.k.a. mucocutaneous lymph node syndrome) is a febrile vasculitis affecting medium-sized vessels, particularly coronary arteries.
  - KD is often included in the differential diagnosis of fever of unknown origin.
- Typically presents in children < 5 years of age with prolonged (≥ 5 days) fever and irritability combined with ≥ 4 of the 5 following criteria:
  - Polymorphous nonbullous rash
  - Mucositis (strawberry tongue, injected pharynx, cracked lips)
  - Nonsuppurative conjunctivitis that spares the limbus
  - Erythema of palms/soles and/or edema of hands/feet leading to peeling during convalescent phase
  - Cervical lymphadenopathy (at least 1 lymph node ≥ 1.5 cm in diameter, usually unilateral)
- Incidence is ~ 25–50 cases per 100,000 children per year in the U.S.
- If untreated, ~ 25% of patients develop coronary artery aneurysms, making it the leading cause of acquired heart disease in children in developed countries.

Manage

- All patients should receive intravenous immunoglobulin (IVIG) 2 g/kg administered over at least 8–12 hours as standard initial therapy.
  - Most effective if administered within the first 10 days
  - Still recommended for patients diagnosed > 10 days after fever onset
  - Significantly reduces the rate of coronary artery aneurysms and duration of fever/symptoms
  - Mainstay of therapy for KD
- In high-risk patients, defined as age < 6 months or Z score ≥ 2.5 of coronary artery dilation on initial echocardiography, addition of glucocorticoids (e.g., prednisone 2 mg/kg/day, maximum 60 mg/day, tapered over 15 days), or other immunomodulators (e.g., infliximab, anakinra, cyclosporine), IVIG is conditionally recommended.
  - Combining these agents with IVIG as initial therapy appears to reduce risk of coronary artery aneurysms and progression in those with aneurysms at diagnosis.
    - However, optimal dosing/duration of glucocorticoids requires further study.
  - Use of IVIG alone may be reasonable if it is unclear that the patient is truly high risk.
- Promptly treat incomplete KD (suspected KD with < 4 principal clinical criteria) with IVIG when the diagnosis is made, rather than waiting until day 10 of illness.
  - Delaying treatment is associated with worse outcomes; the risk of coronary artery dilatation increases each day without treatment.

- Use the American Heart Association (AHA) diagnostic algorithm for incomplete KD to establish the diagnosis.
- Resolution of fever before day 10 is not a reason to withhold treatment if diagnostic criteria are met.

- For KD with macrophage activation syndrome (MAS), treat both conditions appropriately.
  - MAS can occur as a complication of KD.
  - Use IVIG for KD along with agents like anakinra or glucocorticoids to treat the cytokine storm in MAS; cytotoxic therapy is generally not warranted.
  - Inadequate treatment of either condition could lead to coronary aneurysms/rupture or death from multiorgan failure.
- Obtain an echocardiogram with coronary artery measurements for:
  - Suspected incomplete KD—to help establish the diagnosis and guide need for prompt IVIG treatment
  - Unexplained shock—Kawasaki shock syndrome can present similarly.
  - Atypical MAS—identifying coronary involvement would lead to targeted KD treatment
  - Children with COVID-19 who do not meet criteria for MIS-C but have features of KD
- Use aspirin for its antiplatelet effect to reduce risk of coronary thrombosis.
  - While high-dose aspirin (80–100 mg/kg/day) was historically used for antiinflammatory effects, there is no evidence it reduces coronary outcomes compared to low-dose aspirin (3–5 mg/kg/day).
  - Continue low-dose aspirin for antiplatelet effects until assured there is no cardiac involvement, which is usually several weeks.
  - Follow AHA guidelines for anticoagulation recommendations in patients with large aneurysms.
- For persistent fever > 36 hours after initial IVIG, repeat a second dose of IVIG or use glucocorticoids (e.g., pulse methylprednisolone 30 mg/kg, maximum 1 gm).
  - No definitive evidence that one is superior to the other
- After repeat IVIG failure, consider glucocorticoids (e.g., prednisone 2 mg/kg/day tapered over 15 days) or other immunosuppressants such as infliximab or cyclosporine.
  - No evidence that one class is superior to the other for refractory disease
  - Can be used simultaneously
- Monitor patients for return of fever (> 38°C [100.4°F] orally or > 37.5°C [99.5°F] axillary) daily for 1–2 weeks after discharge given the risk of disease recurrence or treatment failure.
  - Parents/Guardians should be instructed on temperature monitoring and to contact the physician if fever returns.
  - The duration of fever is a risk factor for coronary artery aneurysms.
- Vaccinations:
  - Postpone administration of live-virus vaccines (measles, mumps, rubella; varicella) for ≥ 11 months following treatment with IVIG for KD.
    - Passively acquired antibodies may interfere with vaccine immunogenicity
  - Schedule for administration of age-appropriate inactivated vaccines should remain unchanged.

Excerpts from *Pediatrics Core*

FROM: RHEUMATOLOGY

VASCULITIDES

MEDIUM-VESSEL VASCULITIDES

Kawasaki Disease (KD)

KD (a.k.a. mucocutaneous lymph node syndrome), a medium-vessel vasculitis, is the 2nd most common vasculitis of childhood. It is t he leading cause of acquired heart disease in children in the U.S. It generally occurs in children < 5 years of age, affects boys more than girls (1.5:1), and occurs year-round with clusters in the winter and spring. Incidence is highest in children of Asian descent. In Japan, the incidence is 90 in 100,000 in children < 5 years of age. The reported incidence in the U.S. is ~ 25–50 in 100,000 children. Nearly 1–3% of affected individuals have a recurrence. Recurrence is most likely in boys < 6 months of age or > 6 years of age. The etiology of this disorder is unknown, although the widespread inflammatory response seen in KD is thought to be triggered by an infectious agent that has yet to be identified. One theory points to staphylococcal and streptococcal superantigen stimulation of the immune system.

Myocardial infarction is the main cause of death in KD and most commonly occurs during the 1st year after the onset of illness. Fatality rates are low in treated patients: 0.16% in infants < 1 year of age and 0.05% in children > 1 year of age.

A clinical diagnosis requires fever for at least 5 days and a minimum of 4 of the following 5 findings (Table 20-3):

1) Bilateral **conjunctival injection** without exudate (occurs in 80–90%).
2) **Rash** (> 90%) is typically macular and polymorphous in character with no vesicles, scaling, or crusting; it is found on the trunk and is frequently more prominent in the perineal area later in the course; desquamation of the area follows.
3) **Changes in lips and oral cavity** (80–90%) present with red pharynx; dry, fissured lips; and/or an injected, strawberry tongue (Figure 20-7).
4) **Peripheral extremity changes** (~ 80%) present with redness and swelling of the hands/feet (Figure 20-8) and, later, desquamation of the fingers/toes (Figure 20-9 on page 346).
5) **Cervical lymphadenopathy** (~ 50%) is typically nonfluctuant with 1 node required to be at least 1.5 cm in diameter.

Diagnosis with < 4 of the 5 criteria is possible if **coronary aneurysm** is demonstrated on echocardiogram or angiogram. Fever is an absolute requirement. Baseline lab tests such as complete blood count (CBC), liver function tests, ESR/C-reactive protein (CRP), and urinalysis

Table 20-3: Classic Clinical Criteria for Kawasaki Disease

Criteria	Frequency (%)
Fever persisting at least 5 days	100
Polymorphous exanthem	> 90
Changes in lips and oral cavity: erythema, lips cracking, strawberry tongue, diffuse injection of oral and pharyngeal mucosae	80–90
Bilateral bulbar conjunctival injection without exudate	80–90
Changes in extremities Acute: erythema of palms, soles; edema of hands, feet Subacute: periungual peeling of fingers, toes in weeks 2 and 3	~ 80
Cervical lymphadenopathy (> 1.5-cm diameter), usually unilateral	~ 50

Adapted from Newburger JW, et al. AHA Scientific Statement 2004. *Textbook of Pediatric Rheumatology*, 7th ed. Ross E. Petty, et al. (eds.) Elsevier, 2015.

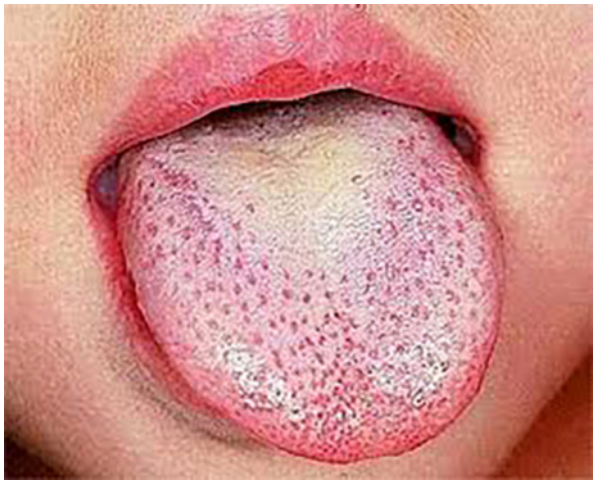

Figure 20-7: Strawberry tongue

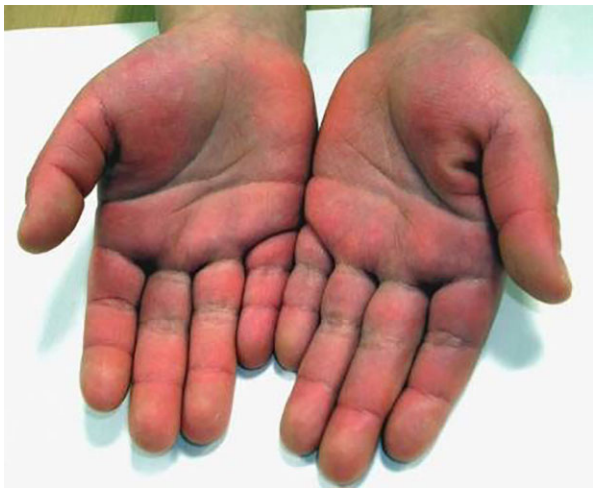

Figure 20-8: Kawasaki disease with redness and swelling of hands

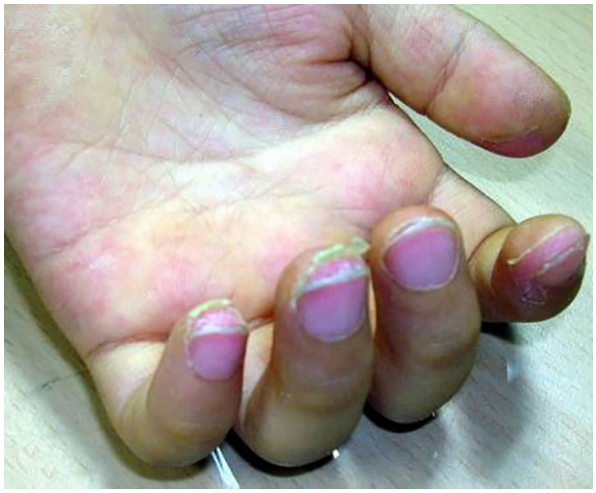

Figure 20-9: Kawasaki disease with desquamation of fingers

are generally obtained. Serologies such as antinuclear antibody, rheumatoid factor, and ANCA are not necessary and are usually negative.

Atypical or **incomplete KD** is diagnosed when patients have 3 or fewer of the required 5 clinical findings. In these patients, specific laboratory findings and/or an abnormal echocardiogram are suggestive of Kawasaki disease. Cervical lymphadenopathy and rash are usually the clinical findings absent in patients diagnosed with atypical or incomplete KD. It occurs more often in younger patients, especially infants < 1 year of age.

Laboratory findings suggestive of KD:

- CRP ≥ 3 mg/dL
- ESR ≥ 40 mm/hour
- WBC count ≥ 15,000/µL
- Normocytic, normochromic anemia for age
- Platelet cell count ≥ 450,000/µL after 7 days of illness
- Sterile pyuria due to urethritis (≥ 10 WBCs/high-power field)
- Serum alanine aminotransferase (ALT) > 50 units/L
- Serum albumin ≤ 3 g/dL

Think of KD in **3 stages**.

The **1st stage**, the acute phase, is the initial febrile period, usually lasting 1–2 weeks with temperatures of ≥ 40.0°C (104.0°F) and with at least 4 of the 5 findings. Irritability is a hallmark in this stage. Additional clinical findings may include aseptic meningitis, acute uveitis, diarrhea, mild obstructive jaundice with elevated transaminases, hydrops of the gallbladder, and sterile pyuria. Nearly 33% have polyarthritis or polyarthralgia, typically of the knees, ankles, and hands. Edema of the hands and feet is more common than localized inflammatory arthritis. Fluid aspirated from an affected joint shows polymorphonuclear leukocytes (PMNs), simulating septic arthritis but with a negative culture.

Be particularly aware of cardiac manifestations. Nearly 33% have pericardial effusions, and myocarditis is also common. Several coronary artery abnormalities (CAAs)—aneurysms are the main worry—may occur as early as day 3 of illness but are more typically seen 10 days to 4 weeks after onset. Even with treatment, CAA may be found in 3–5% of patients.

Risk factors for coronary aneurysm include:

- Male sex
- Age < 1 year or > 8 years
- Fever > 10 days
- Thrombocytopenia
- Hyponatremia
- Hypoalbuminemia
- WBC > 15,000/µL
- Recurrence of fever 36 hours after IV immunoglobulin (IVIG) administration

The **2nd stage**, the subacute phase, starts ~ 10–25 days after the initial fever presentation and persists until all clinical signs of inflammation subside. The fever, rash, and lymph nodes usually resolve early in this phase, but irritability and conjunctival injection can persist. Skin changes occur during this stage, most commonly desquamation. Thrombocytosis generally occurs after day 7 of the illness. Coronary artery aneurysms occur in 25% of untreated individuals and in 5–9% of those who are treated. Oligoarticular disease can occur in 25% during the 2nd and 3rd weeks but is self-limited.

The **3rd stage**, the convalescent phase, occurs in the 3rd or 4th week, when clinical signs disappear, and usually lasts for 3–4 weeks. Although less likely, coronary artery aneurysms may occur in this phase.

KD is mostly a clinical diagnosis. Use laboratory tests to help exclude other diagnoses. Laboratory findings include leukocytosis with a left shift, platelet counts commonly > 1 million during the subacute phase of the illness, and an elevated ESR and/or CRP. Elevation of gamma-glutamyl transferase (GGT) can help differentiate KD from other fever and rash syndromes that do not have gallbladder involvement. Be cognizant of possible multiorgan dysfunction. Approximately 1% of these patients can develop overt macrophage activation syndrome (MAS).

Treatment for KD is well established. Recommendations are to give aspirin and a single dose of IVIG (2 g/kg). Give aspirin at antiinflammatory doses (30–100 mg/kg/day) initially, and later decrease to antiplatelet doses (3–5 mg/kg/day) when the fever resolves, the CRP and ESR begin to decline, and the platelet count starts to rise. Although there is no evidence that high-dose aspirin reduces coronary outcomes compared to low-dose aspirin, many centers still use the higher dosage until the presence or absence of an aneurysm can be determined. If there are no aneurysms by 6–8 weeks, aspirin can be discontinued. The IVIG typically causes a rapid improvement in fever and clinical symptoms. If the condition relapses or the patient does not respond well to treatment, repeat the dose of IVIG. Retreatment is needed in < 5–10% of cases. IVIG side effects are uncommon, but look for anaphylaxis and aseptic meningitis, which can occur 1–2 days after treatment. Corticosteroid therapy is controversial. Recent

studies suggest that corticosteroid use may be beneficial as adjunctive therapy to ASA and IVIG (vs. corticosteroid use in cases refractory to IVIG) when used in patients at high risk for developing coronary artery aneurysms. Infliximab, anakinra, and cyclosporine have also been used safely and successfully in patients who fail to improve with IVIG.

Every child with KD should have initial echocardiography at the time of diagnosis and a 2nd round of echocardiography performed 6–8 weeks later.

FROM: CARDIOLOGY

KAWASAKI DISEASE (KD)

PREVIEW | REVIEW

- What are the criteria to diagnose Kawasaki disease (KD)?
- What is the pathognomonic cardiac finding of KD?

KD (a.k.a. mucocutaneous lymph node syndrome) is an acute inflammatory vasculitis of unknown etiology. It probably represents an autoimmune inflammatory response to a currently undefined infection. 85% of cases occur between 6 months and 5 years of age, and KD is most common in the Asian population.

The diagnosis of KD is made clinically, with fever for ≥ 5 days and 4 of the following 5 criteria:

- Conjunctival injection without drainage
- Cervical lymphadenopathy (at least one lymph node > 1.5 cm)
- Extremity changes with erythema and edema of the hands and feet and later desquamation
- Mucous membrane changes with erythema, cracked and peeling lips, or strawberry tongue
- Polymorphous rash—usually macular or maculopapular erythematous but any rash except vesicles and bullae

Incomplete (atypical) KD is diagnosed in a patient with fever for ≥ 5 days, < 4 of the 5 clinical criteria, at least 2 clinical criteria, laboratory evidence of inflammation (elevated ESR or CRP), and several supplemental laboratory criteria.

Laboratory findings include leukocytosis, elevated ESR and CRP, thrombocytosis (often with very high platelet counts), elevated liver enzymes, sterile pyuria, aseptic meningitis, hydrops of the gallbladder, and lipid abnormalities.

Patients can develop carditis, pericarditis, or even valvulitis, but the pathognomonic cardiac manifestation (and the most concerning) is **coronary artery aneurysms** that develop in 20–25% of inadequately treated cases. These can be bilateral and have a predilection for the proximal vessels. If > 8 mm in diameter or Z score (coronary diameter adjusted for body surface area) ≥ 10, they are classified as "giant" aneurysms and have a much greater risk for complications. About 50% of aneurysms "resolve" to normal-appearing coronary arteries over time. Long term, they (particularly giant aneurysms) can develop thrombosis, stenosis, and ischemia. This can lead to myocardial ischemia and infarction or death in < 1% of properly treated cases.

The primary diagnostic modality for evaluating coronary arteries is echocardiography. This is initially performed at the time of diagnosis or suspected diagnosis and then repeated in 2–8 weeks to look for aneurysms that most often develop in the subacute phase. Catheterization is reserved for patients with complex or giant aneurysms or evidence of coronary insufficiency.

Treatment for KD and incomplete KD is primarily with IV immunoglobulin (IVIG) infusion of 2 g/kg over 12 hours. This improves the fever, inflammatory response, and clinical picture, but most importantly, it decreases the risk of coronary aneurysms to 5–8%. About 7–8% of children require a 2nd dose of IVIG for persistent fever and inflammation 36 hours after the initial dose. If still not responding, IV steroids or other antiinflammatory agents are an option. Give aspirin at antiinflammatory doses (30–100 mg/kg/day) initially, and later decrease to antiplatelet doses (3–5 mg/kg/day) when the fever resolves, the CRP and ESR begin to decline, and the platelet count starts to rise. Although there is no evidence that high-dose aspirin reduces coronary outcomes compared to low-dose aspirin, many centers still use the higher dosage until the presence or absence of an aneurysm can be determined. If there are no aneurysms by 6–8 weeks, aspirin can be discontinued.

Long-term care and follow-up depend on the degree of coronary artery involvement. Those patients with persisting aneurysms are maintained on aspirin (or warfarin with giant aneurysms) and followed regularly by cardiology with echocardiography and later by myocardial perfusion imaging and stress testing when old enough.

Resource

Gorelik M, Chung SA, et al. 2021 American College of Rheumatology/Vasculitis Foundation Guideline for the Management of Kawasaki Disease. Arthritis Care Res (Hoboken). 2022 Apr;74(4):538-548. https://doi.org/10.1002/acr.24838