Kawasaki Disease: Clinical Features, Diagnosis and Treatment Guidelines

Definition:
Kawasaki disease (KD, previously called mucocutaneous lymph node syndrome) is one of the most common vasculitides of childhood. KD also occurs rarely in adults. It is typically a self-limited condition, with fever and manifestations of acute inflammation lasting for an average of 12 days without therapy. However, complications may develop and lead to significant morbidity and mortality.

Risk Factors:
- **Geographic variation (ethnicity)** (The incidence of KD is greatest in children who live in East Asia or are of Asian ancestry living in other parts of the world)
- **Gender** (Boys are affected as much as 50 percent more commonly than girls)
- **Age** (children younger than five years, although KD is relatively uncommon among children younger than six months. Older children can develop KD and may experience delays in diagnosis and higher rates of coronary artery disease)

Clinical manifestations:
The clinical features of KD reflect widespread inflammation of primarily medium-sized muscular arteries. The following findings are often not present at the same time, and there is no typical order of appearance:
- **Fever**: minimally responsive to antipyretic agents. Typically remains above 38.5°C (101.3°F) during most of the illness.
- **Conjunctivitis**: A predominantly bulbar injection typically begins within days of the onset of fever, and the eyes often have a brilliant erythema, which characteristically spares the limbus.
- **Mucositis**: Cracked, red lips and a "strawberry tongue" are characteristic.
- **Rash**: Perineal erythema and desquamation, followed by macular, morbilliform, or targetoid skin lesions of the trunk and extremities.
- **Extremity changes**: Indurated edema of the dorsum of hands and feet and a diffuse erythema of palms and soles.
- **Lymphadenopathy**: involves the anterior cervical nodes overlying the sternocleidomastoid muscles.
- **Arthritis**: large joints (ie, knee, ankle, and hip) were primarily involved.
- **Others**: commonly occur 7 to 10 days before the typical mucocutaneous features develop: (Diarrhea\vomiting or abdominal pain, irritability, cough or rhinorrhea, decreased oral intake, and Joint pain)

Diagnosis:
Diagnosis of KD requires the presence of fever lasting ≥5 days, combined with at least four of the five following physical findings:
- Bilateral bulbar conjunctival injection
- Oral mucous membrane changes including injected or fissured lips, injected pharynx, or strawberry tongue
- Peripheral extremity changes, including erythema of palms or soles, edema of hands or feet (acute phase), or periungual desquamation (convalescent phase)
- Polymorphous rash
- Cervical lymphadenopathy (at least one lymph node >1.5 cm in diameter)

**Incomplete (Atypical) KD:**
It should be suspected in patients less than six months of age with unexplained fever ≥7 days, even if they have no clinical findings of KD, and in patients of any age with unexplained fever ≥5 days and only two or three clinical criteria.
Kawasaki Disease—Clinical Features, Diagnosis and Treatment Guideline | By: PharmD Students Enas Khazaleh & Sara Al-Rahhal

Laboratory Findings:
No laboratory studies are included among the diagnostic criteria for typical KD. However, certain findings may support the diagnosis of KD, particularly in incomplete cases:

- Elevation of acute-phase reactants (eg, C-reactive protein [CRP] or erythrocyte sedimentation rate [ESR], ferritin), thrombocytosis that generally develops after the seventh day of illness, leukocytosis, and a left-shift (increased immature neutrophils) in the white blood cell (WBC) count.
- Normocytic, normochromic anemia (test: CBC with differential)
- Pyuria
- CSF may display a mononuclear pleocytosis without hypoglycorrhachia, or elevation of CSF protein
- Significant perturbations in serum lipid profiles
- Hyponatremia
- Abnormal liver function (AST, ALT albumin)

Echocardiography

- Should be performed in all patients with KD as soon as the diagnosis is suspected in order to establish a reference point for longitudinal follow-up and treatment efficacy.
- Initial CA (Coronary Artery) diameter is a factor in identifying patients at high risk of developing a coronary aneurysm and therefore warranting augmentation of initial intravenous immune globulin (IVIG) therapy.
- CA diameters are useful for identifying patients who should be treated with IVIG despite failing to meet classical diagnostic criteria for KD.

Differential Diagnosis

<table>
<thead>
<tr>
<th>Differential diagnosis of Kawasaki disease</th>
<th>Kawasaki disease</th>
<th>Toxic shock syndrome</th>
<th>Streptococcal scarlet fever</th>
<th>Stevens-Johnson syndrome</th>
<th>Systemic onset JIA</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>Usually &lt;5</td>
<td>Usually &gt;10</td>
<td>Usually 2 to 8</td>
<td>All ages</td>
<td>2 to 5</td>
</tr>
<tr>
<td>Fever</td>
<td>Persistent</td>
<td>Usually &lt;10</td>
<td>Variable, usually &lt;10 days</td>
<td>Prolonged</td>
<td>Prolonged</td>
</tr>
<tr>
<td>Eyes</td>
<td>Noninfectious conjunctivitis, iridal sparring, anterior uveitis</td>
<td>Conjunctivitis</td>
<td>Normal</td>
<td>Exudative conjunctivitis, keratitis</td>
<td>Normal</td>
</tr>
<tr>
<td>Oral mucosa</td>
<td>Diffuse edema, “strawberry tongue”</td>
<td>Erythematous</td>
<td>Pharyngitis, “strawberry tongue”</td>
<td>Erythema, ulceration, pseudomembrane formation</td>
<td>Normal</td>
</tr>
<tr>
<td>Peripheral extremities</td>
<td>Erythema of palms and soles, indurative oedema, peringual desquamation</td>
<td>Swelling of hands and feet</td>
<td>Raynaud desquamation</td>
<td>Normal</td>
<td>Arthritis</td>
</tr>
<tr>
<td>Rash</td>
<td>Erythematous polymorphous; targetted or purpuric in 20%</td>
<td>Erythema</td>
<td>Papular erythema, Petita’s lines, circular pain</td>
<td>Target lesions</td>
<td>Transient, salmon, pink</td>
</tr>
<tr>
<td>Cervical lymph nodes</td>
<td>Nontender swelling</td>
<td>Normal</td>
<td>Painful swelling</td>
<td>Normal</td>
<td>Diffuse adenopathy</td>
</tr>
<tr>
<td>Other</td>
<td>Arthritis</td>
<td>Mental status changes, coagulopathy, shock</td>
<td>Throat culture positive for group A streptococcus</td>
<td>Arthritis, associated hepatitis infection (30 to 75%)</td>
<td>Arthritis, pericarditis</td>
</tr>
<tr>
<td>Characteristic lab results</td>
<td>Systemic inflammation, anemia, transaminis</td>
<td>Thrombocytopenia</td>
<td>Positive throat culture</td>
<td>Associated hepatitis infection (30 to 50%)</td>
<td>Systemic inflammation, anemia</td>
</tr>
</tbody>
</table>

JIA: Juvenile idiopathic arthritis

Delayed Diagnosis

It is desirable to diagnose KD as soon as possible after the onset of symptoms in order to initiate treatment and reduce the risk of CA lesions. However, timely
identification is challenging because the diagnosis is based upon nonspecific clinical signs and there is no definitive diagnostic test.

**Treatment:**

- Fulfill criteria for KD or incomplete KD
- Other explanations for presenting complaints unlikely
- Refer to UpToDate topics on diagnosis of KD for specific criteria and diagnostic algorithm

**Is the patient at high risk for IVIG resistance?**

- **Yes**
  - Standard initial therapy:
    - IVIG 2 g/kg x 1 dose administered over 8 to 12 hours
    - Aspirin 30 to 50 mg/kg/day orally in 4 divided doses; maximum 4 g/day (decrease dose to 3 to 5 mg/kg/day 48 hours after resolution of fever; stop after normalization of ESR) unless CA abnormalities are detected on echocardiography
  - PLUS
    - Glucocorticoids (prednisolone 2 mg/kg/day IV or orally in 3 divided doses for 30 days; then 1 mg/kg/day for 5 days) 6

- **No**

**Persistence or recurrence of fever between 36 hours to 2 weeks after the start of the IVIG infusion?**

- **Yes**
  - Rule out other causes of fever
  - Retreat with IVIG 2 g/kg x 1 dose 9
  - Remains febrile 24 hours after completion of second dose of IVIG?
    - **Yes**
      - Treat with a 1.5-day taper of prednisone/prednisolone IV/oral starting with 2 mg/kg/day IV
    - **No**
      - Remains febrile 24 hours after completion of a course of glucocorticoids?
        - **Yes**
          - Treatment options include twice-daily prednisolone (IV then oral) for 15 days, IV pulse methylprednisolone, infliximab, cyclosporine, anakinra, or cyclophosphamide
        - **No**
          - Routine follow-up for KD

- **No**
IVIG should be administered in a healthcare setting equipped with equipment, medications (IM epinephrine), and staff who are trained to respond in the event of a rare serious reaction (e.g., anaphylaxis). Patients should be well hydrated prior to IVIG administration. Infusion rate is adjusted based on tolerability. Some patients may receive acetaminophen and/or H1 antihistamine prior to or during the infusion to prevent or blunt an infusion reaction. For specific recommendations, refer to UpToDate topics on overview of IVIG therapy and IVIG adverse effects.

KD: Kawasaki disease; IVIG: intravenous immune globulin; ESR: erythrocyte sedimentation rate; CA: coronary artery; IV: intravenous; IM: intramuscular.

For Japanese patients, use the Kobayashi criteria or similar validated criteria to determine if at high risk of IVIG resistance. Kobayashi criteria (score ≥ 5 is positive):
- Sodium ≤ 133 mmol/L (2 points)
- Aspartate aminotransferase ≥ 100 international units/L (2 points)
- C-reactive protein ≥ 10 mg/dL (1 point)
- Neutrophils ≥ 10% of the white blood cell count differential (2 points)
- Platelet count ≤ 300,000/mm² (1 point)
- Days of illness at initial treatment ≤ 4 (2 points)
- Age ≤ 12 months (1 point)

Non-Japanese patients are considered at high risk of IVIG resistance if they have 1 or more of the following:
- Enlarged CA (score ≥ 2.5 to 3) at presentation (prior to IVIG treatment)
- Age ≤ 12 months, with infants age ≤ 6 months at highest risk
- KD associated with shock
- KD presenting with macrophage activation syndrome

A normalization of ESR typically takes 1 to 2 months. Thus, aspirin therapy is generally complete within 2 months of disease onset in children with no CA abnormalities.
- IV prednisolone may be unavailable in some settings (e.g., United States). The equivalent dose of methylprednisolone is 1.6 mg/kg/day for 10 days then 0.8 mg/kg/day for 5 days. For review of considerations in timing of switch from IV to oral glucocorticoids, refer to UpToDate topic on treatment of KD.

Patients who were treated initially with glucocorticoids plus IVIG regardless of outcome or who did not respond to treatment with a single dose of IVIG without glucocorticoids are considered at high risk for development of CA aneurysms and should be followed more carefully, including earlier and more frequent clinical, laboratory, and echocardiographic evaluations.

Graphic 115593 Version 3.0
Recurrence:
To determine a true recurrence rate, follow-up studies must use a more precise definition of recurrence: Separate episode fulfilling KD criteria after an earlier occurrence has fully resolved, typically at least two months later. Practitioners should adopt a more conservative approach to possible recurrences of KD, including a lower threshold for using IVIG if the diagnosis is uncertain, and earlier use of salvage therapy for incomplete responses to IVIG.

Complications:
Cardiac:
- Coronary artery (CA) aneurysms
- Depressed myocardial contractility and heart failure
- Myocardial infarction, arrhythmias, and peripheral arterial occlusion.

Noncardiac (uncommon):
- Shock
- Multiple organ dysfunction syndrome
- Macrophage activation syndrome (MAS)
- Altered renal function
- Acute abdominal catastrophes
- Sensorineural hearing loss

Patients with KD shock syndrome or MAS are at higher risk of failing to respond to IVIG and are therefore often given augmented initial therapy.

Follow up:
- **Monitoring for fever** — Check the child's temperature orally or rectally every six hours until 48 hours after the last fever. At this point, the aspirin is decreased to 3 to 5 mg/kg once daily, and the temperature is taken daily before the aspirin dose. The temperature should also be taken if the child feels warm or recurrent clinical signs of KD seem to be developing. Any child who develops a fever should be evaluated for recurrence of other manifestations of inflammation, for interval coronary artery (CA) dilatation on echocardiogram, and for other causes of fever. These patients should be retreated for presumed recrudescence of KD unless there is clear evidence of another explanation for fever.

- **Cardiac evaluations** — After the baseline echocardiogram is obtained at diagnosis, echocardiography is usually repeated at approximately two and six weeks of illness to evaluate for CA involvement. Children with CA aneurysms, or those at higher risk for developing CA dilatation, warrant more frequent echocardiograms. Patients also should have repeated clinical evaluations during the first one to two months following diagnosis of KD to detect arrhythmias, heart failure, valvular insufficiency, or myocarditis. Children with CA abnormalities generally receive antithrombotic therapy with aspirin, warfarin, or other agents, as well as regular cardiac evaluation.

- **Physical activity** — Children generally do not feel completely well for several weeks after KD, and they therefore tend to limit their own activity level. Restrictions are dependent upon the risk of myocardial infarction and should be imposed only in children with increased risk of thrombosis during the convalescent stage of disease, particularly those with giant CA aneurysms.
The restrictions should be determined in consultation with the child’s cardiologist.

- **Vaccinations** — The administration of live-virus vaccines, including measles and varicella, should be postponed for at least 11 months in children who have been treated with IVIG. Patients may be vaccinated during a measles outbreak or after a varicella exposure as long as the vaccine is repeated at least 11 months after the administration of IVIG (unless there is serologic evidence of adequate immunity). Schedules for other routine childhood vaccinations do not need to be altered. Influenza immunization, recommended in all children over six months of age, is particularly important in those who require long-term high-dose aspirin therapy because of the possible increased risk of Reye syndrome. In addition, giving the varicella vaccine to patients receiving long-term low-dose aspirin therapy is suggested.

**References:**