CLINICAL GUIDELINE

Kawasaki Disease

(<18 years of age)

Children's MINNESOTA

Aim: To guide the evaluation of patients with suspected Kawasaki Disease and to guide primary therapy

Suspicion for Kawasaki Disease

Clinical assessment + Labs: CBC w/ diff, CMP, voided UA, ESR, CRP, GGT, Serum to Save **(notes 1 & 4)**

Meets Classic Kawasaki Disease definition? (**note 1**)

- No → Evaluate for Incomplete KD (note 1*) and alternative etiologies (note 2 and 3).
  - Does Infectious Disease recommend treatment for Incomplete KD?
    - No → Off Guideline
    - Yes ↓
- Yes ↓

Admit to med-surg and initiate KD treatment ASAP (see note 5 on admission location)

- **Determine risk status:**
  - ➔ **High-risk for CAA development?** *(z-score ≥2 and/or age ≤6 months; see note 6)*
    - Consult both Cardiology and ID (24/7; exception: Cardiology can wait for daytime hours if echo is normal and there is no cardiac dysfunction).
    - Likely will require intensification of therapy (see Table 1), in addition to the Standard risk treatment.
  - ➔ **Standard-risk KD** *(absence of above criteria)*
    - No Cardiology/ID consult required at this stage; treat per Table 1.
- **Treat per Table 1:**
  - IVIG 2 g/kg over 8–12 hours (once patient admitted to med-surg)
  - Aspirin 30–50 mg/kg/day PO divided QID (avoid NSAIDs).
  - *See above for intensification therapies for high-risk patients.*
- **Obtain echocardiogram if not already done (do not delay IVIG while awaiting imaging)**. If abnormal, repeat as per Cardiology (usually every 2–3 days) until stable; if worsening, discuss escalation of therapy promptly with consulting teams (even if afebrile), see reference 12.
  - Repeat before discharge if high-risk features (note 6) or IVIG resistance (note 7).
- **Monitor for fever** while off scheduled antipyretics
- **Assess for whether anticoagulation is indicated if aneurysm present.** If so, consult Hematology (refer to reference 12; consider z-score, presence of thrombus; see note 10).

EXCLUSION CRITERIA

Patients **whose care is not directed by** this guideline

- IVIG resistance, progressive coronary enlargement, giant aneurysms (see note 7)
- Previous KD
- Suspicion for multisystem inflammatory syndrome in children (MIS-C), see note 2
- Underlying immunodeficiency or chronic medical complexity

Note 1: Classic KD Definition (this is a clinical diagnosis):

Fever for ≥ 4 days (day of fever onset = day 1)
Plus
≥ 4 out of 5 clinical features*
at any point during the illness; they do not need to be concurrent:

Clinical features:

- ❑ **Palmar and plantar erythema:** swelling common; periungual desquamation in subacute phase
- ❑ **Rash**: usually maculopapular, diffuse erythroderma, or erythema multiforme–like. Perineal desquamation may occur. Vesicular/pustular rash suggests alternate diagnosis.
- ❑ **Bilateral bulbar conjunctival injection** without exudate
- ❑ **Oral changes:** cracked erythematous lips, strawberry tongue, and/or oral/pharyngeal mucosal erythema
- ❑ **Cervical lymphadenopathy:** usually unilateral, cluster of nodes >=1.5 cm

Irritability, vomiting, diarrhea, arthritis/arthralgia may also occur in acute KD

*Incomplete KD diagnostic criteria: fever ≥ 5 days and 2-3/5 clinical criteria, plus compatible labs (≥3 supplemental findings, see note 4) and/or a positive echo (see note 4). Consider also in infants ≤6 months of age with unexplained fever ≥ 7 days. Prolonged fever and irritability may be the only clinical manifestations.

Discharge Planning: (see discharge criteria in note 8)

- Evaluate for response to therapy, for recurrent/persistent fever, and evolving coronary artery changes (these patients fall outside this guideline: keep managing them in partnership with Cardiology/ID +/- Rheumatology/KD referral center; background: reference 12; see note 7 for timing of monitoring and discharge).
- At time of discharge, decrease aspirin dose to 3–5 mg/kg once daily (max dose 81 mg) until discontinued by Cardiology.
- Discharge education: see note 9
- Follow-up with primary care provider within ~2 days of discharge
- Follow-up with Cardiology for clinic visit and repeat echocardiogram at 7–14 days or sooner for high-risk (confirm with Cardiology before discharge). Next echo (typically 4–6 weeks) is scheduled at that visit. If the patient is on a steroid wean, Cardiology will order and follow up a CRP at that visit (see Table 1 steroid notes).

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Note 2: Kawasaki Disease vs. MIS-C

- KD can be challenging to differentiate from MIS-C. MIS-C patients tend to be older (average age ~8-9 yrs vs. 2 yrs with KD), have significant GI symptoms, lymphopenia and thrombocytopenia, hypotension, and non-coronary abnormalities on echo (e.g., LV dysfunction, valvular regurgitation, pericardial effusion). Lymphocyte count <1500 is strongly associated with MIS-C instead of KD.
- If MIS-C is suspected, the patient should be evaluated per the MIS-C guideline: MIS-C Clinical Guideline

Note 3: Differential Diagnosis

Differential diagnosis for KD is broad and includes infectious and post-infectious mimics (MIS-C, staphylococcal and streptococcal toxin-mediated disease, measles, adenovirus, enterovirus, RMSF, meningococcemia) and non-infectious mimics (systemic JIA, Stevens Johnson, DRESS). ID consultation covers KD, incomplete KD, and infectious mimics; if a non-infectious mimic is suspected, consult with Rheumatology, Dermatology, or other specialties as appropriate.

Note 4: Supplemental lab findings used to define incomplete KD (not needed for classic KD, which is a clinical diagnosis):

- Elevated CRP ≥3.0 mg/dL and/or ESR ≥ 40mm/hr, plus ≥ 3 of the following (or a positive echo, defined below):
    - Leukocytosis: WBC count of ≥15,000/mm3
    - Anemia for age
    - Hypoalbuminemia ≤ 3.0 g/dL
    - Platelets >450,000 (typically after 7 days)
    - Elevated ALT
    - Sterile pyuria from voided urine WBC ≥10/hpf
- Hyponatremia, elevated GGT, and eosinophilia are often seen but not diagnostic criteria.
- Positive echo (AHA 2024): LAD or RCA z score ≥ 2.5; a coronary artery aneurysm; or ≥ 3 other suggestive features (decreased LV function, mitral regurgitation, pericardial effusion, or LAD/RCA z score 2.0–2.5). The local protocol z score ≥ 2 in note 6 is a consult trigger, not a diagnostic cutoff.

Note 5: Admission location:

Recommend admission (or transfer) to ICU (CVICU vs PICU) if unstable hemodynamics or poor perfusion, giant aneurysms, rapidly evolving aneurysms, or coronary thrombosis or ischemia. Discuss with Cardiology and the intensivist.

Note 6: High risk factors associated with development of coronary artery aneurysms:

Consult Cardiology and Infectious Disease if either of the following is present:

- **Any coronary z-score ≥ 2**
- **Age ≤ 6 months**

Why: Patients at high risk for progression or worsening of coronary artery aneurysms may benefit from intensification of primary therapy. Multi-ethnic risk prediction is unreliable, so our consult trigger is broader than the treatment threshold.
Roles: Cardiology - echo z-score and risk stratification, thromboprophylaxis, and cardiac monitoring; ID - infection assessment and intensification of immunomodulation.
Local vs AHA: these trigger the consult only; consultants may apply AHA 2024 criteria and the Son Risk Score (see Table 1 footnote) to define high risk for treatment.

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Note 7: Observation during after IVIG completion.

- **Findings during observation that take management beyond this guideline (escalate and co-manage with KD consulting teams; may require Rheumatology input):**
  - **IVIG resistance:** Defined by recrudescent or persistent fever ≥36 hours after completion of the first IVIG dose (AHA 2024). Occurs in ~15–20% and raises the risk of coronary artery abnormalities (CAA). Discuss contingency planning with Cardiology and ID if intensification may be needed overnight. Patients with persistent fever after the first IVIG resistance intensification therapy, or with rapidly enlarging coronary arteries or giant aneurysms, are managed with Rheumatology or a KD referral center (Boston Children's KD Program consult line, or Rady Children's KD Research Center), in addition to Cardiology. These patients typically need further immunomodulation escalation (e.g. TNF-α inhibitor, IL-1 receptor antagonist; cyclophosphamide or plasma exchange are reserved for refractory cases, see reference 12).
  - **New or enlarging coronary artery dimensions on serial echocardiography, or giant aneurysms:** Coronary status is judged by echocardiography, not by fever, and can progress after the patient is afebrile. See the AHA scientific statement (reference 12); consults should include Rheumatology/KD referral center in addition to Cardiology; for anticoagulation and when to consult Hematology, see note 10 and reference 12.
  - **Clinical deterioration during observation:** Hemodynamic instability or poor perfusion (KD shock syndrome), or features suggesting macrophage activation syndrome — falling platelet and WBC counts, rising ferritin and triglycerides, hepatosplenomegaly — rather than the expected thrombocytosis. Transfer to ICU (note 5); involve Cardiology, ID, and Rheumatology if MAS is suspected.

- **Post-infusion fever and complications:** Fever within 36 hours of IVIG completion is often infusion-related and does not by itself indicate treatment failure. Other potential IVIG side effects: aseptic meningitis, hemolytic anemia (higher risk in non–type O blood groups and after repeat IVIG dosing).

- **ESR caution:** ESR rises with plasma immunoglobulin concentration, leading to elevated values for weeks after IVIG infusion independent of disease activity, and should not be used to monitor response to IVIG.

- **Duration of inpatient observation:** AHA 2024 does not specify a duration and evidence is limited. We recommend 36–48 hours after IVIG completion, especially for:
  - Age ≤6 months
  - Coronary artery abnormalities on echocardiogram (Z score ≥2)
  - Ongoing fever (>38.0°C) in the first 36 hours after IVIG and/or lack of improvement — not yet IVIG resistance, but a reason to complete the full observation period
  - Barriers to reliable return for care (transportation, adherence, or knowledge)

- **Earlier discharge:** For patients meeting none of the above, earlier discharge may be appropriate based on individual risk factors, multidisciplinary assessment, and family preference. The AvoMD IVIG Nonresponse Calculator (Hester et al., Children's Minnesota, 2019) may help identify lower-risk patients.

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Note 8: Discharge Criteria

- **All patients:**
  - Kawasaki signs significantly improved/resolved
  - Afebrile, ≥ 36 hours after IVIG completion (see note 7 for earlier discharge exceptions)
  - If indicated, pre-discharge echo is done and reviewed (indications: for high-risk features (note 6) or IVIG resistance (note 7))
  - Discharge planning complete — aspirin step-down, follow-up appointments, and discharge education (see Discharge Planning, page 1, and note 9)
- **If consultants were involved or the patient received intensification, also:**
  - Primary team and consultants (Cardiology, ID, +/- Rheumatology/ KD referral center +/- Hematology) agree the patient is ready. Steroid wean plan documented, Endocrine consulted if patient will be on steroids ≥ 2 weeks (note 9), and, if Hematology was consulted, the anticoagulation plan is documented and prescribed for home (note 10)

Note 9: Discharge education

- No MMR, Varicella, or MMRV for 11 months after receipt of IVIG (children at high risk of exposure may receive sooner and be re-immunized after 11 months if they have an inadequate serological response). Oral live vaccines including rotavirus (RV) and Ty21A typhoid are permissible. Yellow fever need not be deferred.
- Live attenuated influenza vaccine (LAIV) and NSAIDs should be avoided while on aspirin.
- If patient will be on steroids ≥ 2 weeks, consult Endocrine prior to discharge.
- Discuss plan for recurrent fever or other KD symptoms (rash, mucositis) with family. Any KD symptom, or fever (oral or rectal temp >38.0C (100.4F), or axillary >37.5C (99.5F) within 7 days of discharge, should be evaluated by PCP or ED as soon as possible, with a repeat echocardiogram unless there is a clear alternate diagnosis (Cardiology +/- Rheumatology consult as indicated; see note 7).
- No strenuous activity until Cardiology follow-up

Note 10: Anticoagulation and when to consult Hematology

- Aspirin is antiplatelet therapy, not anticoagulation. At each echocardiogram, note the maximum coronary z-score and whether thrombus is present.
- Per AHA 2024: a giant aneurysm (z ≥ 10 or absolute diameter ≥ 8 mm) warrants anticoagulation in addition to aspirin; Z score 5–10 or aneurysms rapidly enlarging should be individualized with Cardiology, including the decision for dual antiplatelet therapy; coronary thrombosis needs urgent treatment.
- Consult Hematology the same day a qualifying echocardiogram is read and reassess at each repeat echo. Cardiology guides the coronary plan and Hematology recommends the agent, dosing, and monitoring.

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Table 1: Therapeutic Management

Standard Risk Kawasaki Disease: Primary Therapy

Intravenous Immune Globulin (IVIG)	2 g/kg infused over 8–12 hours	• In patients with obesity, confirm dosing weight with pharmacy. • Premedicate with diphenhydramine and acetaminophen. May also pre-medicate with methylprednisolone but not required. • If giving a second dose of IVIG (out of scope of this guideline), obtain a type and screen (serum to save) prior, as the risk of IVIG-induced hemolysis on repeat IVIG is increased based on blood type.
Aspirin	Initial: 30–50 mg/kg orally per **day** divided every 6 hours Step Down: 3–5 mg/kg (max 81 mg) orally once daily	• Do not administer with NSAIDs, as NSAIDs inhibit ASA's antiplatelet effects. • Oral administration only, tablets only (no liquid formulation exists due to stability issues) • Consider clopidogrel if patient is not eligible for aspirin or cannot tolerate the tablets. Clopidogrel is available in tablets or a compounded suspension.

High Risk Kawasaki Disease: Intensification of Primary Therapy*

All standard-risk treatment above, plus at least one of the following (to be given in consultation with ID and Cardiology):		
Infliximab	10 mg/kg IV Once over 2 hours	• Premedicate with acetaminophen and diphenhydramine. • 1–2 mg/kg IV methylprednisolone is an optional pre-medication, as well. • Dose may be extended if patient experiences infusion reaction

Methylprednisolone	2 mg/kg IV per **day** (max 60 mg/day) divided every 12 hours until afebrile x24 hours or up to max 5 days, then proceed with taper (see suggested taper to the right)	• Ulcer prophylaxis: prescribe famotidine during steroid treatment.
		• Sequencing with IVIG: if IVIG has not started, steroids may go first; otherwise wait until the end of the infusion if only one IV is available (or use a second IV).
		• Check CRP before discharge to guide taper below
		• After afebrile x24 hours or at 5 days, convert to prednisone (tablets) or prednisolone (liquid):
		  • 1 mg/kg twice daily (max 30 mg/dose; 60 mg/day) until CRP normalizes (< 1 mg/dL ▲); then:
		  • 1 mg/kg/dose once daily for 5 days (max 30 mg/dose); then
		  • 0.5 mg/kg/dose once daily for 5 days (max 15 mg/dose); then stop.
		  • If patient will be on steroids ≥ 2 weeks, consult Endocrine prior to discharge.
		  • At discharge: ensure the full taper above is prescribed for home.
		▲ If CRP ≥1 at discharge, CRP should be rechecked at time of Cardiology visit (and echo). Cardiology to order and follow up on CRP and advise family if able to start taper as prescribed above. Persistent CRP elevation may prompt further discussion with Rheumatology.

*For patients deemed high risk at diagnosis (note 6), intensification is given together with IVIG. Our local consult triggers are intentionally broader than the AHA criteria; Cardiology and ID determine true high risk and agent choice. AHA high-risk criteria used by consulting teams may include: age ≤ 6 months; LAD or RCA z ≥ 2.5 on baseline echo; or Son North American score ≥ 3 (LAD or RCA z ≥ 2.0 = 2 points, plus 1 point each for age < 6 months, Asian race, CRP ≥ 13 mg/dL). Treatment of IVIG resistance or evolving CAA is out of scope of this guidance (see note 7); additional agents are described in the AHA scientific statement (reference 12).

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