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2021 American College of Rheumatology/Vasculitis Foundation Guideline for the Management of Kawasaki Disease

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Abstract

OBJECTIVE: To provide evidence-based recommendations and expert guidance for the management of Kawasaki disease (KD), with a focus on clinical situations more commonly addressed by rheumatologists.

METHODS: Sixteen clinical questions regarding the diagnostic testing, treatment, and management of KD were developed in the Patient population, Intervention, Comparator, and Outcome (PICO) question format. Systematic literature reviews were conducted for each PICO question. We used the Grading of Recommendations, Assessment, Development and Evaluation (GRADE) methodology to assess the quality of evidence and formulate recommendations. Each recommendation required consensus from at least 70% of the Voting Panel.

RESULTS: We present one good practice statement, eleven recommendations, and one ungraded position statement to guide management of KD and clinical scenarios of suspected KD. These recommendations for KD focus on areas where input from rheumatologists may be requested by other managing specialties, such as in refractory, severe, or complicated KD. The 'good practice statement' affirms that all patients with KD should be treated initially with intravenous immunoglobulin (IVIG). In addition, seven strong and four conditional recommendations were developed. Strong recommendations include prompt treatment of incomplete KD, aspirin therapy, and obtaining an echocardiogram in the setting of unexplained macrophage activation syndrome or shock. Conditional recommendations include use of IVIG with other adjuvant agents for patients with KD and high-risk features for IVIG resistance and/or coronary artery aneurysms. These recommendations endorse minimizing risk to the patient by using established therapy promptly at disease onset and identifying areas where adjunctive therapy may be warranted.

CONCLUSION: These recommendations provide guidance regarding diagnostic strategies, use of pharmacologic agents, and role of echocardiography for patients with suspected or confirmed KD.

Keywords

Kawasaki Disease; guideline; treatment; management; diagnostic testing

Introduction:

Kawasaki disease (KD) is a medium vessel vasculitis as presented by the Chapel Hill Consensus Conference nomenclature system[1]. KD is distinguished as being one of two primary common vasculitis syndromes that predominantly affect children (the other being Henoch-Schönlein purpura/IgA vasculitis). KD continues to be seen with relative frequency in young children, at an incidence of 25–50/100,000 in the US, similar to that of type 1 diabetes[2, 3]. KD typically presents in children under 5 years of age as an acute, self-limited febrile illness, and is characterized by a combination of several characteristic clinical signs, which include polymorphic rash, non-purulent conjunctival injection, oropharyngeal and lip mucositis, tongue papillitis, erythema and edema of the hands and feet, as well as unilateral cervical lymphadenopathy.

From a histopathologic standpoint, KD is characterized by aggressive neutrophil-mediated panmural vascular necrosis without granuloma formation, followed by intimal hyperplasia and sub-acute lymphocytic inflammation in advanced disease. KD primarily affects the coronary arteries but can also affect medium caliber arteries throughout the body. [4]Therefore, KD shares some features with polyarteritis nodosa, and prior to the recognition of KD as a distinct entity, infants with fatal fulminant forms of KD were labeled as ‘infantile polyarteritis nodosa’.[5]

KD treated appropriately is associated with a low rate of mortality (approximately 0.08% case fatality rate in the largest series)[6]. However, in the developed world, it is the most common cause of acquired cardiac disease in childhood, with 25% of untreated and 5% of treated cases developing coronary artery aneurysms. In infants less than 6 months of age, the risk of a coronary artery aneurysm is 50% even in KD patients treated with IVIG within the first 10 days of illness.[7]

Given increasing options available to treat systemic vasculitis, the American College of Rheumatology and Vasculitis Foundation supported the development of guidelines for the management of large-, medium-, and small-vessel vasculitis. This guideline presents evidence-based recommendations for the diagnostic testing, treatment, and management of KD. Recognizing the comprehensive guidelines developed by the American Heart Association (AHA) for the management of KD,[3] this guideline focuses on clinical management questions generally posed to rheumatologists, such as the use of adjunctive therapies for initial treatment of severe disease and the treatment approaches for refractory disease. Although this guideline may inform an international audience, these recommendations were developed considering the experience with and availability of treatment and diagnostic options in the United States (US).

Methods:

This guideline follows the ACR guideline development process (<https://www.rheumatology.org/Practice-Quality/Clinical-Support/Clinical-Practice-Guidelines>) using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) methodology to rate the quality of evidence and develop recommendations.[8, 9] ACR policy guided management of conflicts of interest and disclosures (<https://www.rheumatology.org/Practice-Quality/Clinical-Support/Clinical-Practice-Guidelines/Vasculitis>). Supplementary Appendix 1 presents a detailed description of the methods.

Sixteen clinical questions addressing the diagnostic testing, treatment, and management of patients with KD were developed by the Core Team, initial Voting Panel, and Expert Panel in the “population, intervention, comparator, and outcomes” (PICO) format. The Literature Review Team undertook systematic literature reviews for pre-specified PICO questions. The Expert Panel, including rheumatologists and a pediatric cardiologist, provided expert knowledge to inform discussion of the PICO questions and findings of the literature review.

An initial Voting Panel, comprised of 8 adult rheumatologists (AMA, DLC, PCG, PAM, RR, PS, JS, AW), 5 pediatric rheumatologists (MFI, LFI, SK, SS, RPS), and 2 patients (KF, OV) reviewed the Literature Review Team’s evidence summaries. The panel formulated and voted on an initial set of recommendations. To incorporate broader expertise from the pediatric community and validate the results from the initial voting panel, a second Voting Panel was established, comprised of 8 pediatric rheumatologists (KA, BAB, MG, KH, SKL, HVM, MBS, CYT) new to the Voting Panel, 4 pediatric rheumatologists who participated in both Voting Panels (SK, SS, LI, RPS), a pediatric infectious disease physician with extensive expertise in KD (AHT), and a pediatric cardiologist with extensive expertise in KD (KF). The second Voting Panel also reviewed the Literature Review Team’s evidence summaries and independently formulated and voted on recommendations. Members of the second Voting Panel who were not on the initial Voting Panel were not provided with the recommendations formulated by the initial Voting Panel prior to the second panel’s voting. Each recommendation required consensus from at least 70% of the Voting Panel.

How to interpret the recommendations:

1. A *strong* recommendation is typically supported by moderate or high-quality evidence (e.g., multiple randomized controlled trials). For a strong recommendation, the recommended course of action would apply to all or almost all patients. Only a small proportion of clinicians/patients would not want to follow the recommendation. A strong recommendation may also be based on low or very low certainty evidence if it is considered low-cost, without harms, and the consequence of not performing the intervention may be catastrophic. An intervention may also be strongly recommended against if there is high certainty that the intervention leads to more harm than the comparison with low or very low certainty about its benefit [10].

2. A *conditional* recommendation is generally supported by lower quality evidence or a close balance between desirable and undesirable outcomes. For a conditional recommendation, the recommended course of action would apply to the majority of patients, but the alternative is a reasonable consideration. Conditional recommendations always warrant a shared decision-making approach. Conditions are specified under which the alternative may be considered.
3. In one instance, the committee found that the evidence for a particular PICO question did not support a graded recommendation, and the Voting Panel did not favor one intervention over the other. However, the Voting Panel believed the PICO question addressed an important clinical question and thus felt that providing guidance for this question was warranted. For this situation, we present an ‘ungraded position statement’ which reflects general views of the Voting Panel.
4. In this evidence-based guideline, we explicitly use the best evidence available and present that in a transparent manner for the clinician reader/user.[10]. In some instances, this includes randomized trials directly comparing the interventions under consideration. The GRADE system rates evidence that comes exclusively from the collective experience of the Voting Panel and Patient Panel members as “very low quality” evidence.
5. For each recommendation, Supplementary Appendix 2 provides details regarding the PICO questions and the GRADE evidence tables.

Results:

For the evidence report, the Literature Review Team summarized 275 articles to address the 16 PICO questions for KD. Details regarding the methods utilized for the literature review are provided in Supplemental Appendix 1. Both the initial and second Voting Panel (see Methods) utilized the evidence report to formulate their recommendations. The recommendations formulated by the second Voting Panel were consistent with the initial Voting Panel. Clinical considerations for the recommendations were further expanded by the second Voting Panel, and thus the recommendations of the second Voting Panel are presented here.

Table 1 presents definitions of selected terms used in the recommendations, and Table 2 presents the recommendations with their supporting PICO questions and level of evidence. Figure 1 provides a schematic highlighting the key recommendations for the treatment of KD. Recommendations that are conditional are indicated as such and are generally due to a lack of high-quality evidence (e.g., multiple randomized controlled trials) supporting the recommendation.

Treatment recommendations:

Good Practice Statement: Intravenous immunoglobulin is the standard-of-care therapy for the initial treatment of Kawasaki disease. Intravenous

immunoglobulin (IVIG) has been established as the standard-of-care treatment for KD for the last 4 decades due to the significant reduction in the rate of coronary artery aneurysms as well as the duration of fever and other symptoms associated with its use.[11] Although no comparative trials of IVIG and glucocorticoids have been conducted, glucocorticoids alone were considered inadequate to treat KD based on an early case series.[12,13]. Thus, IVIG use is a mainstay of KD therapy. The mechanisms of IVIG's therapeutic effect in KD are still under study.[14]

For patients with acute Kawasaki disease who are at high risk of IVIG resistance or developing coronary artery aneurysms, using IVIG with adjunctive glucocorticoids as initial therapy is *conditionally* recommended over IVIG alone. Risk scores have been developed to identify patients at high risk of IVIG resistance in Japanese populations, but these scores have poor sensitivity and specificity in a multiethnic US population.[15–17]. A recent study of patients in North America identified the following patient characteristics as predictors for the development of coronary artery aneurysms at 2 to 8 weeks: z-score of left anterior descending or right coronary artery ≥ 2.0 , age < 6 months, Asian race, and C-reactive protein ≥ 13 mg/dL[18] Features that suggest an increased likelihood of morbidity in KD in the US include age < 6 months or age > 9 years at diagnosis [19, 20] Patients with giant (z-score > 10) or multiple aneurysms are also more likely not to regress (via remodeling) at late stages[21] and large aneurysms carry the greatest morbidity.[21, 22]

Emerging evidence suggests that the addition of glucocorticoids to IVIG as primary therapy can decrease the risk of developing coronary artery aneurysms, albeit the strongest evidence is in a Japanese population[16], and that the addition of glucocorticoids can decrease the progression of coronary artery aneurysms in patients with coronary aneurysms at diagnosis. [23, 24]

Thus, the use of glucocorticoids with IVIG is a treatment option for patients who are at high risk for coronary artery aneurysms. For this recommendation, the Voting Panel defines high risk features as z-score ≥ 2.5 [25–27] for left anterior descending or right coronary artery at the time of initial echocardiogram and age < 6 months. This definition uses the z-score of 2.5 instead of 2.0, as 2.5 is defined as a true aneurysm. We also do not use patients > 9 years of age as only a portion of these patients are felt to be “high risk.” The Voting Panel acknowledges that further investigation clarifying the features of “high risk” KD in a US population is needed. Optimal dosing and duration of glucocorticoids are still to be determined and need more study in a US population, but a typical dose would be prednisone starting at 2 mg/kg/day (maximum 60 mg/day), with the dose tapered over 15 days. As a conditional recommendation, the use of IVIG alone is appropriate when the treating physician is unsure whether a patient is at high risk for developing coronary artery aneurysms, or when additional steroid exposure may be detrimental to the patient. The use of glucocorticoids is generally *not* recommended for patients who do not have features suggestive of high risk.

For patients with acute KD who are at high risk of IVIG resistance or developing coronary artery aneurysms, using IVIG with other non-

glucocorticoid immunomodulatory immunosuppressive agents as initial therapy is *conditionally recommended over IVIG alone*. For patients with features of high risk disease, adjunctive therapy with a non-glucocorticoid immunomodulatory agent such as infliximab, anakinra, or cyclosporine may improve outcomes in acute disease and improve cardiac outcomes.[21, 23, 28, 29] Thus, adjunctive therapy with a non-glucocorticoid immunomodulatory agent can be considered in patients with KD at high risk for not responding to IVIG. For any patient considered to have features of high risk disease, a rheumatologist or other clinician with expertise in KD should be consulted before adding an adjunctive agent (glucocorticoids or non-glucocorticoid immunomodulatory agents), to ensure the correct diagnosis and appropriate utilization of adjunctive therapies. The Voting Panel also advocated for a stepwise therapeutic algorithm, in which either a glucocorticoid or non-glucocorticoid immunosuppressive agent is initially prescribed for high risk patients, along with IVIG. Currently, there is more evidence supporting the use of glucocorticoids than non-glucocorticoid immunosuppressive agents for this patient population, and further study is warranted to compare the efficacy of glucocorticoid to non-glucocorticoid therapy in this population. There may be specific situations where glucocorticoids are contraindicated, but the patient exhibits high risk features which would indicate need for adjunctive non-glucocorticoid immunomodulatory therapy. Once again, use of IVIG alone is appropriate if the treating physician is unsure if a patient has high risk features as described in the previous recommendation, or if using a non-glucocorticoid immunomodulatory agent presents a greater risk of an adverse effect to the patient.

For patients with incomplete Kawasaki disease, prompt treatment at time of diagnosis with IVIG is *strongly recommended over delaying treatment until $\geq$ day 10*. Incomplete KD is defined a condition of suspected KD lacking sufficient number of features to fulfill criteria for KD (Table 1).[3, 30] Patients with incomplete KD should be evaluated using the algorithm for incomplete KD as outlined in the American Heart Association (AHA) guidelines for KD.[3, 30] The performance of this algorithm for identifying patients with incomplete KD has been validated.[30] The practice of completing diagnostic testing and initiating treatment by day 10 of fever is not based on mechanisms or studies of disease pathogenesis, or treatment outcomes. Instead, this “treatment deadline” was chosen as a research endpoint in the original studies in KD.[31] Prompt treatment is recognized to prevent adverse outcomes, and patients should be treated as soon as the diagnosis of incomplete KD is made rather than waiting until day 10 to see if they meet criteria for complete KD. Although IVIG treatment delayed after 10 days of fever is associated with worse outcomes[32], IVIG treatment should still be given to patients even if they present after more than 10 days of fever. Thus, patients who meet the criteria for incomplete KD by the AHA guidelines should be treated promptly to avoid adverse consequences since the risk of developing coronary artery dilatation increases each day without treatment. This is a strong recommendation because the intervention is standard-of-care and the consequence of delaying treatment may lead to significant coronary artery aneurysms or rupture, which is a severe adverse outcome. In addition, resolution of fever prior to 10 days is not an indication to withhold treatment for patients meeting criteria for incomplete or complete KD. In patients with characteristically elevated acute phase

reactants, treatment is recommended as these patients remain at a high risk of adverse outcomes.[3, 33]

For patients with acute Kawasaki disease and suspected or diagnosed macrophage activation syndrome, treatment with IVIG for Kawasaki disease and additional agents to treat macrophage activation syndrome is *strongly recommended*. Macrophage activation syndrome (MAS), a form of secondary hemophagocytic lymphohistiocytosis (HLH), is a potentially under-recognized complication of KD[34, 35]. Formal diagnostic criteria for MAS in the setting of KD have not been developed. However, drawing on experience from other secondary HLH presentations, MAS may be suspected in the setting of KD patients with persistent fever, splenomegaly, elevated ferritin, and thrombocytopenia.[35] Inadequate treatment of either KD or MAS could result in severe consequences for the patient. These include large coronary aneurysms or coronary artery stenosis leading to death via cardiac infarct or coronary rupture in KD, or death due to multi-organ dysfunction in MAS. [36]

Thus, to ensure appropriate therapy, each entity should be considered separately with appropriate targeted therapy. KD should be treated with IVIG as first-line therapy, and MAS should also be treated with appropriate agents targeting cytokine storm or underlying triggers. Anakinra and glucocorticoids are favored for treatment in these patients over a primary HLH-directed treatment protocol with cytotoxic agents. Although no head-to-head comparison trials are published, primary HLH-directed therapy has considerably more associated toxicity, which may not be warranted for patients without an underlying genetic predisposition to HLH. This is a strong recommendation because the consequence of not appropriately treating KD or MAS may be associated with an increase in mortality.

For patients with acute Kawasaki disease and persistent fevers after initial treatment with IVIG, a second course of IVIG is *conditionally recommended over use of glucocorticoids*. Six studies provide indirect evidence for this recommendation, with no direct comparative studies available.[37–42] For patients with KD and persistent fevers after the initial course of IVIG, studies suggest that there is no difference in coronary artery outcomes between repeating IVIG versus a dose of pulse glucocorticoids (i.e., 30 mg/kg × 1 dose with a maximum of 1 g) [43]. A meta-analysis of 12 studies involving 372 patients who were resistant to treatment with a single course of IVIG failed to find significant differences in coronary artery outcomes between a second dose of IVIG, corticosteroids, or infliximab.[44] Although current evidence does not clearly indicate superiority of a second course of IVIG over glucocorticoids, a second course of IVIG in patients who have persistent fever for more than 36 hours after the first dose is conditionally recommended as it is the current standard of care. However, as a conditional recommendation, glucocorticoids (e.g., starting at 2 mg/kg/day and tapering over 15 days or 20–30mg/kg × 1 dose) are a reasonable alternative. Repeated doses of IVIG may place patients at risk of hemolytic anemia, and results of ongoing studies may alter this recommendation in the future.[45–47] In patients with risk factors for hemolytic anemia with IVIG, such as non-type O blood groups, alternative therapies such as glucocorticoids or non-glucocorticoid immunomodulatory therapy should be considered.[48, 49] Combination

therapy (i.e., multiple anti-cytokine agents) is not recommended for routine care, and generally are only considered for patients with extremely severe disease.

Ungraded Position Statement: For patients with acute KD and persistent fevers after repeated treatment with IVIG, either non-glucocorticoid immunosuppressive therapy or glucocorticoids may be used. In patients with KD and persistent fevers after two doses of IVIG, use of another agent is indicated. Studies of infliximab and cyclosporine for the treatment of refractory KD suggest some potential benefit for these agents.[28, 29]. Head-to-head comparisons between these non-glucocorticoid immunosuppressive agents and glucocorticoids have not been performed. There is no clinical evidence to suggest superiority of either glucocorticoids or non-glucocorticoid immunomodulatory agents, and the Voting Panel was evenly split as to which to recommend. Thus, the Voting Panel believes that use of either class of agents would be appropriate based on the clinical scenario at hand. Combination therapy (glucocorticoid with a non-glucocorticoid immunosuppressive agent) can be considered for severe cases, such as rapidly expanding aneurysms or imminently life-threatening disease.

For patients with acute Kawasaki disease, using aspirin is strongly recommended over no aspirin. The use of aspirin in patients with KD to reduce inflammation and prevent thrombosis through its anti-platelet effect is considered standard of care. However, the optimal dose is unclear. Historically, high doses (80–100 mg/kg/day) for anti-inflammatory effects were used during the acute phase, but there is no evidence of benefit for high versus low dose aspirin (3–5 mg/kg/day) when considering coronary vascular damage.[50–52] The American Heart Association (AHA) guidelines should be consulted for recommendations regarding anticoagulation for patients with larger aneurysms.[3] This is a strong recommendation because aspirin is recognized to be a low-cost intervention with limited toxicity at antiplatelet dosing, and there are significant consequences of not inhibiting platelet activity, such as coronary artery thrombosis.

For patients with acute Kawasaki disease with subsequent resolution of fevers, continued daily monitoring for fevers is strongly recommended over no monitoring for fevers. Patients with KD may have recurrence of disease or refractory disease heralded by return of fever and other symptoms. In addition, duration of fever is a predictor of coronary artery aneurysms.[53] Thus, patients should be monitored daily for fevers for 1–2 weeks after discharge, with fever defined as having oral temperature in older children and a rectal temperature in infants above 38.0°C or an axillary temperature above 37.5°C. Parents and/or guardians should be instructed by the discharging physician on how to take a temperature and to contact their physician should a fever recur. This is a strong recommendation because daily fever monitoring is low cost and without harms and may identify recrudescence KD.

For patients with acute Kawasaki disease with arthritis that persists after IVIG treatment and without coronary artery aneurysms, using non-steroidal anti-inflammatory drugs (NSAIDs) to treat arthritis is conditionally recommended over not using NSAIDs. Patients with acute and subacute KD can develop arthritis,

but treatment with IVIG has decreased the incidence of arthritis in this setting from 30% to approximately 2–12%. [54] Arthritis in KD is usually short lived, lasting between 7–21 days. [54–56] In general, arthritis can be treated with NSAIDs, but NSAIDs directly inhibit aspirin's ability to acetylate COX-1, thus decreasing aspirin's protective effects. [57] The impact of NSAID use can be partially mitigated by dosing aspirin prior to NSAIDs, but combination therapy is usually not recommended given the potential increased toxicity. [57]

Patients without coronary artery aneurysms generally do not require long term treatment with aspirin. The optimal duration of treatment with aspirin in these patients is not well defined but is generally 6–8 weeks in practice. Patients with coronary artery aneurysms require long term and potentially indefinite aspirin use. [3] For patients *without* coronary artery aneurysms who do not require long-term use of aspirin and with arthritis requiring additional therapy, aspirin can be temporarily suspended and a short course of NSAIDs (3–4 weeks) can be used as needed. Conversely, if indefinite or long-term aspirin use is needed due to coronary artery aneurysms, then either acetaminophen, a short course of glucocorticoids, or non-systemic NSAID pain management options (e.g., a topical NSAID) can be used. A pediatric hematologist or cardiologist should be consulted to consider an alternative anti-coagulant (e.g., clopidogrel) if prolonged use of systemic NSAIDs (i.e., > 3 weeks) is required, especially in a patient with coronary artery aneurysms.

Diagnostic imaging:

For children with suspected incomplete Kawasaki disease and fever, obtaining an echocardiogram with coronary artery measurements without delay is *strongly* recommended over not obtaining an echocardiogram. Patients with incomplete KD have at least the same or increased risk of coronary artery lesions compared to patients with classic KD. [58] Therefore, patients who are suspected to have incomplete KD should have their diagnosis confirmed as soon as possible so that features associated with high risk of coronary artery aneurysms can be assessed, treatment can be initiated without delay, and adverse outcomes can be prevented. Echocardiographic assessment of the coronary artery absolute dimensions and body surface area-adjusted z scores can help establish a diagnosis of incomplete KD and should be obtained promptly when the diagnosis is suspected. The AHA guidelines for KD treatment and management provide an algorithm for evaluation and treatment of patients with suspected incomplete KD, [3] which has been validated. [30] This is a strong recommendation because echocardiography has minimal potential harms and may prevent adverse outcomes by prompting the treatment of incomplete KD.

For children with unexplained shock physiology, obtaining an echocardiogram with coronary artery measurements is *strongly* recommended. Unexplained shock can be due to Kawasaki shock syndrome, a recognized manifestation of KD. [59] Echocardiograms are often obtained in children with unexplained shock, especially in those with a prodrome of prolonged fever, to evaluate cardiac function and help identify the potential etiology. We recommend that the coronary arteries be interrogated as part of the echocardiogram to evaluate for KD as a potential etiology of shock. This is a strong recommendation because echocardiography has minimal potential

harms and may prevent catastrophic outcomes by facilitating the diagnosis and prompt treatment of KD.

For children with unexplained macrophage activation syndrome, obtaining an echocardiogram with coronary artery measurements is strongly recommended. As noted above, KD is one of the clinical inflammatory entities that can predispose patients to develop macrophage activation syndrome (MAS).[60] For patients with unexplained MAS, KD should be considered as a potential underlying etiology. Obtaining an echocardiogram with interrogation of the coronary arteries is one method of identifying KD as a potential treatable underlying condition. This is a strong recommendation because echocardiography has minimal potential harms and may prevent adverse outcomes by facilitating the diagnosis and prompt treatment of KD.

Discussion:

This is the first guideline issued by the American College of Rheumatology, in conjunction with the Vasculitis Foundation, for the management of KD. These recommendations constitute a guide to help physicians treat patients with KD. This guideline should not be used by any agency to restrict access to therapy or require that certain therapies must be utilized prior to other therapies.

Patients with KD in the US are often diagnosed and treated by physicians with expertise in other areas besides rheumatology (e.g., pediatric cardiology, hospitalists, or infectious disease). This guideline's recommendations focus on situations where rheumatologists are often consulted, such as the management of severe disease, refractory disease, arthritis, and macrophage activation syndrome with KD. However, these recommendations are relevant to physicians treating patients with KD independent of their area of expertise.

The AHA has presented recommendations for the initial treatment as well as long term management of KD.[3] Recommendations presented in this guideline are intended to supplement the AHA guidelines and serve as an additional reference for rheumatologists who may be less familiar with KD. Emerging evidence suggesting that adjunctive therapy decreases the incidence of severe coronary artery aneurysms and hastens regression of these aneurysms provides the basis for the recommendations concerning "high-risk" KD. [23] Although aneurysms that have regressed are affected by endothelial dysfunction and therefore remain abnormal vasculature, normalized vessel caliber decreases morbidity from vessel thrombosis.[3]

Finally, during the COVID-19 pandemic, a novel multisystem inflammatory syndrome in children (MIS-C) associated with SARS-CoV-2 infection emerged with some features suggestive of KD.[61, 62] While as many as 50% of these patients could meet criteria for KD, many patients demonstrate manifestations that are unusual for KD, including colitis, myocarditis and neurologic changes, and often present with or deteriorate into shock.[63] Further study is needed to understand the relationship between MIS-C and KD, especially Kawasaki shock syndrome. Based on clinical experience with many of these patients, recognition and differentiation of these patients from classic KD is important. Patients

who meet criteria for KD should be treated using the therapies discussed in this guideline. Additional study is needed to determine optimal treatment for MIS-C with and without KD features.

In summary, the American College of Rheumatology and Vasculitis Foundation present these recommendations to assist physicians in managing patients with KD. This guideline can serve as a touchstone for basic principles of management and will evolve as new treatment strategies for this disease are identified.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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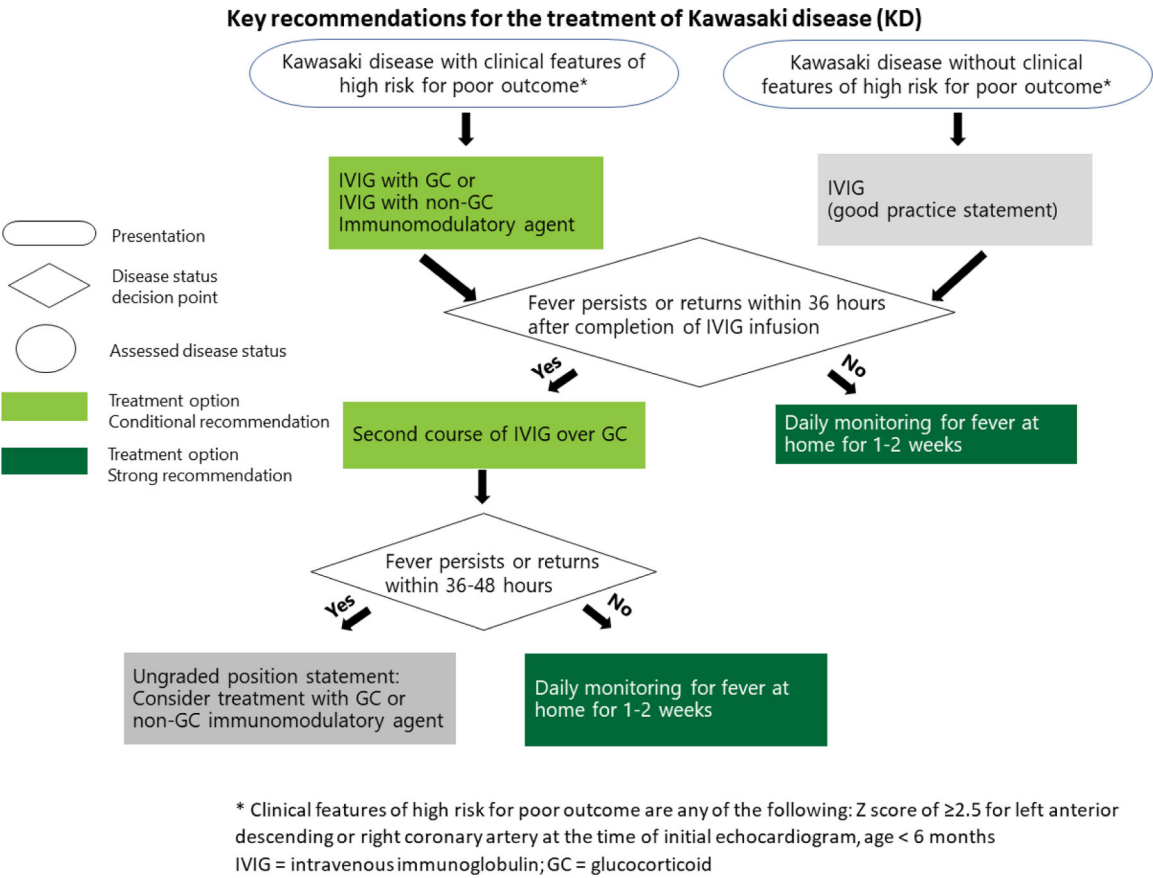


Figure 1. Key recommendations for the treatment of Kawasaki disease in patients with and those without clinical features indicating a high risk for poor outcome.

Table 1.

Definitions for selected terms used in the recommendations/ungraded position statements for Kawasaki Disease (KD).

Term	Definition
A. Disease states	
Kawasaki Disease (KD)	Fever lasting at least five days without any other explanation with at least four of the five following principal clinical findings: • Bilateral bulbar conjunctival injection without exudate • Erythema and cracking of lips, strawberry tongue, and/or erythema of oral and pharyngeal mucosa • Erythema and edema of the hands or feet (acute phase), and/or periungual desquamation (subacute phase) • Maculopapular, diffuse erythroderma, or erythema multiforme-like rash • Cervical lymphadenopathy (at least one lymph node >1.5 cm in diameter), usually unilateral The diagnosis may be made with only 4 days of fever if ≥ 4 principal clinical findings are present.
Incomplete KD	Prolonged unexplained fever in an infant or child with fewer than 4 of the principal clinical findings of KD (see above), and compatible laboratory studies (elevated ESR/CRP, elevated transaminases, UA with leukocyte esterase negative WBC) or echocardiographic findings (coronary artery dilatation). Defined according to the algorithm in [31] and [3].
Acute KD	Initial febrile phase of KD
B. Medications	
Intravenous immunoglobulin (IVIG)	Single dose of 2 g/kg (no defined maximum dose, however reasonable maximum ranges are 100–140 g)
Non-glucocorticoid immunomodulatory therapy	Anakinra, cyclosporine, or infliximab
Glucocorticoids	Prednisone 2 mg/kg/day (maximum dose 60 mg/day) for 15 days, or equivalent
Aspirin	High dose: 30–50 or 80–100 mg/kg/day Low dose: 3–5mg/kg/day

Table 2.

Recommendations and Ungraded Position Statements regarding diagnostic testing and treatment of patients with Kawasaki disease (KD).

Recommendations/Ungraded Position Statements/Good Practice Statement	Level of evidence	PICO*
Good Practice Statement: Intravenous immunoglobulin is the standard-of-care therapy for the initial treatment of Kawasaki disease.	High	3
For patients with acute Kawasaki disease who are at high risk of IVIG resistance or developing coronary artery aneurysms, using IVIG with adjunctive glucocorticoids as initial therapy is <i>conditionally</i> recommended over IVIG alone.	Low	4
For patients with acute KD who are at high risk of IVIG resistance or developing coronary artery aneurysms, using IVIG with other non-glucocorticoid immunomodulatory immunosuppressive agents as initial therapy is <i>conditionally</i> recommended over IVIG alone.	Very Low	5
For patients with incomplete Kawasaki disease, prompt treatment at time of diagnosis with IVIG is <i>strongly</i> recommended over delaying treatment until >=day 10.	Low	1
For patients with acute Kawasaki disease and suspected or diagnosed macrophage activation syndrome, treatment with IVIG for Kawasaki disease and additional agents to treat macrophage activation syndrome is <i>strongly</i> recommended.	Very Low	2
For patients with acute Kawasaki disease and persistent fevers after initial treatment with IVIG, a second course of IVIG is <i>conditionally</i> recommended over use of glucocorticoids.	Very Low	10
Ungraded Position Statement: For patients with acute KD and persistent fevers after repeated treatment with IVIG, either non-glucocorticoid immunosuppressive therapy or glucocorticoids may be used.	Low	11
For patients with acute Kawasaki disease, using aspirin is <i>strongly</i> recommended over no aspirin.	Very Low	6
For patients with acute Kawasaki disease with subsequent resolution of fevers, continued daily monitoring for fevers is <i>strongly</i> recommended over no monitoring for fevers.	Very low	12
For patients with acute Kawasaki disease with arthritis that persists after IVIG treatment and without coronary artery aneurysms, using non-steroidal anti-inflammatory drugs (NSAIDs) to treat arthritis is <i>conditionally</i> recommended over not using NSAIDs.	Very Low	13
Additional Diagnostic Testing Recommendations		
For children with suspected incomplete Kawasaki disease and fever, obtaining an echocardiogram with coronary artery measurements without delay is <i>strongly</i> recommended over not obtaining an echocardiogram.	Very Low	D1
For children with unexplained shock physiology, obtaining an echocardiogram with coronary artery measurements is <i>strongly</i> recommended.	Very Low	D2
For children with unexplained macrophage activation syndrome, obtaining an echocardiogram with coronary artery measurements is strongly recommended	Very Low	D3

* PICO= Population Intervention Comparator Outcome question used in GRADE methodology. Please refer to Supplementary Appendix 2 for the PICO questions developed for KD.