Guidelines for the Evaluation and Management of Kawasaki Disease

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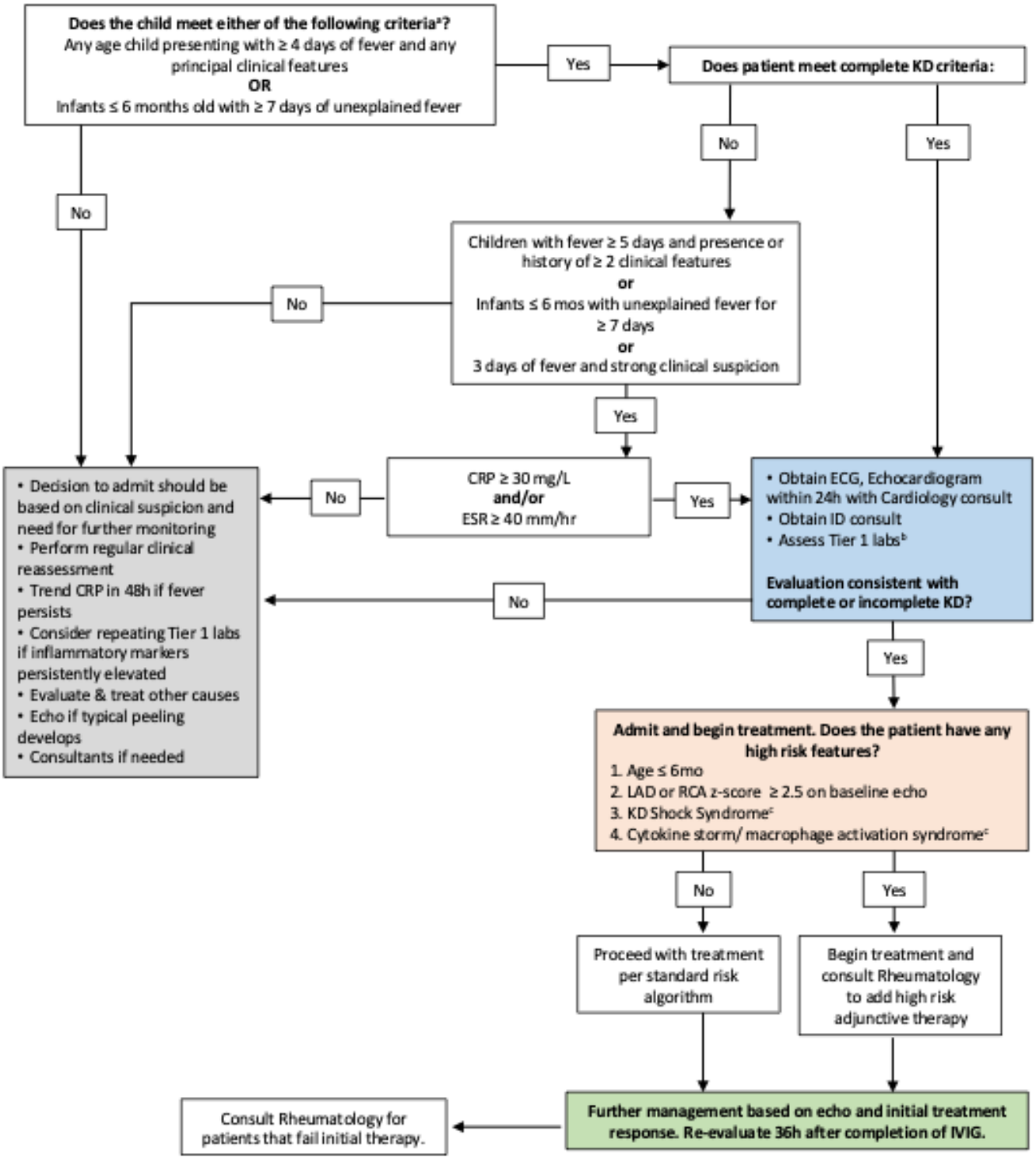
I. Background:

- This clinical guideline is intended to assist clinicians with initial evaluation and management of patients suspected to have KD. It does not replace clinical judgement. It is based on expert opinion and published society guidelines.

Kawasaki Disease Diagnostic Criteria
Must have fever for at least 4 days* **AND** At least 4 of 5 clinical features at any point during the illness (not necessarily concurrent)[1,2]: 1. Polymorphous rash 2. Bilateral bulbar conjunctival injection without exudate 3. Oral changes: Erythema and cracking of lips, strawberry tongue, erythema of oral and pharyngeal mucosa 4. Palmar and plantar erythema, usually with associated swelling; resolves with subsequent periungual desquamation during subacute phase 5. Cervical adenopathy (typically unilateral, ≥ 1.5cm diameter) **Diagnosis can be made with 4d of fever if 4 clinical features are present. Fever ≥38°C but typically is high (>39°C–40°C), spiking, and unremitting. Illness must not be explained by known alternative disease process.*

Incomplete Kawasaki Disease Diagnostic Criteria		
If a child of any age has fever for at least 5 days and 2–3 of the 5 clinical features (above) at any point during the illness		
OR an infant ≤ 6 months presents with 7 days of unexplained fever		
AND if CRP ≥ 30mg/L or ESR ≥ 40mm/h, or both[a], then assess for lab and echo criteria.[1,2] *Patient must meet either the lab or echo criteria to diagnose incomplete KD.*		
Laboratory Criteria, must have ≥ 3 of the following to diagnose: 1. Anemia for age 2. Platelets ≥ 450,000 after the 7th day of fever[b] 3. Albumin ≤ 3g/dL 4. Elevated ALT level 5. Elevated WBC ≥ 15,000/mm^3 6. Urine ≥ 10 WBC/hpf, first catch from clean voided or bagged urine	OR	Echocardiogram criteria, must have one or more of the following: 1. Z score left anterior descending (LAD) or right coronary artery (RCA) ≥ 2.5 2. Coronary artery aneurysm observed 3. Or ≥ 3 other suggestive features: decreased left ventricular function, mitral regurgitation, pericardial effusion, z-score of LAD or RCA 2-2.5
[a]If CRP or ESR do not meet these criteria, KD is unlikely but close clinical and laboratory surveillance warranted, obtain echo if typical peeling develops. *[b]Thrombocytosis generally occurs after 7d, but if present earlier can be counted towards the diagnosis.*		

II. Algorithm for Evaluation of Suspected Kawasaki Disease



Notes:

[a] Possible alternative diagnoses should be assessed throughout evaluation. Differential diagnosis includes, but is not limited to: other viral infections, sepsis, toxic shock syndrome, MIS-C, hemophagocytic lymphohistiocytosis (HLH)/macrophage activation syndrome (MAS), rickettsial disease (Ehrlichiosis, Rocky Mountain Spotted Fever), systemic juvenile arthritis, other vasculitis, malignancy.

[b] Tier 1 evaluation: CBC w/diff, CMP, ESR, CRP, IgG level, Blood type, save serum, Respiratory pathogen panel, urinalysis with reflex to microscopy only, from bag or clean catch (not catheterized). Consider: blood culture, Pro-BNP, troponin, Ferritin, PT/PTT, D-dimer, fibrinogen.

[c] Defined in section IV on Management.

III. General Principles for Evaluation and Management:

- The differential diagnosis of KD is broad. It is important to consider alternative diagnoses. The incidence of MIS-C has decreased significantly since 2022, but differences in clinical, laboratory, and cardiac manifestations have been published [3-6]. Initial management of KD involves treatment with IVIG and aspirin and risk-stratification to determine if primary therapy intensification is indicated [2,7-10]. Glucocorticoids have been shown effective across multiple cohorts and are most likely to be added as adjunctive therapy unless contraindicated [11-15].

IV. Management.

- Treatment with IVIG and aspirin should commence as soon as the diagnosis of complete or incomplete KD is made. If high-risk features are present, consult Rheumatology prior to starting adjunctive therapy with steroids.

	Standard Risk	High Risk
Intravenous immunoglobulin (IVIG)[a]	IVIG 2 g/kg once over 8–12 hours	
Aspirin[b,c]	In the acute phase, 10 mg/kg/dose every 6 hours (30–50 mg/kg/DAY divided every 6 hours) with a max of 325 mg/dose. Round to nearest 1/2 tablet size. Once patient afebrile for at least 48 to 72 hours, transition to 3–5 mg/kg/DAY once daily (max 81 mg/dose). Round to nearest 1/4 tablet size	
Steroids[d]	None initially	Methylprednisolone 1mg/kg/dose IV q12h (max 60 mg/day div q12h) Duration: ~5 days Taper over ~2 weeks Suggested taper (Prednisone 2mg/kg/day div BID x 5 days, 1 mg/kg/day div BID x 5 days, 0.5 mg/kg/day DAILY x 5 days) ***Alternate steroid dosing regimens may be used at the discretion of Rheumatology*

[a]IVIG will lead to increase in ESR, which should not be repeated after administration of IVIG.
[b]Due to the risk of Reye Syndrome, unimmunized patients ≥ 6mo of age who present during influenza season and are administered aspirin should receive an influenza vaccine before discharge if not contraindicated.
[c]Patients with coronary artery aneurysms may have different anti-platelet or anti-coagulation requirements, to be managed at the discretion of the Cardiologist.
[d]Rheumatology consultation required for patients who are refractory to IVIG or those with high-risk features that are candidates for steroids.

<u>KD or incomplete KD diagnosed:</u>

- All treatment decisions should be considered in coordination with consulting teams and may sometimes deviate from this protocol, especially in patients with underlying medical problems.
- Shock should be managed using existing protocols. Therapies listed are not directed at the management of shock and should not await input from consulting team.
- Please obtain an IgG level and save serum prior to administration of intravenous immunoglobulins.
- Consider repeating the following labs after 48 hours, depending on guidance from consulting teams: CBC w/diff, CMP, CRP.

<u>High- Risk KD Presentations</u>:

- KD shock syndrome is an uncommon presentation of KD, found in <10% of cases. Patients may present with hypotension, decreased perfusion, or myocardial dysfunction, and lab values may include elevated CRP, hypoalbuminemia, and thrombocytopenia, as compared to KD without shock [1,2].

- Cytokine storm/macrophage activation syndrome is an uncommon hyperinflammatory condition found in patients with KD. Patients may present with splenomegaly, cytopenias, hepatic dysfunction, hyperferritinemia, hypofibrinogenemia, hypertriglyceridemia, elevated serum lactate dehydrogenase, coagulopathy, and multiorgan dysfunction[16-18]. If suspected, consult to Rheumatology is recommended.

IVIG Resistance and Refractory KD:

- IVIG resistance is defined as persistent or recurrent fever (≥38°C) occurring ≥36 hours after the completion of the initial IVIG infusion, up to two weeks after the start of treatment.
- Other signs of failed therapy include progressive coronary artery dilation and lingering clinical signs such as shock.
- Intensification therapy will be at the discretion of the treating Rheumatologist and will depend on the echocardiogram findings and initial treatment. Second line therapies may include but are not limited to: corticosteroids, infliximab, anakinra, a second dose of IVIG, cyclosporine or cyclophosphamide[2].

Possible KD:

- Patients suspected to have KD who do not meet criteria may merit admission and observation depending on the clinical judgement of treating providers.
- Repeat CRP in 48h if fever persists and consider repeating Tier 1 labs if inflammation persists.
- Consider subspecialist consultation based on presenting symptoms to evaluate for alternative etiologies and re-evaluate diagnosis and management.

V. Discharge and Outpatient Follow-Up

KD or Incomplete KD diagnosed

Discharge preparation and criteria:

- Obtain repeat echocardiogram prior to discharge for patients with IVIG resistance or high-risk features.
- Discharge readiness should be discussed with all consulting teams. Minimum discharge criteria:
  - ≥ 36 hours without fever after completion of IVIG, off vasoactive medications
  - ECG without arrhythmia
  - Latest echocardiogram improved/stable

Follow-up:

- All patients should follow up with the primary care clinician 48–72 hours and 2 weeks after discharge.

Clinical Course	Follow up
Normal echocardiogram, IVIG +ASA only	Echo at 1–2 weeks and follow up with Infectious disease team
Abnormal echocardiogram, IVIG +ASA only	Cardiology follow-up and Echo at 1–2 weeks (sooner if high risk)
Abnormal echocardiogram and/or additional therapies given (beyond IVIG, ASA) or ongoing concern for auto-inflammatory process	Cardiology follow-up and Echo at 1–2 weeks (sooner if high risk) Rheumatology follow-up at 1–2 weeks *Infectious disease follow-up only if residual concerns*

- All patients who received steroids or more intensive therapy should follow up with Cardiology and Rheumatology 1–2 weeks after discharge, Cardiology to see patients sooner if higher-risk classification.
  - 2-week follow-up to include ECG, Echo, labs if indicated
- Follow-up with other subspecialists to be determined on a case-by-case basis per consultants.

- If temperature is ≥ 38°C or other symptoms of KD return before first scheduled follow-up, patient should have an urgent primary care provider visit or return to the ED for evaluation.
- In general, NSAIDs should be avoided while the patient is on aspirin.
- Live vaccines should be deferred for 11 months following IVIG therapy.

Unlikely KD

- Patients discharged from the ED or inpatient setting deemed unlikely to have KD should receive anticipatory guidance regarding progression of symptoms (persistent fever or other symptoms of KD) that would merit re-evaluation for KD and should follow up with primary care provider within 24–48 hours.

VI. References

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