A 4-year-old fully immunized male presents with 2 days of fever and irritability. His examination is normal. He is presumed to have a viral syndrome and discharged with reassurance and instructions to bring him back if his fever continues or if any other symptoms of concern develop.

Three days later, the patient is brought back. His fevers have persisted, rising as high as 103°F. He has been particularly irritable, and new symptoms include red eyes and a rash. There has been no recent travel or known animal exposures. He has been on no medications other than intermittent acetaminophen and ibuprofen for the fever.

What is the differential diagnosis of a child with fevers and a rash?

There are a few important pieces of information in the history so far that can help narrow down the differential. Measles may be at the top of the differential in nonimmunized children, but it is much less likely in this patient as by the age of 4 years, most children have received the complete measles vaccine series.

Other emergent things to consider are meningococcal infection and toxic shock syndrome, especially if the patient is ill appearing. Meningococcal infections may present with maculopapular rash and irritability. This rash may disappear quickly or the patient may develop a petechial rash. Toxic shock syndrome can also present with fever and a rash, and there is often conjunctival involvement. The rash is often a subtle, diffuse, macular erythema resembling a sunburn in the setting of a group A *Streptococcus* infection or *Staphylococcus aureus* infection.

Scarlet fever caused by group A *Streptococcus* causes a blanching, erythematous, papular “sandpapery” (scarlatiniform) rash over the trunk. Adenovirus can cause fever and rash, along with conjunctivitis, pharyngitis, and coryza. Roseola due to human herpes virus 6 or 7 (HHV-6 or -7) results in a fever and rash, but the fever typically resolves before the rash appears. Parvovirus B19 infection presents with red “slapped” cheeks followed by a reticular rash on the trunk, arms, and legs.

Geography and travel history is also important to consider. For instance, Rocky Mountain spotted fever—a tick-borne illness that can cause fever, headache, and a rash in a patient with a history of a tick bite—is primarily seen in the southeastern and south central United States.

Noninfectious causes to consider include Kawasaki disease (KD) and systemic juvenile idiopathic arthritis (JIA). KD is an acute vasculitis that has specific diagnostic criteria but would include several of this patients’ symptoms, including the fever of 5 days or more, rash, and conjunctival injection. Systemic JIA may present with fever, arthritis, rash, and lymphadenopathy.

**BASIC SCIENCE/CLINICAL PEARL**

Maculopapular rashes are both common and nonspecific. Such rashes are most commonly associated with viral infections in children.

**CLINICAL PEARL**

Measles may be mistaken for Kawasaki disease and should be considered in nonimmunized children.
Case Point 18.1

His blood pressure is 118/70 mm Hg, pulse rate is 140/min, respiration rate is 20/min, oxygen saturation is 99% on room air, and temperature is 102.3°F.

On physical examination, the child is irritable but mostly consolable by his mother when not being examined. The bulbar conjunctiva of his eyes are injected bilaterally, with noted limbic sparing (Fig. 18.1A). His lips are erythematous, with a dry, cracked appearance (see Fig. 18.1B). A palpable 2 cm lymph node is noted in his left anterior cervical chain. His trunk is covered in a diffuse, blanching maculopapular rash (see Fig. 18.1C). His hands are swollen and red.

What is the most likely diagnosis at this time?
Clinical findings that help narrow the differential diagnosis include exudative conjunctivitis (suggestive of bacterial infection), exudative pharyngitis (group A Streptococcus), ulcerative oral lesion, bullous or vesicular rash, generalized adenopathy, or splenomegaly (JIA).

Of the list of possibilities discussed above, the patient’s presentation is most consistent with KD.

What are the diagnostic criteria of Kawasaki disease? What other clinical features can be seen in Kawasaki disease?
The diagnostic criteria for KD are listed in Box 18.1.

KD is an acute systemic inflammatory inflammation in all medium-sized arteries which affects multiple organs and tissues, leading to several other associated clinical findings. The diagnostic criteria exist to distinguish KD from other infectious or inflammatory disorders, and do not include the many other manifestations seen, which are summarized in Box 18.2.

BASIC SCIENCE/CLINICAL PEARL

Exudative conjunctivitis or pharyngitis are almost never Kawasaki disease. Viral and bacterial infections should be considered instead (group A Streptococcus pharyngitis, for example).

Supportive laboratory tests can help confirm the diagnosis if a patient does not meet the strict clinical criteria. Infants in particular may present with fever and no other clinical criteria.

In children with persistent fever (5+ days) and at least two clinical criteria, OR in infants with at least 7 days of fever without an identifiable source, a C-reactive protein (CRP) level of 3 mg/dL or higher and/or an erythrocyte sedimentation rate of 40mm/hr or higher, either a positive echocardiogram OR any three (or more) of the following laboratory findings is an indication to presumptively treat: white blood cell count 15 × 10^9/L or higher, anemia, platelet count of 450 × 10^9/L or higher after the seventh day of fever, albumin level of 3 g/dL or less, elevated serum alanine aminotransferase (ALT) and/or 10/hpf or more urine leukocytes (sterile pyuria).

Case Point 18.2

The child is admitted to the hospital. An echocardiogram is performed, revealing dilation of the right coronary artery (Fig. 18.2).

Diagnosis: Kawasaki disease, classic.

CLINICAL PEARL

Cardiac presentations in Kawasaki may range from no cardiac manifestations to severe presentations including myocardial infarction and/or cardiogenic shock. The initial echocardiogram is typically normal in the first week of illness, however, and a normal echocardiogram should not delay therapy to prevent late cardiac complications.
Fig. 18.1 (A) Bulbar conjunctivitis, (B) cheilitis, and (C) an erythematous rash are seen. (Reprinted with permission from Burns JC, et al. Kawasaki syndrome. Lancet. 2004;364(9433):533–544.)

BOX 18.1 Diagnosis of Classic Kawasaki Disease

Classic KD is diagnosed in the presence of fever for at least 5 days (the day of fever onset is taken to be the first day of fever) together with at least four of the five following principal clinical features. In the presence of ≥4 principal clinical features, particularly when redness and swelling of the hands and feet are present, the diagnosis of KD can be made with 4 days of fever, although experienced clinicians who have treated many patients with KD may establish the diagnosis with 3 days of fever in rare cases:

1. Erythema and cracking of lips, strawberry tongue, and/or erythema of oral and pharyngeal mucosa
2. Bilateral bulbar conjunctival injection without exudate
3. Rash: maculopapular, diffuse erythroderma, or erythema multiforme-like
4. Erythema and edema of the hands and feet in acute phase and/or periungual desquamation in subacute phase
5. Cervical lymphadenopathy (≥1.5 cm diameter), usually unilateral

A careful history may reveal that ≥1 principal clinical features were present during the illness but resolved by the time of presentation.

Patients who lack full clinical features of classic KD are often evaluated for incomplete KD. If coronary artery abnormalities are detected, the diagnosis of KD is considered confirmed in most cases.

Laboratory tests typically reveal normal or elevated white blood cell count with neutrophil predominance and elevated acute-phase reactants such as C-reactive protein and erythrocyte sedimentation rate during the acute phase. Low serum sodium and albumin levels, elevated serum liver enzymes, and sterile pyuria can be present. In the second week after fever onset, thrombocytosis is common.

KD, Kawasaki disease.

**BOX 18.2 Associated Clinical Findings in Classic Kawasaki Disease**

Other clinical findings may include the following:

- **Cardiovascular**
  - Myocarditis, pericarditis, valvular regurgitation, shock
  - Coronary artery abnormalities
  - Aneurysms of medium-sized noncoronary arteries
  - Peripheral gangrene
  - Aortic root enlargement

- **Respiratory**
  - Peribronchial and interstitial infiltrates on CXR
  - Pulmonary nodules

- **Musculoskeletal**
  - Arthritis, arthralgia (pleocytosis of synovial fluid)

- **Gastrointestinal**
  - Diarrhea, vomiting, abdominal pain
  - Hepatitis, jaundice
  - Gallbladder hydrops
  - Pancreatitis

- **Nervous system**
  - Extreme irritability
  - Aseptic meningitis (pleocytosis of cerebrospinal fluid)
  - Facial nerve palsy
  - Sensorineural hearing loss

- **Genitourinary**
  - Urethritis/meatitis, hydrocele

- **Other**
  - Desquamating rash in groin
  - Retropharyngeal phlegmon
  - Anterior uveitis by slit lamp examination
  - Erythema and induration at BCG inoculation site
  - The differential diagnosis includes other infectious and noninfectious conditions, including the following:
    - **Measles**
    - Other viral infections (e.g., adenovirus, enterovirus)
    - Staphylococcal and streptococcal toxin-mediated diseases (e.g., scarlet fever and toxic shock syndrome)
    - Drug hypersensitivity reactions, including Stevens Johnson syndrome
    - Systemic onset juvenile idiopathic arthritis
    - With epidemiologic risk factors:
      - Rocky Mountain spotted fever or other rickettsial infections
      - Leptospirosis

BCG, Bacillus Calmette-Guérin; CXR, chest radiography.


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**BASIC SCIENCE/CLINICAL PEARL**

Although Kawasaki disease affects children of all races and ethnicities, it is more common in those of Asian, particularly Japanese, descent.
What is the pathophysiology of Kawasaki disease?

The exact cause of KD is unknown but is thought to involve both a hereditary predisposition and environmental triggers.

The pathophysiology of arterial damage involves three processes: (1) a necrotizing arteritis within the first 2 weeks of illness in mid-sized arteries that results in saccular aneurysms that may potentially thrombose or rupture; followed by (2) a subacute chronic vasculitis that may continue for months to years; and finally (3) progressive arterial stenosis over months to years (Fig. 18.3).

All layers of the heart may be affected from the pericardium to the myocardium to the endocardium. Small pericardial effusions are common. Valvular dysfunction—especially that of the mitral valve—may occur in up to 25% of patients. Arrhythmia, prolonged PR interval, non-specific ST and T wave changes, as well as low voltage due to myocardial or pericardial involvement, may all be seen on an electrocardiogram.

**BASIC SCIENCE/CLINICAL PEARL**

Tachycardia out of proportion to the fever, a flow murmur, and/or a gallop rhythm all suggest decreased compliance or diastolic dysfunction. Tachycardia is often a sign of myocardial inflammation in Kawasaki disease.

What is the initial management of Kawasaki disease?

A single dose of intravenous immunoglobulin (IVIG) 2 g/kg should be administered together with an antiinflammatory dose of acetylsalicylic acid (ASA, aspirin). IVIG should be started within the first 10 days of illness marked by the onset of fever if at all possible, as delayed therapy puts the child at a higher risk of coronary artery abnormalities. The exact mechanism of action of IVIG is not known but thought to be antiinflammatory in nature.

ASA does not decrease the incidence of coronary abnormalities but is used for its antiinflammatory and antiplatelet effects. For children that do go on to develop coronary artery aneurysms, ASA is continued indefinitely.
Case Point 18.3

The patient is treated with high-dose IVIG and ASA. His fever resolves over the next 24 hours, and the ASA dose is reduced to a low dose (antiplatelet dose) after resolution of the fever.

**What instructions should be given to the family upon discharge?**

It is important to note that some patients will have complications despite IVIG therapy. Therefore, it is important to instruct the patient to return to the hospital for evaluation if the fever recurs. Additionally, parents should be warned of the desquamating rash that typically occurs 2 to 3 weeks after the onset of fever, starting under the nails of the fingers and toes, and potentially spreading to involve the palms and soles.

For uncomplicated patients, an echocardiogram should be repeated within 1 to 2 weeks. ASA therapy should continue for at least 4 to 6 weeks after the onset of illness, and another echocardiogram will be performed at that time. For any patient with evolving coronary artery abnormalities during the acute illness, echocardiography should be performed twice a week until the coronary artery luminal dimensions have stabilized.

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**Fig. 18.3** Theorized progression of vasculitic events in Kawasaki disease. (From Kato H. Cardiovascular complications in Kawasaki disease: coronary artery lumen and long-term consequences. Prog Pediatr Cardiol. 2004;19(2):137–145.)
What is the prognosis for children with Kawasaki disease?
The patients at highest risk for coronary abnormalities are those who are less than 1 year old, those whose diagnosis and treatment were delayed beyond 10 days, patients who are IVIG-resistant, patients with recurrent KD, male gender, and those with prolonged fever, high CRP levels, low albumin levels, and anemia.

Long-term management is focused on preventing thrombosis and maintaining optimal cardiovascular health. The extent of cardiology care will depend on the level of risk as defined by coronary artery luminal dimensions.

For any patients with a small, medium or large aneurysm, follow-up with cardiology may include stress echocardiography, stress electrocardiography, or stress magnetic resonance perfusion imaging.

ASA should be continued in those with current or persistent aneurysm(s). Additionally, long-term anticoagulation may be considered, as well as dual-antiplatelet therapy with ASA and clopidogrel. A $\beta$-blocker may be considered in a patient with a large aneurysm. Statin therapy may be considered in any patient with an aneurysm as well.

**BASIC SCIENCE/CLINICAL PEARL**

Without IVIG therapy, up to 25% of children will develop coronary artery abnormalities. With high-dose IVIG, the risk is reduced to approximately 4%.

**BEYOND THE PEARLS**

- Although Kawasaki disease is uncommon in children under 6 months of age or over 5 years of age, these two groups are at higher risk for coronary artery complications than children between 6 months and 5 years of age.
- Some vaccine considerations: Measles-mumps-rubella and varicella vaccines should be deferred for 11 months after IVIG. Only inactivated flu vaccine can and should be given to those on ASA therapy.
- The cause of Kawasaki is not known but is likely to be a combination of genetic risk and infectious cause Siblings of patients appear to be at higher risk of developing Kawasaki disease.
- The 10%–20% of patients whose fevers do not resolve after administration of IVIG have disease termed IVIG-resistant. Such patients often have a poorer prognosis, with more cardiac complications.
- Second-line agents used in IVIG-resistant patients include glucocorticoids and antiinflammatory biologic therapy (e.g., infliximab).
- Ibuprofen should be avoided in patients on ASA therapy as it antagonizes the irreversible platelet inhibition induced by ASA.
- ASA is rarely used in pediatrics due to the increased risk of Reye Syndrome, a rapidly progressive encephalopathy due to hepatic dysfunction, especially in the setting of influenza or varicella infection. The low dose (antiplatelet) therapy has not been shown to lead to Reye syndrome.

**Case Summary**

**Complaint/History:** A 4-year-old fully immunized male presents with 5 days of fever and irritability.

**Findings:** Bulbar conjunctivitis, cheilitis, lymphadenopathy, and a rash.

**Labs/Tests:** Echocardiogram reveals mild coronary artery dilation.

**Diagnosis:** Kawasaki disease.

**Treatment:** Intravenous immunoglobulin and aspirin.
Bibliography


