### Inclusion Criteria

- Patients suspected of having Kawasaki Disease (KD)
- ≥ 4 days since onset of fever

### Principal Clinical Features

1. Mucositis – “strawberry tongue”
2. Nonpurulent conjunctivitis
3. Erythematous rash
4. Extremity changes – swelling/peeling
5. Cervical lymphadenopathy (≥ 1.5 cm diameter)

*Not all features need to be present at the same time*

### Laboratory Tests

- CBC + Diff
- CRP
- ESR
- Albumin
- ALT
- UA (microscopic)
- Red top tube to hold

#### Off Pathway

<table>
<thead>
<tr>
<th>4 days of fever</th>
<th>5 to 10 days of fever</th>
<th>&gt; 10 days of fever</th>
</tr>
</thead>
<tbody>
<tr>
<td>Presence of 2 or 3 principal clinical features</td>
<td>Suspected Incomplete KD</td>
<td>Complete KD</td>
</tr>
<tr>
<td>Presence of 4 or 5 principal clinical features</td>
<td>Complete KD</td>
<td>Complete KD</td>
</tr>
</tbody>
</table>

### Differential Diagnosis

- Exudative conjunctivitis
- Exudative pharyngitis
- Oral ulcerations
- Splenomegaly
- Vesiculobullous rashes
- Petechial rashes

### Suggested Readings

For questions concerning this pathway, contact: KawasakiPathway@seattlechildrens.org

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Kawasaki Disease Pathway v3.0: Management Phase

PHASE II (MANAGEMENT)

Inclusion Criteria
- Complete KD or Incomplete KD diagnosis

Echocardiogram should be performed when the diagnosis of KD is considered, but unavailability or technical limitations should not delay treatment.

Treatment
- High-dose IVIG: 2 g/kg single infusion over 12 hours
- Moderate-dose aspirin: 30 to 50 mg/kg/day divided every 6 hours
- Verify Echocardiogram and Electrocardiogram have been done (repeat if abnormal per Cardiology)
- Steroid use as adjunct to primary treatment is controversial

Monitor for 36 hours after IVIG completion
(Fevers may be related to IVIG)

Fever between hour 24 and hour 36 after IVIG completion?

Yes

Continue to monitor

Fever beyond 36 hours after IVIG completion

Fever defined as:
- ≥ 38.5 °C for 1 reading
- ≥ 38.0 °C for 2 readings at least 2 hours apart

Refractory KD

Repeat Laboratory Tests
- CBC + Diff
- CRP

Management Options
- Reassess differential diagnosis
- Notify Cardiology and Rheumatology
- Second dose of IVIG (2 g/kg)
- Clinical judgment is needed to determine whether to consider additional/alternate therapies

Off Pathway

Discharge Criteria
- Patient afebrile for at least 12 hours before discharge
- Patient received 6-week supply of low-dose aspirin
- Cardiology consult and Echocardiogram completed
- Cardiology follow-up and Echocardiogram scheduled in 2 weeks
- Patient received inactivated flu vaccine if in season
- Family received education materials regarding fever monitoring

Transition to Low-dose Aspirin
- Whichever comes first: at discharge OR if not ready for discharge, when afebrile for 48 hours
- 3 to 5 mg/kg once per day

Do not give ibuprofen or other NSAIDs while on aspirin

Patients with initial coronary artery z-score ≥ 2.5 should be considered for intensified initial treatment in consultation with Cardiology
Principal Clinical Features

Not all features need to be present at the same time

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
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
- Meningococcemia

Viral and bacterial infections can have symptoms that overlap with KD and should be considered and treated.

! A respiratory viral infection should not be used to exclude a diagnosis of KD.
Special Consideration (> 10 days of fever)

If greater than 10 days since fever onset AND Presence of 2 to 5 principal clinical features

THEN

- It is reasonable to administer IVIG to children presenting after the 10th day of illness (ie, in whom the diagnosis was missed earlier) if they have either persistent fever without other explanation or coronary artery abnormalities together with ongoing systemic inflammation, as manifested by elevation of ESR or CRP (CRP >3.0 mg/dL)
  [LOE: Guideline: Class IIa, Level of Evidence B (McCrindle, 2017)]
- IVIG generally should not be administered to patients beyond the tenth day of illness in the absence of fever, significant elevation of inflammatory markers, or coronary artery abnormalities
  [LOE: Guideline: Class III, Level of Evidence C (McCrindle, 2017)]

! High suspicion for KD in infants ≤ 6 months of age with onset of fever ≥ 7 days and without other clinical criteria for KD
Steroid use as adjunct to primary treatment is controversial

Recommendations for adjunctive therapies for primary treatment:

- **Single-dose pulse methylprednisolone should not be administered with IVIG as routine primary therapy for patients with KD**
  
  [LOE: Guideline: Class III, Level of Evidence B (McCrindle, 2017)]

- **Administration of a longer course of corticosteroids (eg, tapering over 2–3 weeks), together with IVIG 2 g/kg and ASA, may be considered for treatment of high-risk patients with acute KD, when such high risk can be identified in patients before initiation of treatment**
  
  [LOE: Guideline: Class IIb, Level of Evidence B (McCrindle, 2017)]

Careful consultation with Cardiology
Clinical judgment is needed to determine whether to consider additional/alternate therapies

- [LOE: Guideline: Class IIb, Level of Evidence B (McCrindle, 2017)]
  - High-dose pulse steroids (usually methylprednisolone +/- subsequent course and taper of oral prednisone)
  - Longer (e.g., 2–3 weeks) tapering course of prednisolone or prednisone, together with IVIG 2 g/kg and ASA

- [LOE: Guideline: Class IIb, Level of Evidence C (McCrindle, 2017)]
  - Infliximab
  - Cyclosporine if second IVIG infusion, infliximab, or a course of steroids has failed
  - Monoclonal antibody therapy (except TNF-α blockers), cytotoxic agents, or (rarely) plasma exchange if second IVIG infusion, infliximab, or extended course of steroids has failed
Approved by the CSW Kawasaki Disease Pathway team for go-live on February 28, 2018

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Rheumatology, Stakeholder
Hospital Medicine, Team Member
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Retrieval Website:  http://www.seattlechildrens.org/pdf/Kawasaki-Disease-Pathway.pdf

Please cite as:
This pathway was developed through local consensus based on published evidence and expert opinion as part of Clinical Standard Work at Seattle Children’s. Pathway teams include representatives from Medical, Subspecialty, and/or Surgical Services, Nursing, Pharmacy, Clinical Effectiveness, and other services as appropriate.

When possible, we used the GRADE method of rating evidence quality. Evidence is first assessed as to whether it is from randomized trial or cohort studies. The rating is then adjusted in the following manner (from: Guyatt G et al. J Clin Epidemiol. 2011;4:383-94.):

Quality ratings are **downgraded** if studies:
- Have serious limitations
- Have inconsistent results
- If evidence does not directly address clinical questions
- If estimates are imprecise OR
- If it is felt that there is substantial publication bias

Quality ratings are **upgraded** if it is felt that:
- The effect size is large
- If studies are designed in a way that confounding would likely underreport the magnitude of the effect OR
- If a dose-response gradient is evident

Guideline – Recommendation is from a published guideline that used methodology deemed acceptable by the team.

Expert Opinion – Our expert opinion is based on available evidence that does not meet GRADE criteria (for example, case-control studies).

**Quality of Evidence:**
- 🌟🌟🌟🌟 High quality
- 🌟🌟🌟 Moderate quality
- 🌟🌟 Low quality
- 🌟🌟🌟 Very low quality

Guideline
Expert Opinion
Summary of Version Changes

- **Version 1.0 (2/28/2018):** Go live.
- **Version 2.0 (4/27/2018):** Changed warning in Management Phase to state, “Do not give ibuprofen or other NSAIDs while on aspirin.”
- **Version 3.0 (12/6/2019):** Added warning in Management Phase to state, “Patients with initial coronary artery z-score ≥ 2.5 should be considered for intensified initial treatment in consultation with Cardiology.”
Medical Disclaimer

Medicine is an ever-changing science. As new research and clinical experience broaden our knowledge, changes in treatment and drug therapy are required.

The authors have checked with sources believed to be reliable in their efforts to provide information that is complete and generally in accord with the standards accepted at the time of publication.

However, in view of the possibility of human error or changes in medical sciences, neither the authors nor Seattle Children’s Healthcare System nor any other party who has been involved in the preparation or publication of this work warrants that the information contained herein is in every respect accurate or complete, and they are not responsible for any errors or omissions or for the results obtained from the use of such information.

Readers should confirm the information contained herein with other sources and are encouraged to consult with their health care provider before making any health care decision.
Studies were identified by searching electronic databases using search strategies developed and executed by a medical librarian, Peggy Cruse. Searches were performed in July, 2017. Queries were run in the following databases: Medline (Ovid platform), Cochrane Database of Systematic Reviews (Ovid platform), Embase (embase.com), National Guideline Clearinghouse (guideline.gov), TRIP (tripdatabase.com), and Cincinnati Children’s Evidence-Based Care Recommendations (cincinnatichildrens.org/service//anderson-center/evidence-based-care/recommendations). Medline and Embase strategies used controlled subject headings, along with text words to capture literature on Kawasaki disease (Mucocutaneous Lymph Node Syndrome). A synthesis-level evidence filter was applied to Kawasaki results to capture higher-level evidence syntheses. All retrieval was limited to English language and papers published from 2000 to July 2017.

Peggy Cruse, MLIS
October 25, 2017
Bibliography


