CLINICAL GUIDELINE

Kawasaki Disease

(<18 years age)

Children's MINNESOTA

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

EXCLUSION CRITERIA

Patients **excluded** from this guideline

- Any alternative etiology *(*presence may not exclude KD. See note 3)*
- Suspicion for multisystem inflammatory syndrome in children (MIS-C), see note 2
- Critically ill
- Refractory KD
- Previous KD
- Underlying immunodeficiency or chronic medical complexity

Meets criteria for classic KD? (note 1)

Yes

•Complete lab workup
CBC w/ diff, CMP, voided UA, ESR, CRP, GGT, ferritin, SARS-CoV-2 IgG/PCR, Serum to Save
•Consult ID

Labs consistent with KD? (note 4)

Yes

Admit to med-surg and initiate KD treatment ASAP

- Consult ID
- IVIG 2 g/kg given over 12 hours (once on med-surg)
  - Premedicate with Tylenol and Benadryl
- Aspirin 30-50 mg/kg /day divided QID (avoid NSAIDs)
- Echocardiogram (do not delay IVIG awaiting echo)
  - If abnormal, formally consult cardiology
- Adjunctive therapies, such as corticosteroids or immunomodulators (e.g., infliximab), may be determined on a case-by-case basis as per ID consultant recommendations, mainly based on the presence of high-risk factors (note 5 and note 6).
- Monitor off scheduled antipyretics to monitor for fever

No

Off guideline
Consult ID, consider evaluation for atypical KD and alternate etiologies

No

Note 1: Classic KD clinical criteria: Fever 4-5 days PLUS ≥ 4 of the following:

- Swelling/erythema/tenderness of hands/feet. Desquamation is more likely in the subacute phase.
- Rash (any)
- Bilateral bulbar conjunctival injection without exudate
- Changes in lips/oral cavity: erythema, lip cracking, strawberry tongue
- Unilateral cervical lymphadenopathy >1.5 cm

**If fever criteria met but only 1-2 other features present, consider atypical Kawasaki disease.*
***Consider Kawasaki Disease in infants <6 months of age with prolonged fever without other explanation. Prolonged fever and irritability may be the only manifestations of KD in this age group.*

Discharge Planning (notes 7 and 8)

- Evaluate for response to therapy, including recurrent/persistent fever. *See note 7 for timing regarding 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.
- Follow-up with primary care provider within ~2 days of discharge
- Follow-up with cardiology for repeat echocardiogram at 2 weeks. Timing of additional echo (typically 4-6 weeks later) will be determined at that time.

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Rev 3/23, Exp 3/26

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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, have lymphopenia and thrombocytopenia, have hypotension, and have 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 (childrensmn.org)

Note 3. Differential Diagnosis

Differential diagnosis for KD is broad and includes MIS-C, measles, streptococcus, adenovirus, enterovirus, RMSF, staphylococcus, systemic JIA, meningococcemia, Stevens Johnson, DRESS

Note 4. Supplemental lab findings often seen in KD

- Leukocytosis: WBC count of ≥15,000/mm3
- Elevated CRP ≥3.0 mg/dL and/or ESR ≥ 40mm/hr
- Anemia for age
- Hypoalbuminemia ≤ 3.0 g/dL
- Thrombocytosis (typically after 7 days)
- Elevated ALT
- Sterile pyuria from voided urine WBC ≥10/hpf
- Hyponatremia and elevated GGT are often seen as well

Note 5. High risk factors associated with development/worsening of coronary artery changes

- Risk factors for progression to coronary artery aneurysms in North American cohort include:
    - Baseline maximum Z score of LAD artery or RCA >/= 2.5
    - Age at fever onset of younger than 12 months or >9 years
    - CRP >/= 13 mg/dL.
    - The Son 2019 study also found that patients identified as “Asian race” had a higher odds ratio of progression to coronary artery aneurysms. However, as race is a social construct, the dynamics of race as a risk factor is unclear.

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Note 6. Adjunctive therapies during primary treatment may include:

- Methylprednisolone IV 1.6 mg/kg/DAY divided q8h (Max: 16mg/DOSE; 48 mg/DAY) until afebrile x24 hours.
    - Then transition to: Oral prednisolone/prednisone 1 mg/kg/DOSE twice daily (Max: 30 mg/DOSE; 60 mg/DAY) until CRP normalizes (<0.5 mg/dL).
    - Then initiate oral prednisolone/prednisone taper suggested as follows:
        - 1 mg/kg/dose BID x 5 days (Max: 30 mg/DOSE; 60 mg/DAY) then:
        - 1 mg/kg/dose Qday (Max: 30 mg/DOSE) x 5 days then:
        - 0.5 mg/kg/dose Qday x 5 days (Max: 15 mg/DOSE).
    - If steroids are utilized, please ensure famotidine is ordered for GI prophylaxis.
- Infliximab 5 mg/kg/dose as a single infusion

Note 7: Observation after IVIG completion.

- Risks of IVIG including: hemolytic anemia (e.g., pallor relative to baseline skin tone, fatigue, tachycardia), aseptic meningitis (headache, stiff neck)
- Fevers in the first 36 hours after IVIG completion may be due to IVIG. Fevers after this time period may necessitate additional treatment. About 15–20% of patients do not respond to first IVIG dose and will require additional treatment.
- American Heart Association national guidelines do not discuss how long to observe patients in hospital following IVIG completion and there is insufficient evidence to guide duration of hospital observation period following IVIG infusion. Consider monitoring as inpatient for 36-48hrs after completion of IVIG, especially in those patients with:
    - Age <6 months
    - Abnormal coronary arteries on echo (Z score ≥ 2)
    - Ongoing fevers (temperature >38.0 C) directly after IVIG completion (first 36 hrs after completion) and/or clinical symptoms not improving
    - Barriers to return to care (limited transport, concerns for poor compliance, knowledge barriers)
- AvoMD Clinical Guideline calculator may help identify patients lower risk for IVIG nonresponse and suitable for consideration of earlier discharge, based upon a study from Children's Minnesota (Hester et. al., 2019)
    - Earlier discharge may be appropriate based on individual patient risk factors; primary team, ID, and cardiology assessment; and family preference.

Note 8: Discharge education

- No MMR, Varicella, or MMRV x 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). Live intranasal (i.e. live attenuated influenza vaccine (LAIV)) and oral vaccines (including rotavirus vaccine (RV) and Ty21A typhoid vaccine) are permissible at any time. Yellow fever vaccine does not need to be deferred secondary to unlikely presence of antibodies in donated blood products.
- Educate family to avoid NSAIDs while on aspirin.
- Most steroid tapers would be completed by ~15 days. However if patient will be on steroids >3 weeks, consult Endocrine prior to discharge.
- Discuss plan for recurrent fever or other KD symptoms (rash, mucositis) with family: recommend any symptoms or fever (oral or rectal temp >38.0C (100.4F), or axillary >37.5C (99.5F)) within 7 days of discharge be evaluated by PCP or ED ASAP, consider direct admit for additional therapy.
- No strenuous activity until cardiology follow-up

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References

- Gorelik M, Chung SA, Ardalan K, Binstadt BA, Friedman K, Hayward K, Imundo LF, Lapidus SK, Kim S, Son MB, Sule S, Tremoulet AH, Van Mater H, Yildirim-Toruner C, Langford CA, Maz M, Abril A, Guyatt G, Archer AM, Conn DL, Full KA, Grayson PC, Ibarra MF, Merkel PA, Rhee RL, Seo P, Stone JH, Sundel RP, Vitobaldi OI, Warner A, Byram K, Dua AB, Husainat N, James KE, Kalot M, Lin YC, Springer JM, Turgunbaev M, Villa-Forte A, Turner AS, Mustafa RA. 2021 American College of Rheumatology/Vasculitis Foundation Guideline for the Management of Kawasaki Disease. Arthritis Care Res (Hoboken). 2022 Apr;74(4):538-548. doi: 10.1002/acr.24838. Epub 2022 Mar 7. PMID: 35257507.
- Son MBF, Gauvreau K, Tremoulet AH, Lo M, Baker AL, de Ferranti S, Dedeoglu F, Sundel RP, Friedman KG, Burns JC, Newburger JW. Risk Model Development and Validation for Prediction of Coronary Artery Aneurysms in Kawasaki Disease in a North American Population. J Am Heart Assoc. 2019 Jun 4;8(11):e011319. doi: 10.1161/JAHA.118.011319. PMID: 31130036; PMCID: PMC6585355.
- Friedman KG, Gauvreau K, Baker A, Son MB, Sundel R, Dionne A, Giorgio T, De Ferranti S, Newburger JW. Primary adjunctive corticosteroid therapy is associated with improved outcomes for patients with Kawasaki disease with coronary artery aneurysms at diagnosis. Arch Dis Child. 2021 Mar;106(3):247-252. doi: 10.1136/archdischild-2020-319810. Epub 2020 Sep 17. PMID: 32943389.
- Miyata K, Miura M, Kaneko T, Morikawa Y, Sakakibara H, Matsushima T, Misawa M, Takahashi T, Nakazawa M, Tsuchihashi T, Yamashita Y, Obonai T, Chiga M, Hori N, Komiyama O, Yamagishi H. Risk Factors of Coronary Artery Abnormalities and Resistance to Intravenous Immunoglobulin Plus Corticosteroid Therapy in Severe Kawasaki Disease: An Analysis of Post RAISE. Circ Cardiovasc Qual Outcomes. 2021 Feb;14(2):e007191. doi: 10.1161/CIRCOUTCOMES.120.007191. Epub 2021 Feb 5. PMID: 33541111.
- Dionne A, Burns JC, Dahdah N, Tremoulet AH, Gauvreau K, de Ferranti SD, Baker AL, Son MB, Gould P, Fournier A, Newburger JW, Friedman KG. Treatment Intensification in Patients With Kawasaki Disease and Coronary Aneurysm at Diagnosis. Pediatrics. 2019 Jun;143(6):e20183341. doi: 10.1542/peds.2018-3341. Epub 2019 May 2. PMID: 31048414.
- Iio K, Morikawa Y, Miyata K, Kaneko T, Misawa M, Yamagishi H, Miura M. Risk Factors of Coronary Artery Aneurysms in Kawasaki Disease with a Low Risk of Intravenous Immunoglobulin Resistance: An Analysis of Post RAISE. J Pediatr. 2022 Jan;240:158-163.e4. doi: 10.1016/j.jpeds.2021.08.065. Epub 2021 Aug 27. PMID: 34461064.
- Miyata K, Kaneko T, Morikawa Y, Sakakibara H, Matsushima T, Misawa M, Takahashi T, Nakazawa M, Tamame T, Tsuchihashi T, Yamashita Y, Obonai T, Chiga M, Hori N, Komiyama O, Yamagishi H, Miura M; Post RAISE group. Efficacy and safety of intravenous immunoglobulin plus prednisolone therapy in patients with Kawasaki disease (Post RAISE): a multicentre, prospective cohort study. Lancet Child Adolesc Health. 2018 Dec;2(12):855-862. doi: 10.1016/S2352-4642(18)30293-1. Epub 2018 Oct 16. PMID: 30337183.
- Kobayashi T, Saji T, Otani T, Takeuchi K, Nakamura T, Arakawa H, Kato T, Hara T, Hamaoka K, Ogawa S, Miura M, Nomura Y, Fuse S, Ichida F, Seki M, Fukazawa R, Ogawa C, Furuno K, Tokunaga H, Takatsuki S, Hara S, Morikawa A; RAISE study group investigators. Efficacy of immunoglobulin plus prednisolone for prevention of coronary artery abnormalities in severe Kawasaki disease (RAISE study): a randomised, open-label, blinded-endpoints trial. Lancet. 2012 Apr 28;379(9826):1613-20. doi: 10.1016/S0140-6736(11)61930-2. Epub 2012 Mar 8. PMID: 22405251.
- McCrindle BW, Rowley AH, Newburger JW, Burns JC, Bolger AF, Gewitz M, Baker AL, Jackson MA, Takahashi M, Shah PB, Kobayashi T, Wu MH, Saji TT, Pahl E; American Heart Association Rheumatic Fever, Endocarditis, and Kawasaki Disease Committee of the Council on Cardiovascular Disease in the Young; Council on Cardiovascular and Stroke Nursing; Council on Cardiovascular Surgery and Anesthesia; and Council on Epidemiology and Prevention. Diagnosis, Treatment, and Long-Term Management of Kawasaki Disease: A Scientific Statement for Health Professionals From the American Heart Association. Circulation. 2017 Apr 25;135(17):e927-e999. doi: 10.1161/CIR.0000000000000484. Epub 2017 Mar 29. Erratum in: Circulation. 2019 Jul 30;140(5):e181-e184. PMID: 28356445.
- Hester GZ, Watson D, Nickel AJ, Ryan N, Jepson B, Gray J, Bergmann KR. Identifying Patients With Kawasaki Disease Safe for Early Discharge: Development of a Risk Prediction Model at a US Children's Hospital. Hosp Pediatr. 2019 Oct;9(10):749-756. doi: 10.1542/hpeds.2019-0049. Epub 2019 Sep 9. PMID: 31501220.

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Reviewer: Harrison
Rev 3/23, Exp 3/26