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Kawasaki Disease: A Systematic Review and Meta-Analysis of Benefits and Harms of Common Treatments

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Objective. Kawasaki disease (KD) is a self-limited vasculitis affecting medium-sized vessels with a predilection for the coronary arteries. Although treatment reduces the likelihood of developing of coronary artery aneurysms, 5% of patients still develop aneurysms despite treatment, making KD the leading cause of acquired heart disease in children in the United States. Consequently, there is a great deal of interest in optimizing treatment regimens, particularly for higher-risk patients, to decrease morbidity. The aim of this systematic review is to support the development of the American College of Rheumatology/Vasculitis Foundation for the diagnosis and management of KD, focusing on the more complex scenarios in which rheumatologists may become involved, such as high-risk and refractory disease.

Methods. Eighty-nine articles were considered for full review in this systematic literature review to address 16 Population, Intervention, Comparison, and Outcome questions related to KD. Data were abstracted in hierarchical fashion. Randomized control trials (RCTs) were considered first; if none were identified or if they contained insufficient information, comparative observational studies were then viewed, followed by single-arm observational studies/single arms from comparative studies. Only observational studies with more than 10 subjects with vasculitis were included.

Results. Eight RCTs and 28 observational studies that addressed the questions were identified. Two questions were addressed by RCTs, seven questions had at least some comparative observational studies, three questions were only addressed by single-arm data, and four questions had no relevant studies.

Conclusion. This systematic review evaluates the benefits and harms of treatments for KD beyond first-line therapy.

INTRODUCTION

Kawasaki disease (KD) is an acute necrotizing vasculitis of the medium-sized arteries with a predilection for the coronary arteries (1). KD is diagnosed based on having fever and at least four of the five following clinical characteristics: mucocutaneous changes, conjunctivitis, rash, extremity changes, and lymphadenopathy. Although KD is generally a self-limited process, if untreated, it may cause coronary artery ectasia and/or aneurysms in 15% to 25% of children (2,3). Children with incomplete KD (fewer than four of the five clinical characteristics) are at higher risk for delay in treatment and development of coronary artery disease (4,5). Treatment with intravenous immunoglobulin (IVIG) and aspirin (ASA) during the acute phase of illness decreases the risk of coronary abnormalities to approximately 5% (6,7). These coronary

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Drs. James and Kalot contributed equally to this manuscript.

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artery abnormalities lead to risk for future ischemic heart disease, myocardial infarction, and sudden death. In the United States, KD is the leading cause of acquired heart disease in children (8).

Aside from coronary artery abnormalities, patients may develop other, potentially life-threatening complications that require additional diagnostic and treatment considerations. Patients with KD may present with or develop Kawasaki shock syndrome (KSS), KD with associated systolic hypotension, or other signs of poor perfusion (9). There has also been increasing recognition that a subset of children may develop macrophage activation syndrome (MAS) secondary to KD (10).

Uncomplicated KD in the United States is typically managed by pediatric hospitalists, cardiologists, and, infectious disease specialists but is uncommonly managed by rheumatologists. In some institutions, rheumatologists may become involved when there is uncertainty as to the diagnosis or in cases of severe illness or illness unresponsive to standard therapy. Consequently, the American College of Rheumatology/Vasculitis Foundation (ACR/VF) guideline committee elected to develop guidelines for rheumatologists to address the scenarios for which rheumatologists are most likely to be consulted.

The aim of this systematic review is to compare the benefits and harms of different treatment options for patients with KD beyond first-line treatment with IVIG and ASA. This review includes randomized control trials (RCTs) and nonrandomized studies and presents the evidence and an assessment of its certainty for important outcomes. These reviews were used to inform evidence-based recommendations on diagnostic and management strategies for KD by the ACR/VF vasculitis management guidelines.

METHODS

Search strategy and data sources. An information specialist made systematic searches of the published English language literature, including Ovid Medline, PubMed, Embase, and the Cochrane Library (including Cochrane Database of Systematic Reviews, Database of Abstracts of Reviews of Effects, Cochrane Central Register of Controlled Trials, and Health Technology Assessments) from the inception of each database through August 2018 to obtain direct evidence in vasculitis patient populations relating to vasculitis questions (Supplementary Appendix 1). The information specialist updated the searches conducted on August 2019. The methods team used DistillerSR software to identify duplicate records (https://distillercer.com/products/distillersr-systematic-reviewsoftware/). The search was specific to address the Population, Intervention, Comparison, and Outcome (PICO) questions asked for each vasculitis type. The ACR/VF Vasculitis Guideline core team developed 16 PICO questions for KD that addressed relevant or commonly encountered patient diagnostic, treatment, and management scenarios (Supplementary Appendix 2).

Study selection. *Studies.* We included studies that would provide the highest certainty evidence. We included RCTs first. When RCTs were not available, we included observational studies (cohort and case-control studies) that reported on patient-important outcomes for the intervention and comparison. When studies with comparative data were not available, we included case series that present patient-important outcomes for either the intervention or the comparison.

Participants. Studies including pediatric patients (<18 years of age) presenting to inpatient or outpatient settings with suspected or confirmed KD were eligible for inclusion. When studies addressed multiple vasculitis types, we included data when results were presented separately or when more than 80% of the population included were patients with KD.

Interventions. Studies reporting outcomes comparatively for the intervention and comparison specified in the PICO question or reporting outcomes for either the intervention or the comparison were included.

Exclusion criteria. The following studies were excluded: studies that have an irrelevant population, intervention, or outcome; studies that have no primary data such as letters, opinion pieces, and commentaries; narrative reviews; systematic reviews; epidemiological studies that only include prevalence or incidence results; any study that had fewer than 10 patients with vasculitis; any study that addressed an organ-limited vasculitis (except renal-limited vasculitis); and any study about basic research in animals.

Screening and data extraction. Pairs of two independent reviewers conducted title and abstract screening and full-text review in duplicate to identify eligible studies. Data extraction was also conducted independently and in duplicate, and conflicts were resolved by a third reviewer (MAK). Each panel of reviewers included at least one of five clinical experts (KB, AD, KEJ, YCCL, and JS). Data extracted included general study characteristics (authors, publication year, country, and study design), duration of follow-up, outcome data for the intervention and/or comparison, and diagnostic index test and reference standard, along with parameters to determine test accuracy (ie, sensitivity and specificity of the index test) when relevant.

Risk of bias and data synthesis. When direct comparative results were available from RCTs, reviewers entered the results into RevMan v.5.3 software (http://tech.cochrane.org/revman), which was used to calculate pooled effect estimates. Reviewers evaluated the risk of bias using the Cochrane risk of bias tool (http://handbook.cochrane.org/).

When direct comparative results were available from observational studies (cohort and case-control studies), reviewers entered the results into RevMan v.5.3 software, which was used to calculate pooled effect estimates. Reviewers evaluated the risk of bias using a modified Newcastle-Ottawa scale for observational studies

(http://www.ohri.ca/programs/clinical_epidemiology/oxford.asp). When comparative results were not available, reviewers abstracted data describing details of the population, interventions, and results into summary tables.

Two investigators familiar with the GRADEpro software (https://gradepro.org) (MAK and NH) formulated Grading of Recommendations Assessment, Development, and Evaluation (GRADE) summary of findings tables for each PICO question when direct comparative data or test accuracy results were available. The investigators used the GRADE framework to assess overall certainty by evaluating the evidence for each outcome on the following domains: risk of bias, imprecision, inconsistency, indirectness, and publication bias.

Data analysis. For questions addressing treatment options, relative risks (eg, risk ratios [RRs] and odds ratios [ORs]) were calculated by pooling results from RCTs and from observational studies comparing treatments. When no direct comparisons between treatments within a study were available, the risk of an event (or proportion) in a study (eg, disease relapse) was calculated, and then the weighted proportions from each study were combined and presented in the outcome description section of the summary tables.

RESULTS

Description of studies. This guideline effort was developed in conjunction with the guideline development effort for six other systemic vasculitides (giant cell arteritis, Takayasu arteritis, polyarteritis nodosa, and three Anti-Neutrophilic Cytoplasmic Autoantibodies-associated vasculitides). The initial search for these seven vasculitides retrieved 13800 nonduplicate studies, of which 2596 were included for full-text review. Following full-text review, 1156 articles were identified as potentially eligible for data abstraction and inclusion in the systematic reviews for the seven different types of vasculitis. A total of 89 articles were considered for data abstraction for KD. Reasons for exclusion at full-text review were ineligible study design, study population, or intervention; sample size of fewer than 10 patients; and unacceptable reference standard or index test. Ultimately eight RCTs and 28 observational studies were identified as having information relevant to the PICO questions used to inform the guidelines (Figure 1).

Study outcomes. A wide variety of outcomes were identified in the selected studies and were largely consistent with those identified by the ACR/VF Guidelines Committee as important. Coronary artery abnormalities were the primary outcome in many studies; however, there was significant variability in how coronary artery abnormality was defined. In some cases, there was no differentiation between coronary artery ectasia, dilation, and aneurysm, whereas others reported aneurysm separately from other abnormalities. Some studies used different definitions of dilation and aneurysm, although the Japanese Ministry of Health definition of coronary aneurysm was most commonly used (11). There were also differences in which coronary arteries were measured and at what time point; most studies reported a 4- to 6-week time point, and some reported multiple timepoints. Some articles reported mean *z* scores of multiple coronary arteries at multiple timepoints without reporting overall rates of abnormality or aneurysm. These differences in reporting made it challenging to determine the rates of coronary artery abnormalities/aneurysms for meta-analysis. Refractory disease was another common primary outcome; most defined refractory disease as a persistence or recurrence of fever more than 12 to 36 hours after the completion of IVIG treatment. Some studies separated patients resistant to initial treatment (never defervesced) from those who had relapsing disease (a recurrence of fever after defervescing), whereas others combined this outcome. Other secondary outcomes included time to defervescence, duration of hospital stay, and adverse events. Death was not reported in any of the RCTs, as no deaths occurred. Other longer-term outcomes reported in observational studies included persistent coronary artery lesions, coronary stenosis, myocardial ischemia, and stroke (12).

Below is a summary of the results of the comparative data abstracted. Results from studies providing data on a single arm of a question can be found in the Supplementary Appendix.

IVIG versus IVIG and glucocorticoids as initial therapy in high-risk patients. Several RCTS evaluated the use of IVIG versus IVIG plus glucocorticoids (GCs) in the initial treatment of KD (13–21). Two studies and one secondary analysis of an RCT focused only on those with high-risk scores (13,16,21). Multiple GC regimens were used (generally, 30 mg/kg ×1 dose methylprednisolone or 2 mg/kg ×1 dose methylprednisolone/prednisolone with varying tapers). Some studies used heparin (16) or dipyridamole in addition to IVIG with or without GCs (14,17). The quality of evidence is shown in Supplemental Table 1. Unfortunately, all studies addressing this question specifically in the high-risk population used different measures of coronary artery outcomes, limiting the ability to perform meta-analysis. Kobayashi et al demonstrated an OR of 0.11 (95% confidence interval [CI]: 0.04-0.34) (low certainty of evidence) for development of any coronary artery abnormality at any point and an OR of 0.24 (95% CI: 0.08-0.75) (low certainty of evidence) for coronary artery abnormality at 4 to 6 weeks in those with high-risk scores given 2 mg/kg/day of prednisolone in addition to the standard therapy of IVIG and ASA (13). Ogata et al showed lower *z* scores in the left main coronary at 36 hours and 1 month after treatment with IVIG, ASA, and a single 30-mg/kg dose of methylprednisolone versus IVIG and ASA alone; however, rates of coronary artery aneurysm/abnormality were not reported (16). Sleeper et al performed a secondary analysis of patients with high-risk disease from the RAISE trial comparing IVIG and ASA versus IVIG and ASA with a single

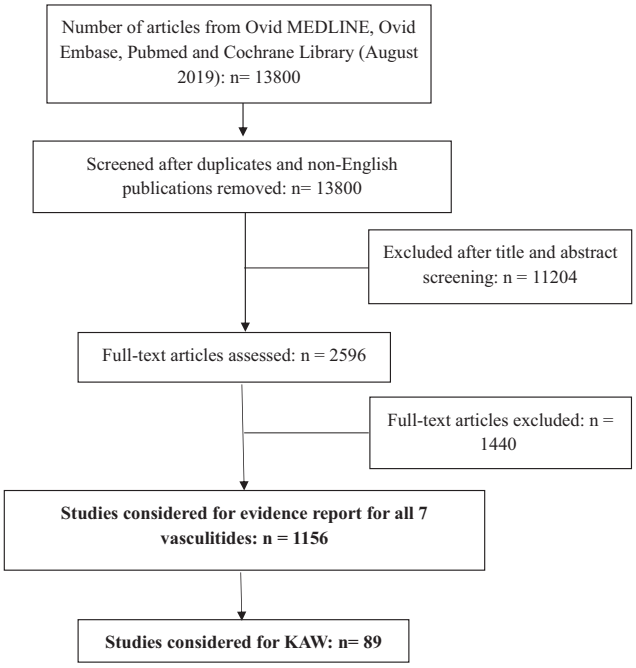


Figure 1. Study flow diagram for included studies in the Kawasaki Disease (KAW) Metanalaysis.

dose of 30 mg/kg of methylprednisolone (18,21). After adjusting for baseline differences in the two groups, there was "no evidence of a differential effect of steroid therapy in the low vs high-risk subgroups" on the maximum coronary artery *z* score at 1 week and 5 weeks when using the Kobayashi risk score, and there were similar findings when using the Egami and Sano risk scores. Of note, this study was performed in a North American population, whereas the other RCTs in high-risk populations were performed in Asian countries (21).

The meta-analysis was performed by looking at coronary artery outcomes including studies that looked at all patients with KDs, as there were limited data on high-risk patients specifically. Coronary artery aneurysms at the 4- to 6-week time point were decreased with IVIG and GC over IVIG (OR: 0.15; 95% CI: 0.04-0.65) (low certainty of evidence) (Figure 2). A similar trend was seen with coronary artery abnormalities at the 4- to 6-week time point (OR: 0.30; 95% CI: 0.10-0.85) (low certainty of evidence) (Supplemental Figure 1). Coronary artery abnormalities at any point in time after the start of treatment were reported in two studies; however, one study showed no subsequent development of coronary artery abnormalities in either arm (14) (Supplemental Figure 1).

Several RCTs evaluated the duration of fever after treatment (looking at both all KD populations and high-risk KD populations), and demonstrated a standard mean difference of 0.97 lower (95% CI: 1.64 lower to 0.31 lower) (low certainty of evidence) in those receiving GCs versus those not receiving GCs (Figure 2). One study (15) in a non–high-risk population showed a slight decrease in duration of hospital stay, and another comparative observational study (19) showed a decrease in refractory disease (Supplemental Table 1). Need for retreatment (either refractory or relapsing disease) was decreased in those receiving GCs. Serious adverse events were not significantly increased with the addition of GCs (Figure 2).

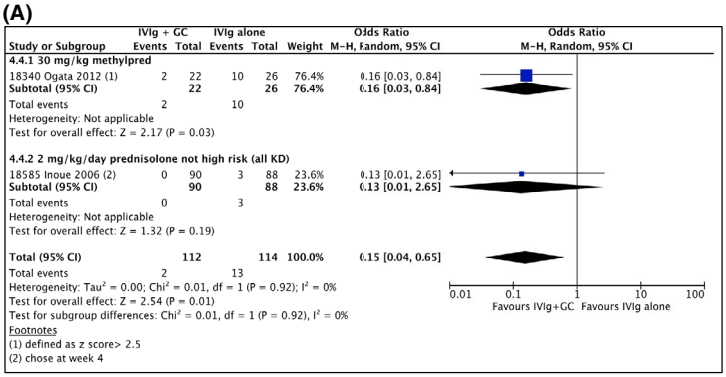
IVIG versus IVIG and non-GC immunosuppressive agents as initial therapy in high-risk patients. Little comparative evidence was available on the use of IVIG in combination with other non-GC immunosuppressants as initial therapy in KD (Table 1). In a 2019 study, Hamada et al compared IVIG with IVIG plus 5 days of cyclosporine in high-risk patients (as defined by the Kobayashi score). The authors did note that the overall incidence of coronary artery abnormality at any point was lower in the IVIG and cyclosporine group (RR: 0.45; 95% CI 0.25-0.86) (low certainty of evidence). The incidence was significantly lower at 2 weeks after treatment (4% versus 16%; $P = 0.009$), but this difference in incidence was not seen at Day 3 or at Weeks 1, 4, or 12. There was a shorter duration of fever in those receiving cyclosporine. Fewer patients in the cyclosporine group failed to have an initial response to treatment (17% versus 37%; $P = 0.004$), but more had a relapse (27% versus 8%; $P = 0.016$), with no difference in the overall number needing second-line therapy (44% versus 45%; $P = 0.99$) or third-line treatment (17% versus 16%; $P = 0.81$) (22).

IVIG versus GCs alone as initial treatment for KD. No comparative studies, RCTs, or observational studies were found that directly addressed this question. Observational data as well as RCTs have strongly demonstrated the efficacy of IVIG at reducing the risk of coronary artery aneurysms in KD, and IVIG is the current standard comparator arm in RCTs (7,14–18,24,25). Early data suggested that GCs alone are insufficient for treating KD (26). A more contemporary observational study looking at delay in IVIG treatment reported on the outcomes of several patients who received GCs alone before IVIG. However, all subjects must have eventually received IVIG, so it was biased to include only those who failed GC monotherapy (5) (single-arm data; Supplementary Appendix 3).

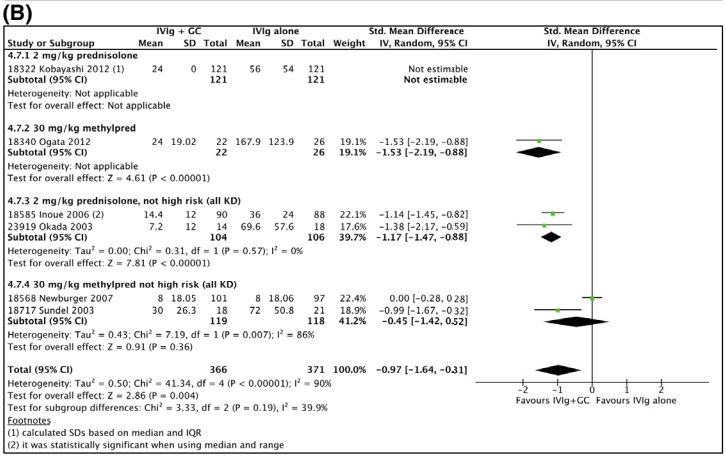
Glucocorticoids versus a second dose of IVIG for treatment of refractory disease. There were several comparative observational studies, but no RCTs, comparing GCs with IVIG as the second-line therapy after the initial IVIG treatment failed. Three studies used 30 mg/kg/day methylprednisolone pulses daily for 3 days (27–29), two of which used a subsequent 1-week taper

Figure 2. Forest plot results of meta-analysis of studies addressing the question of intravenous immunoglobulin (IVIG) versus IVIG plus glucocorticoids (GCs) as initial treatment in high-risk Kawasaki disease (KD). **A**, Coronary artery aneurysm at 4- 6-week time point. **B**, Duration of fever. **C**, Need for retreatment (includes refractory and relapsing disease). **D**, Serious adverse events. CI, confidence interval; Std, standard.

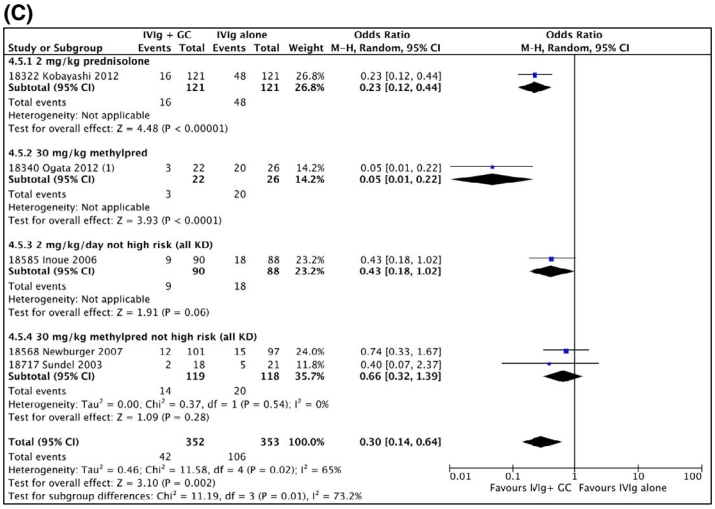
(A)


IVIg + GC
IVIg alone
Odds Ratio
Odds Ratio
Study or Subgroup Events Total Events Total Weight M-H, Random, 95% CI
M-H, Random, 95% CI
4.4.1 30 mg/kg methylpred
18340 Ogata 2012 (1) 2 22 10 26 76.4% 0.16 [0.03, 0.84]
Subtotal (95% CI) 22 26 76.4% 0.16 [0.03, 0.84]
Total events 2 10
Heterogeneity: Not applicable
Test for overall effect: Z = 2.17 (P = 0.03)
4.4.2 2 mg/kg/day prednisolone not high risk (all KD)
18585 Inoue 2006 (2) 0 90 3 88 23.6% 0.13 [0.01, 2.65]
Subtotal (95% CI) 90 88 23.6% 0.13 [0.01, 2.65]
Total events 0 3
Heterogeneity: Not applicable
Test for overall effect: Z = 1.32 (P = 0.19)
Total (95% CI) 112 114 100.0% 0.15 [0.04, 0.65]
Total events 2 13
Heterogeneity: Tau² = 0.00; Chi² = 0.01, df = 1 (P = 0.92); I² = 0%
Test for overall effect: Z = 2.54 (P = 0.01)
Test for subgroup differences: Chi² = 0.01, df = 1 (P = 0.92), I² = 0%
0.01 0.1 1 10 100
Favours IVIg+GC Favours IVIg alone
Footnotes
(1) defined as z score> 2.5
(2) chose at week 4

(B)


IVIg + GC
IVIg alone
Std. Mean Difference
Std. Mean Difference
Study or Subgroup Mean SD Total Mean SD Total Weight IV, Random, 95% CI
IV, Random, 95% CI
4.7.1 2 mg/kg prednisolone
18322 Kobayashi 2012 (1) 24 0 121 56 54 121 Not estimable
Subtotal (95% CI) 121 121 Not estimable
Heterogeneity: Not applicable
Test for overall effect: Not applicable
4.7.2 30 mg/kg methylpred
18340 Ogata 2012 24 19.02 22 167.9 123.9 26 19.1% -1.53 [-2.19, -0.88]
Subtotal (95% CI) 22 26 19.1% -1.53 [-2.19, -0.88]
Heterogeneity: Not applicable
Test for overall effect: Z = 4.61 (P < 0.00001)
4.7.3 2 mg/kg prednisolone, not high risk (all KD)
18585 Inoue 2006 (2) 14.4 12 90 36 24 88 22.1% -1.14 [-1.45, -0.82]
23919 Okada 2003 7.2 12 14 69.6 57.6 18 17.6% -1.38 [-2.17, -0.59]
Subtotal (95% CI) 104 106 39.7% -1.17 [-1.47, -0.88]
Heterogeneity: Tau² = 0.00; Chi² = 0.31, df = 1 (P = 0.57); I² = 0%
Test for overall effect: Z = 7.81 (P < 0.00001)
4.7.4 30 mg/kg methylpred not high risk (all KD)
18568 Newburger 2007 8 18.05 101 8 18.06 97 22.4% 0.00 [-0.28, 0.28]
18717 Sundel 2003 30 26.3 18 72 50.8 21 18.9% -0.99 [-1.67, -0.32]
Subtotal (95% CI) 119 118 41.2% -0.45 [-1.42, 0.52]
Heterogeneity: Tau² = 0.43; Chi² = 7.19, df = 1 (P = 0.007); I² = 86%
Test for overall effect: Z = 0.91 (P = 0.36)
Total (95% CI) 366 371 100.0% -0.97 [-1.64, -0.31]
Heterogeneity: Tau² = 0.50; Chi² = 41.34, df = 4 (P < 0.00001); I² = 90%
Test for overall effect: Z = 2.86 (P = 0.004)
Test for subgroup differences: Chi² = 3.33, df = 2 (P = 0.19), I² = 39.9%
-2 -1 0 1 2
Favours IVIg+GC Favours IVIg alone
Footnotes
(1) calculated SDs based on median and IQR
(2) it was statistically significant when using median and range

(C)


IVIg + GC
IVIg alone
Odds Ratio
Odds Ratio
Study or Subgroup Events Total Events Total Weight M-H, Random, 95% CI
M-H, Random, 95% CI
4.5.1 2 mg/kg prednisolone
18322 Kobayashi 2012 16 121 48 121 26.8% 0.23 [0.12, 0.44]
Subtotal (95% CI) 121 121 26.8% 0.23 [0.12, 0.44]
Total events 16 48
Heterogeneity: Not applicable
Test for overall effect: Z = 4.48 (P < 0.00001)
4.5.2 30 mg/kg methylpred
18340 Ogata 2012 (1) 3 22 20 26 14.2% 0.05 [0.01, 0.22]
Subtotal (95% CI) 22 26 14.2% 0.05 [0.01, 0.22]
Total events 3 20
Heterogeneity: Not applicable
Test for overall effect: Z = 3.93 (P < 0.0001)
4.5.3 2 mg/kg/day not high risk (all KD)
18585 Inoue 2006 9 90 18 88 23.2% 0.43 [0.18, 1.02]
Subtotal (95% CI) 90 88 23.2% 0.43 [0.18, 1.02]
Total events 9 18
Heterogeneity: Not applicable
Test for overall effect: Z = 1.91 (P = 0.06)
4.5.4 30 mg/kg methylpred not high risk (all KD)
18568 Newburger 2007 12 101 15 97 24.0% 0.74 [0.33, 1.67]
18717 Sundel 2003 2 18 5 21 11.8% 0.40 [0.07, 2.37]
Subtotal (95% CI) 119 118 35.7% 0.66 [0.32, 1.39]
Total events 14 20
Heterogeneity: Tau² = 0.00; Chi² = 0.37, df = 1 (P = 0.54); I² = 0%
Test for overall effect: Z = 1.09 (P = 0.28)
Total (95% CI) 352 353 100.0% 0.30 [0.14, 0.64]
Total events 42 106
Heterogeneity: Tau² = 0.46; Chi² = 11.58, df = 4 (P = 0.02); I² = 65%
Test for overall effect: Z = 3.10 (P = 0.002)
Test for subgroup differences: Chi² = 11.19, df = 3 (P = 0.01), I² = 73.2%
0.01 0.1 1 10 100
Favours IVIg+ GC Favours IVIg alone

(D)

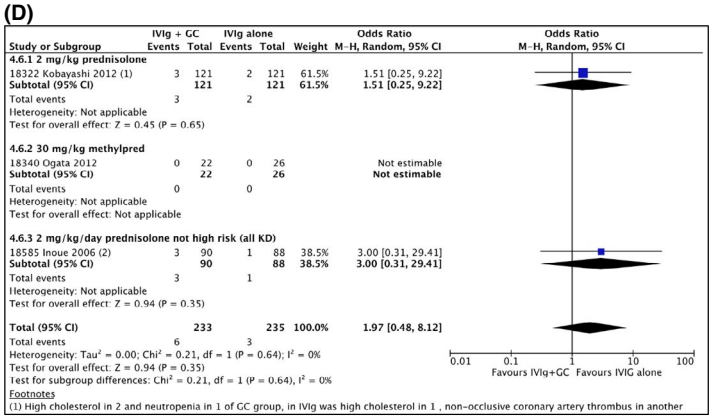

IVIg + GC
IVIg alone
Odds Ratio
Odds Ratio
Study or Subgroup Events Total Events Total Weight M-H, Random, 95% CI
M-H, Random, 95% CI
4.6.1 2 mg/kg prednisolone
18322 Kobayashi 2012 (1) 3 121 2 121 61.5% 1.51 [0.25, 9.22]
Subtotal (95% CI) 121 121 61.5% 1.51 [0.25, 9.22]
Total events 3 2
Heterogeneity: Not applicable
Test for overall effect: Z = 0.45 (P = 0.65)
4.6.2 30 mg/kg methylpred
18340 Ogata 2012 0 22 0 26 Not estimable
Subtotal (95% CI) 22 26 Not estimable
Total events 0 0
Heterogeneity: Not applicable
Test for overall effect: Not applicable
4.6.3 2 mg/kg/day prednisolone not high risk (all KD)
18585 Inoue 2006 (2) 3 90 1 88 38.5% 3.00 [0.31, 29.41]
Subtotal (95% CI) 90 88 38.5% 3.00 [0.31, 29.41]
Total events 3 1
Heterogeneity: Not applicable
Test for overall effect: Z = 0.94 (P = 0.35)
Total (95% CI) 233 235 100.0% 1.97 [0.48, 8.12]
Total events 6 3
Heterogeneity: Tau² = 0.00; Chi² = 0.21, df = 1 (P = 0.64); I² = 0%
Test for overall effect: Z = 0.94 (P = 0.35)
Test for subgroup differences: Chi² = 0.21, df = 1 (P = 0.64), I² = 0%
0.01 0.1 1 10 100
Favours IVIg+GC Favours IVIG alone
Footnotes
(1) High cholesterol in 2 and neutropenia in 1 of GC group, in IVIg was high cholesterol in 1 , non-occlusive coronary artery thrombus in another

Table 1. Grading of evidence for studies addressing the question of using IVIG versus IVIG plus nonglucocorticoid immunosuppressives as initial treatment for high-risk Kawasaki disease

Certainty Assessment							Number of Patients		Effect		
Number of Studies	Study Design	Risk of Bias	Inconsistency	Indirectness	Imprecision	Other Considerations	Initial Therapy With IVIG and Other Nonglucocorticoid Immunosuppressive Agents	IVIG Alone	Relative (95% CI)	Absolute (95% CI)	Certainty
Duration of fever											
One (23)	Randomized trial	Not serious	Not serious	Not serious	Serious[a]	None	98	97	-	SMD: **1.45 lower** (1.77 lower to 1.14 lower)	⊕⊕⊕◯ Moderate
Treatment resistance											
One (23)	Randomized trial	Not serious	Not serious	Not serious	Serious[a]	None	11/98 (11.2%)	11/97 (11.3%)	**OR: 0.99** (0.41-2.40)	**1 fewer per 1000** (from 64 fewer to 121 more)	⊕⊕⊕◯ Moderate
Duration of hospital stay											
One (23)	Randomized trial	Not serious	Not serious	Not serious	Serious[a]	None	98	97	-	SMD **0** (0.28 lower to 0.28 higher)	⊕⊕⊕◯ Moderate
Any coronary abnormality											
One (23)	Randomized trial	Not serious	Not serious	Not serious	Serious[a]	None	26/96 (27.1%)	27/97 (27.8%)	**OR: 0.96** (0.51-1.81)	**8 fewer per 1000** (from 114 fewer to 133 more)	⊕⊕⊕◯ Moderate
Any coronary aneurysm											
Two (22,23)	Randomized trials	Not serious	Not serious	Not serious	Serious[a]	None	38/182 (20.9%)	54/184 (29.3%)	**OR: 0.60** (0.23-1.58)	**94 fewer per 1000** (from 206 fewer to 103 more)	⊕⊕⊕◯ Moderate
Giant aneurysm											
One (23)	Randomized trial	Not serious	Not serious	Not serious	Very serious[a]	None	1/96 (1.0%)	1/97 (1.0%)	**OR: 1.01** (0.06-16.39)	**0 fewer per 1000** (from 10 fewer to 136 more)	⊕⊕◯◯ Low
Adverse events											
Two (22,23)	Randomized trials	Not serious	Not serious	Not serious	Serious[a]	None	64/184 (34.8%)	72/185 (38.9%)	**OR: 0.81** (0.41-1.62)	**49 fewer per 1000** (from 182 fewer to 119 more)	⊕⊕⊕◯ Moderate

Abbreviation: CI, confidence interval; IVIG, intravenous immunoglobulin; OR, odds ratio; SMD, standardized mean difference.
[a] Clinical action would differ if the upper boundary versus the lower boundary of the CI represented the truth.
⊕⊕⊕◯ Moderate certainty in evidence; ⊕⊕◯◯ Low certainty in evidence.

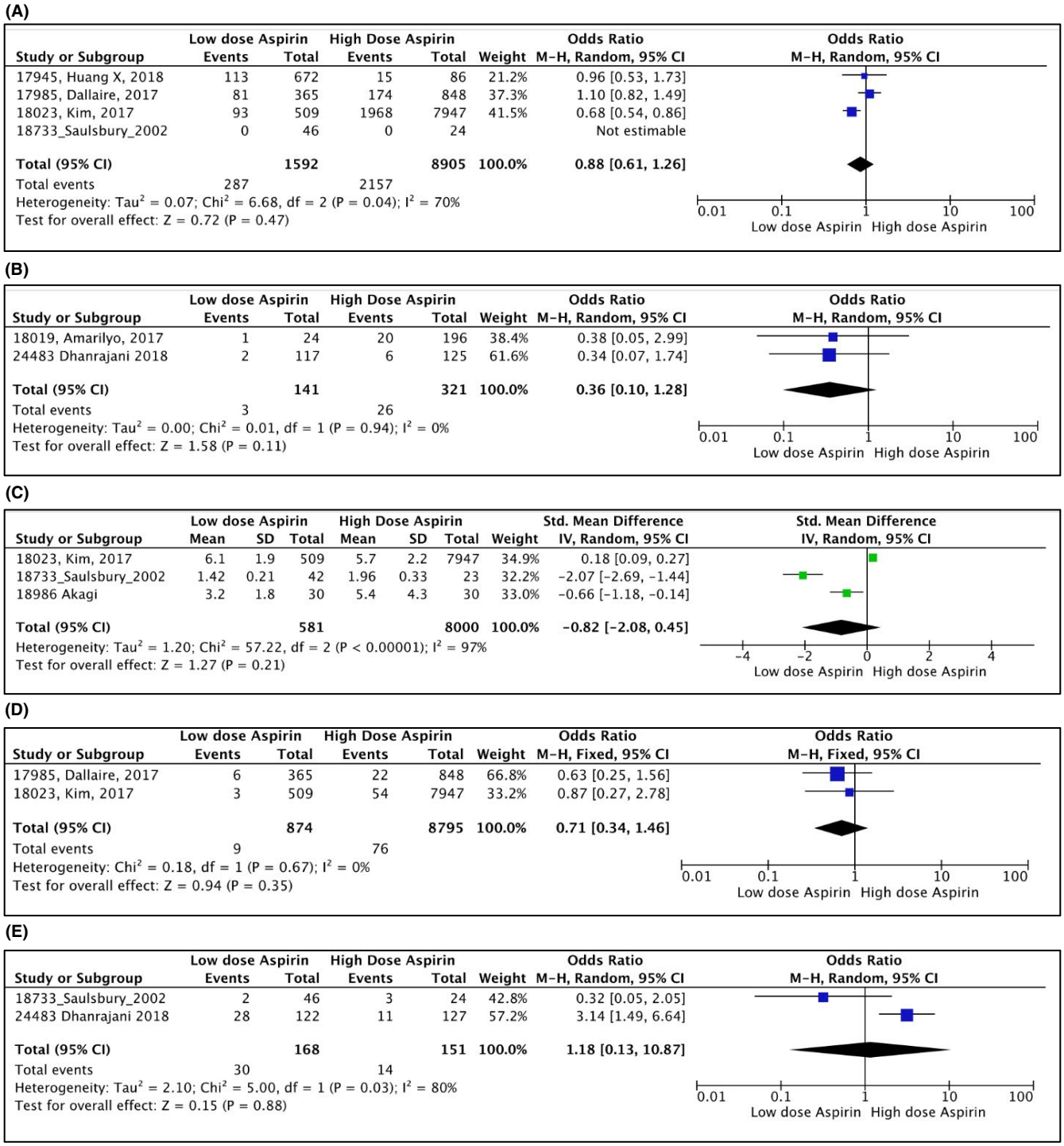


Figure 3. Forest plot of studies evaluating low-dose aspirin versus higher-dose (moderate- or high-dose aspirin) aspirin during the acute phase of Kawasaki disease (KD) for the following outcomes: any coronary abnormality at any time (**A**), coronary artery aneurysm at any time point (**B**), duration of fevers (as standard mean difference) (**C**), giant aneurysm (**D**), and refractory disease (requiring retreatment for either initial nonresponse or recurrence of fever) (**E**). CI, confidence interval.

(28,29), and one used 2 mg/kg/day prednisolone with a 15-day taper (13). No statistically significant difference was seen in terms of clinical response to therapy, failure to respond to rescue therapy, and coronary artery aneurysm at one month. The quality of evidence was low (Supplementary Table 2) [13,27,28,30].

GCs and non-GC immunosuppressives versus GCs alone in treatment of disease refractory to initial IVIG. One case-control study of KD with and without giant coronary artery aneurysms directly addressed this question. Of the 318 needing second-line therapy, 22 received GCs alone (six with

giant aneurysms) and 68 received GCs and IVIG (25 with giant aneurysms), giving an OR of 1.55 (95% CI: 0.54-4.47) of having received GCs and IVIG versus GCs alone (31).

Several case series as well as RCTs on initial therapy report outcomes of refractory disease with a variety of treatments, including GC, IVIG, cyclosporine, and infliximab, alone or in combination with GCs and/or IVIG (Supplementary Appendix 3). Unfortunately, in these case series, many of the patients had failed multiple courses of IVIG and/or other non-GC immunosuppressive agents prior to going on to receive GCs alone or GC and additional non-GC immunosuppressive agents, leaving a lack of standardization of initial therapy that may have affected outcomes. Outcomes of refractory patients were frequently combined regardless of treatments. Furthermore, many studies noted patients having coronary artery abnormalities before starting second-line treatments without then differentiating how many were new coronary abnormalities after the second-line treatment, making it difficult to assess outcomes relative to treatment (32–38).

ASA in acute disease management. ASA has been a mainstay of treatment for acute KD management for decades, so there is little data comparing ASA with no ASA in combination with the current standard of care IVIG as first-line therapy. One observational study addressed this by prospectively giving all patients meeting criteria for KD over a 1-year period IVIG without ASA during the acute phase, followed by low-dose ASA (3-5 mg/kg/day) after defervescence and compared them with a historical control that received high-dose ASA (80-100 mg/kg/day) during the acute phase followed by low-dose ASA in addition to IVIG. They identified no statistically significant difference in terms of duration of fever, incidence of coronary artery lesions at 4 weeks or at any point, and response to IVIG (39). Another retrospective study looked at the ASA dose during the acute phase, with three groups (no ASA, low-dose ASA, and moderate-dose ASA [30-50 mg/kg/day]) and dosing decisions based on the degree of inflammation and physician choice, introducing a significant risk for bias. There was no difference in risk for coronary artery lesions between any of the three dosing regimens. Combined, there was no difference in the incidence of coronary artery lesions (40) (Supplemental Table 3).

Several observational studies compared low-, moderate-, and/or high-dose ASA (40–46). In a meta-analysis of these studies, no difference was seen comparing low-dose ASA with higher-dose ASA (moderate or high dose) in terms of developing any coronary abnormality at any point, coronary artery aneurysm in the subacute phase, giant aneurysm, total duration of fever, or needing second-line treatment; however, the quality of evidence for this is low (Figure 3 and Supplemental Table 3).

Anticoagulation therapy and non-ASA antiplatelet agents in patients with coronary artery aneurysms. One observational study evaluated the use of dalteparin in combination with IVIG and ASA during the acute phase of KD and compared these patients with patients in historical controls. They found a lower risk of coronary artery lesions within the first month (OR: 0.34; 95% CIL 0.17-0.66) (low certainty of evidence) and decreased odds of needing additional treatment for refractory disease (OR: 0.48; 95% CI: 0.30-0.76) (low certainty of evidence). There was no statistically significant difference in the odds of having a coronary artery lesion persist longer than 1 month when pooling their two cohorts (OR: 0.21; 95% CI: 0.04-1.03) (low certainty of evidence) (47) (Tables 2 and 3).

Levy et al retrospectively reviewed a cohort of 22 patients with KD and giant coronary artery aneurysms, looking at outcomes relative to use of various combinations of ASA, warfarin, and dipyridamole. Three subjects had myocardial infarctions, including one receiving warfarin alone, one receiving warfarin and ASA, and one receiving warfarin, ASA, and dipyridamole. One subject receiving warfarin alone suffered a stroke (12).

When pooling coronary artery outcomes from these two studies, there were fewer patients with coronary artery lesions at 1 month (OR: 0.34; 95% CI: 0.17-0.66) (low certainty of evidence) and with refractory disease (OR: 0.48; 5% CI: 0.30-0.76) (low certainty of evidence) in those given anticoagulation. However, there was no statistically significant difference in the number of patients having a persistent coronary artery lesion (OR: 0.21; 95% CI: 0.04-1.03) (low certainty of evidence) (Tables 2 and 3).

Treatment before or after Day 10 in patients with suspected incomplete KD and fever for more than 5 days. No studies directly addressed this question specifically for incomplete KD. However, there are several studies that demonstrate that outcomes are improved when IVIG is administered before Day 10 of illness. These studies generally compared patients with delayed diagnosis (and therefore delayed treatment) with those with prompt treatment and found worse outcomes in those with delayed diagnosis. They also noted higher proportions of incomplete disease in the delayed diagnosis arm (5,48–50).

IVIG and GCs or anakinra versus IVIG alone in KD with features of MAS. No comparative studies were found to address this question. There was a very limited number of case series with more than 10 patients reporting on outcomes of patients with KD and MAS, for a total of 32 patients. There was a broad range of treatments used, with many patients receiving multiple courses of IVIG and/or GCs and some also receiving etoposide and/or cyclosporine in varying orders. The limited number of cases and the broad spread of treatment regimens make it difficult to draw any conclusions on optimal treatment (51–53).

Daily monitoring of fevers following defervescence and discharge. A post hoc analysis of the RCT by Tremoulet et al of IVIG versus IVIG and infliximab reported on fever patterns after IVIG treatment. Families were instructed to check temperatures

Table 2. Grading of evidence addressing the question of the impact of treating with anticoagulation versus no anticoagulation

Certainty assessment							№ of patients		Effect		
Number of studies	Study Design	Risk of Bias	Inconsistency	Indirectness	Imprecision	Other Considerations	Anticoagulation	No Anticoagulation	Relative (95% CI)	Absolute (95% CI)	Certainty
Coronary artery lesion at 1 month											
One (47)	Observational study	Not serious	Not serious	Not serious	Not serious	None	9/238 (3.8%)	4490/44 205 (10.2%)	**OR: 0.34** (0.17-0.66)	**65 fewer per 1000** (from 83 fewer to 32 fewer)	⊕⊕○○ Low
Refractory disease (additional treatment needed)											
One (47)	Observational study	Not serious	Not serious	Not serious	Not serious	None	19/238 (8.0%)	6909/44 205 (15.6%)	**OR: 0.48** (0.30-0.76)	**75 fewer per 1000** (from 104 fewer to 33 fewer)	⊕⊕○○ Low
Persistent coronary artery lesion											
One (47)	Observational study	Not serious	Not serious	Not serious	Serious[a]	Strong association	1/238 (0.4%)	1468/44 205 (3.3%)	**OR: 0.21** (0.04-1.03)	**26 fewer per 1000** (from 32 fewer to 1 more)	⊕⊕○○ Low

Abbreviation: CI, confidence interval; OR, odds ratio.

Table 3. Grading of evidence addressing the question of the impact of treatment with nonaspirin antiplatelet agents versus treatment with aspirin

Certainty assessment							№ of patients		Effect		
Number of Studies	Study Design	Risk of Bias	Inconsistency	Indirectness	Imprecision	Other Considerations	Treatment With Antiplatelet Agents Apart From Aspirin	Aspirin Alone	Relative (95% CI)	Absolute (95% CI)	Certainty
Myocardial ischemia											
One (12)	Observational study	Serious[a]	Not serious	not serious	very serious[b]	none	1/5 (20.0%)	3/17 (17.6%)	**OR: 1.17** (0.09-14.52)	**24 more per 1000** (from 158 fewer to 580 more)	⊕○○○ Very low
Stroke											
One (12)	Observational study	Serious[a]	Not serious	not serious	very serious[b]	none	0/5 (0.0%)	1/17 (5.9%)	**OR: 1.00** (0.04-28.30)	**0 fewer per 1000** (from 56 fewer to 580 more)	⊕○○○ Very low
Coronary stenosis											
One (12)	Observational study	Serious[a]	Not serious	Not serious	Very serious[b]	Strong association	2/5 (40.0%)	3/17 (17.6%)	**OR: 3.11** (0.35-27.55)	**223 more per 1000** (from 107 fewer to 679 more)	⊕○○○ Very low

Abbreviation: CI, confidence interval; OR, odds ratio.
[a] The choice for dipyridamole versus no dipyridamole was left entirely to the discretion of treating physician, so was likely influenced by disease severity factors. There was variable follow-up (minimum 1 year), which likely is not long enough to observe ischemic events.
[b] Clinical action would differ if the upper boundary versus the lower boundary of the CI represented the truth.

once daily for 72 hours after discharge. Of the 51/190 subjects with coronary artery abnormalities, 43/51 were found on baseline echocardiogram, making it difficult to perform any statistical analysis relative to fever timing. Four patients were readmitted after discharge because of a recurrence of fever (23,54). There were otherwise no data focusing on routine temperature checks after discharge.

Other PICO questions. No studies were identified that directly addressed the following issues: nonsteroidal anti-inflammatory drugs in KD-associated arthritis, echocardiography by Day 10 in suspected incomplete KD, unexplained shock physiology, and unexplained MAS.

DISCUSSION

This review presents a summary of available studies on the benefits and harms of treatments on outcomes in KD. This review has several strengths. The comprehensive and systematic approach for identifying studies makes it unlikely that relevant studies were missed. Additionally, we assessed the certainty of evidence in this area and identified sources of bias. We noted a few limitations in this comprehensive systematic review. We limited our review by English language. Meta-analysis of the data collected was somewhat limited for coronary artery abnormalities because of the wide range in how these outcomes were reported.

There have been several large-scale RCTs of treatment in KD, focused largely on intensification of initial treatment to improve outcomes, particularly in high-risk populations. Overall, there is low to moderate certainty that the use of GCs in addition to IVIG as initial therapy for high-risk KD improves treatment response, decreases fever duration, and improves coronary artery outcomes in high-risk patients)and potentially in non–high-risk patients). Of note, the RCTs that focused specifically on high-risk populations were conducted in Japanese populations, and all saw beneficial effects of the additional GCs, regardless of dose (16,25). The post hoc analysis of high-risk populations from an RCT performed in a North American cohort showed no benefit of adding GCs regardless of the risk scoring system used. Although this could reflect a lack of efficacy in North American populations, it may also reflect of the poor performance of scoring systems to predict high-risk disease in Western populations (21,55–57).

This review also demonstrated that, although ASA remains a mainstay of treatment, the dose used during the acute phase of illness remains controversial. ASA use at anti-inflammatory doses began in the pre-IVIG era, and ASA has continued to be used in addition to IVIG despite a lack of clear evidence that there is an added anti-inflammatory benefit in addition to the effect provided by IVIG (39,46,58). The American Heart Association currently recommends high-dose ASA (80-100 mg/kg/day) during the acute phase of KD until patients are afebrile (59). Conversely, in Japan, the standard is to use moderate-dose ASA (30-50 mg/kg/day) (60). Some centers reported using low-dose ASA as their standard of care (41). Although a meta-analysis of the data suggested no difference between using low-dose ASA versus moderate- or high-dose ASA, this was limited to comparative observational data. Although further evidence is needed to evaluate dose, it is likely reasonable to not use high-dose ASA in KD.

There were limited data evaluating the efficacy of treatment for MAS associated with KD. As this is a potentially life-threatening complication, further studies are warranted to evaluate optimal treatment for this. There was also a paucity of data on long-term outcomes in KD relative to treatment. Coronary artery abnormalities are potentially a surrogate marker for risk for myocardial ischemia and death. Small coronary artery aneurysms may regress and return to normal arterial luminal contour following the acute phase, whereas others persist and may progress to stenosis. Progressive aneurysms carry a risk for thrombosis and myocardial ischemia, but even patients with regressed aneurysms may be at risk (61,62). Anticoagulation and non-ASA antiplatelet agents may be used in KD, particularly in those with aneurysms; however, there was little evidence on the effect on longer-term outcomes.

Very recent developments indicate the emergence of a post–coronavirus disease 2019 (COVID-19) inflammatory syndrome, which may have resemblance to KD, named multisystem inflammatory syndrome associated with COVID-19 (63,64). Evolving data suggest that as many as 50% of these patients, who are predominantly pediatric, could qualify as meeting criteria for KD. However, many of these patients demonstrate unusual extracardiac features of colitis and neurologic changes and often present or deteriorate into a shock phenotype. This new syndrome is not believed to be KD but may have similar underlying features. Based on similarities with KD, many patients are currently being treated with IVIG and GCs. As further data emerge, future comprehensive studies will need to be undertaken to learn the most appropriate treatment modalities for these patients.

This systematic review evaluates the risks and benefits of treatment options for KD in different clinical situations. These results were used to inform the ACR/VF Vasculitis Management Guidelines for KD.

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AUTHOR CONTRIBUTIONS

All authors were involved in drafting the article or revising it critically for important intellectual content, and all authors approved the final version to be published. Drs. Kalot, James and Mustafa had full access to all of the

data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Study conception and design. Kalot, Mustafa, Husainat.

Acquisition of data. James, Dua, Byram, Springer, Lin, Villa-Forte, Turgunbaev.

Analysis and interpretation of data. Kalot, Husainat, James, Dua, Springer, Lin, Villa-Forte, Gorelik, Abril, Langford, Maz, Chung, Mustafa.

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