**SUPPLEMENTARY APPENDIX 2: Evidence Report**

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

# Kawasaki Disease (KD)

### Treatment

- **PICO question 1:** In patients with incomplete KD with unexplained fever ≥7 days, what is the impact of treatment with IVIG therapy before day 10 vs. after day 10 on the development of disease-related outcomes and treatment-related adverse events?

- **Critical Outcomes:** coronary artery abnormalities, myocardial infarction, relapse, serious adverse events, toxicity leading to discontinuation of therapy (e.g., hemolysis, adverse reaction to IVIG, headache)

1. In patients with incomplete KD with unexplained fever ≥7 days, what is the impact of treatment with IVIG therapy before day 10 vs. after day 10 on the development of disease-related outcomes and treatment-related adverse events?

| 2. Certainty assessment | | | | | | | № of patients | | Effect | | Certainty | Importance |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| № of studies | Study design | Risk of bias | Inconsistency | Indirectness | Imprecision | Other considerations | treatment with IVIG therapy before day 10 | treatment with IVIG therapy after day 10 | Relative (95% CI) | Absolute (95% CI) | | |
| **coronary artery abnormality** | | | | | | | | | | | | |
| 1 | observational studies | not serious | not serious | not serious | very serious [a] | strong association | 7/8 (87.5%) | 9/35 (25.7%) | **OR 20.22** (2.18 to 187.72) | **618 more per 1,000** (from 173 more to 728 more) | ⨁◯◯◯ VERY LOW | |

**CI:** Confidence interval; **OR:** Odds ratio

## Explanations

a. Clinical action would differ if the upper versus the lower boundary of the CI represented the truth, leading to very serious imprecision

- **References:**

- Randomized controlled trials:

  None

- Comparative observational studies:

| Refid | Author | Year | Title |
|---|---|---|---|
| 18374 | Sittiwangkul | 2013 | Delayed diagnosis of Kawasaki disease: risk factors and outcome of treatment |

- Studies reviewed and excluded:

| Refid | Author | Title | Comments |
|---|---|---|---|
| 18015 | M. L. Downie, C. Manlhiot, T. H. Collins, N. Chahal | Factors associated with development of coronary artery aneurysms after Kawasaki disease are similar for those treated promptly and those with delayed or no treatment | They took all KD patients, not incomplete. They presented univariate analysis of factors associated with delayed treatment (incomplete disease being one of those). They then did two models looking at factors associated with coronary artery aneurysms |
| 18219 | A. K. Bal, D. Prasad, M. A. Umali Pamintuan | Timing of intravenous immunoglobulin treatment and risk of coronary artery abnormalities in children with Kawasaki disease | It has great models on outcomes on treatment < or> 10 days, but again, it is in the entire KD population, not those with incomplete disease. They do provide the proportion of patients with atypical KD, but they do not provide outcomes specific to that group, and incomplete disease is not even used in their final multivariate model |
| 17914 | H. Qiu, Y. He, X. Rong, Y. Ren | Delayed intravenous immunoglobulin treatment increased the risk of coronary artery lesions in children with Kawasaki disease at different status | It has great models on outcomes on treatment < or> 10 days, but again, it is in the entire KD population, not those with incomplete disease. They do provide the proportion of patients with atypical KD, but they do not provide outcomes specific to that group. |

# Kawasaki Disease (KD)

## Treatment

- **PICO question 2:** In patients with acute KD and features of macrophage activation syndrome (MAS), what is the impact of treatment with IVIG with glucocorticoids or anakinra vs. IVIG alone on the development of disease-related outcomes, treatment-related adverse events, and persistence of MAS?

- **Critical Outcomes:** persistent macrophage activation syndrome, coronary artery abnormalities, myocardial infarction, relapse, infection, serious adverse events, toxicity leading to discontinuation of therapy (e.g., hemolysis, adverse reaction to IVIG, headache)

3. In patients with acute KD and features of macrophage activation syndrome (MAS), what is the impact of treatment with IVIG with glucocorticoids or anakinra vs. IVIG alone on the development of disease-related outcomes, treatment-related adverse events, and persistence of MAS?
   No comparative data available

4. In patients with acute KD and features of macrophage activation syndrome (MAS), what is the impact of treatment with IVIG with glucocorticoids or anakinra on the development of disease-related outcomes, treatment-related adverse events, and persistence of MAS?
   - **Patient important outcomes:**

| Outcomes (Name + Summary) | Author, year, RefID | Study type | Duration of follow up | Population (number and description) | Intervention used in relevant population (Describe the intervention) | Results | Comments |
|---|---|---|---|---|---|---|---|
| Outcome 1 Death | 17906, Choi JE 2018 | Retrospective records review | Not stated | 8 subjects had incomplete KD (fever +2-3 clinical features) in association with MAS/HLH (5/8 criteria) | Received IVIG 2g/kg, 4 received a second dose for failure to respond, and one went on to receive additional remicade. Once developed MAS features, all subsequently received HLH2004 protocol (dexamethasone, etoposide, cyclosporine) | 2/8 died, both of whom only received IVIG to treat the KD followed by the HLH 2004 protocol- 1 died within 1 day the other 7 days from HLH diagnosis | |
| | 18231 | Retrospective records review of patients identified via survey of Korean society | Median follow up 45.1 months | 12 patients identified as having had KD with HLH | All initially treated with IVIG and aspirin (unknown doses) for their KD. When HLH developed, 2/12 received additional IVIG initially for | 2/12 died at days 10 and 14 after chemo both received HLH2004, 1 had resolution of MAS during 10 day stay, then lost to follow up (supportive | |

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|---|---|---|---|---|---|---|---|
| | | of pediatric heme-onc | | | recurrent KD. 1 received steroids and antibiotics for 5 days, 1 only supportive care and antibiotics, 8 received HLH2004 protocol, and 2 received HLH 1994 protocol | care, remaining 9 alive including one who received steroids alone alive at 36 months | |
| | 18429 2010 Latino GA | Retrospective chart review of single tertiary center | | 12 subjects with KD and MAS, 3 had incomplete KD | All received at least 1 dose of IVIG, 6 received 2 doses, and 2 received 3 doses. 11 received IVMP x3 days, 4 of whom received 2 3 day courses, 10 received oral pred or dex. 3 received cyclosporine.<br>1 subject received no steroids or cyclosporine, just 2 courses of IVIg.<br>Of those receiving steroids, 4 only got 1 course of IVIG | All survived regardless of treatments | It is unclear what treatments were done for refractory KD and what were done for MAS- most cases MAS was suspected within 1 day of KD diagnosis but was up to 13 days later (vaguely described) |
| Outcome 2 Coronary Artery Aneurysm any time | 18429 2010 Latino GA | Retrospective chart review of single tertiary center | | 12 subjects with KD and MAS, 3 had incomplete KD | All received at least 1 dose of IVIG, 6 received 2 doses, and 2 received 3 doses. 11 received IVMP x3 days, 4 of whom received 2 3 day courses, 10 received oral pred or dex. 3 received cyclosporine.<br>1 subject received no steroids or cyclosporine, just 2 courses of IVIg.<br>Of those receiving steroids, 4 only got 1 course of IVIG | 4/12 had mild coronary abnormalities at some point, 3 had received multiple IVIg and GC but no cyclosporine, one received 1 IVIG +GC, + cyclosporine | It is unclear what treatments were done for refractory KD and what were done for MAS- most cases MAS was suspected within 1 day of KD diagnosis but was up to 13 days later (vaguely described) |
| Outcome 3 Coronary artery aneurysm persistent | 18429 2010 Latino GA | Retrospective chart review of single tertiary center | | 12 subjects with KD and MAS, 3 had incomplete KD | All received at least 1 dose of IVIG, 6 received 2 doses, and 2 received 3 doses. 11 received IVMP x3 days, 4 of whom received 2 3 day courses, | No persistent abnormalities | It is unclear what treatments were done for refractory KD and what were done for MAS and their timing- most cases MAS was suspected |

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| | | | | | 10 received oral pred or dex. 3 received cyclosporine.<br>1 subject received no steroids or cyclosporine, just 2 courses of IVIg.<br>Of those receiving steroids, 4 only got 1 course of IVIG | | within 1 day of KD diagnosis but was up to 13 days later (vaguely described) |

5. In In patients with acute KD and features of macrophage activation syndrome (MAS), what is the impact of IVIG alone on the development of disease-related outcomes, treatment-related adverse events, and persistence of MAS?
   No single arm data available

- **References:**

- Randomized controlled trials:
  None

- Comparative observational studies:
  None

- Single arm studies and test accuracy studies:

| Refid | Author | Year | Title | Comments |
|---|---|---|---|---|
| 17906 | J. E. Choi, Y. Kwak, J. W. Huh, E. S. Yoo, K. H. Ryu, S. Sohn, Y. M. Hong | 2018 | Differentiation between incomplete Kawasaki disease and secondary hemophagocytic lymphohistiocytosis following Kawasaki disease using N-terminal pro-brain natriuretic peptide | Few MAS patients- all actually treated with HLH2004 chemo protocol for HLH, only outcome reported specifically in the HLH subset was death as article was focused on biomarker |
| 18231 | H. R. Kang, Y. H. Kwon, E. S. Yoo, K. H. Ryu, J. Y. Kim, H. S. Kim, H. M. Kim, Y. H. Lee | 2013 | Clinical characteristics of hemophagocytic lymphohistiocytosis following Kawasaki disease: differentiation from recurrent Kawasaki disease | |
| 18429 | G. A. Latino, C. Manlhiot, R. S. Yeung, N. Chahal, B. W. McCrindle | 2010 | Macrophage activation syndrome in the acute phase of Kawasaki disease | |

- Studies reviewed and excluded

| Refid | Author | Year | Title | Comments |
|---|---|---|---|---|
| 17903 | I. Kone-Paut, R. Cimaz, J. Herberg, O. Bates, A. Carbasse, J. P. Saulnier, M. C. Maggio, J. Anton, M. Piram | 2018 | The use of interleukin 1 receptor antagonist (anakinra) in Kawasaki disease: A retrospective cases series | Not abstracted, patients did not have features of MAS- article was on anakinra use in refractory KD. |
| 17963 | L. Ma, Y. Y. Zhang, H. G. Yu | 2018 | Clinical Manifestations of Kawasaki Disease Shock Syndrome | Not abstracted, this article was not on KD patients with MAS, it was on KD patients with KD shock syndrome, a different entity. 2/21 with KDSS did have MAS, however there is no data on specifically their treatments or outcomes-all got IVIG but unclear if any of these two got additional IVIg. 1 was identified as discontinuing aspirin due to GI bleed. |
| 18005 | J. E. Schuster, H. L. Palac, N. Innocentini, A. H. Rowley, L. T. Young, S. T. Shulman | 2017 | Hyponatremia Is a Feature of Kawasaki Disease Shock Syndrome: A Case-Control Study | Not abstracted, this article did not was not on KD patients with MAS, it was on KD patients with KD shock syndrome, a different entity. No identification of patients with MAS |
| 18124 | Y. J. Lin, M. C. Cheng, M. H. Lo, S. J. Chien | 2015 | Early Differentiation of Kawasaki Disease Shock Syndrome and Toxic Shock Syndrome in a Pediatric Intensive Care Unit | Could this be used for PICO additional 1? Not abstracted, this article did not was not on KD patients with MAS, it was on KD patients with KD shock syndrome, a different entity. No identification of patients with MAS |
| 22887 | Z. Górnicka-Banach M. Szymanowska Z. Turowska-Heydel D. Sobczyk M. Rutkowska-Sak L. Zuber | 2014 | The use of intravenous immunoglobulin in pediatric rheumatology | No patients with KD and MAS, only patients in article with MAS were systemic JIA patients. |

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# Kawasaki Disease (KD)

## Treatment

- **PICO question 3:** In patients with acute KD, what is the impact of initial treatment with glucocorticoids vs. IVIG on the development of disease-related outcomes and treatment-related adverse events?

- **Critical Outcomes:** coronary artery abnormalities, myocardial infarction, relapse, infection, serious adverse events, toxicity leading to discontinuation of therapy (e.g., hyperglycemia, hemolysis, adverse reaction to IVIG, headache)

6. In patients with acute KD, what is the impact of initial treatment with glucocorticoids vs. IVIG on the development of disease-related outcomes and treatment-related adverse events?
   No comparative data available

7. In patients with acute KD, what is the impact of initial treatment with glucocorticoids on the development of disease-related outcomes and treatment-related adverse events?

| Outcomes (Name + Summary) | Author, year, RefID | Study type | Duration of follow up | Population (number and description) | Intervention used in relevant population (Describe the intervention) | Results | Comments |
|---|---|---|---|---|---|---|---|
| Outcome 1 Coronary artery lesion at 1 month | 17914 | Retrospective study- record review | Variable, about ½ to 6 months, and 1/3 to 1 year | 930 patients with KD admitted to single center in China, included complete and incomplete KD per clinical definitions. 578 with 6 month follow up, 332 with 1 year follow up | All patients received IVIG, some early and some after day 10. Some of the patients were reported to have received steroids before diagnosis (and then subsequently went on to get IVIG) | Odds ratio 1.22, 95% CI 0.81, 1.84 | Using steroids before diagnosis as a surrogate for steroids alone as initial treatment, however it is important to note that all of these patients subsequently got IVIG as well |
| Outcome 2 Coronary artery lesion at 6 months | 17914 | Retrospective study- record review | Variable, about ½ to 6 months, and 1/3 to 1 year | 930 patients with KD admitted to single center in China, included complete and incomplete KD per clinical definitions. 578 with 6 month | All patients received IVIG, some early and some after day 10. Some of the patients were reported to have received steroids before diagnosis (and then subsequently went on to get IVIG) | Odds ratio 1.19, 95% CI 0.57, 2.46 | Using steroids before diagnosis as a surrogate for steroids alone as initial treatment, however it is important to note that all of these patients subsequently got IVIG as well |

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| | | | | follow up, 332 with 1 year follow up | | | |
| Outcome 3 Coronary artery lesion overall | 17914 | Retrospective study- record review | Variable, about ½ to 6 months, and 1/3 to 1 year | 930 patients with KD admitted to single center in China, included complete and incomplete KD per clinical definitions. 578 with 6 month follow up, 332 with 1 year follow up | All patients received IVIG, some early and some after day 10. Some of the patients were reported to have received steroids before diagnosis (and then subsequently went on to get IVIG) | Odds ratio 1.12, 95% CI 0.31, 4.06 | Using steroids before diagnosis as a surrogate for steroids alone as initial treatment, however it is important to note that all of these patients subsequently got IVIG as well |

8. In patients with acute KD, what is the impact of initial treatment with IVIG on the development of disease-related outcomes and treatment-related adverse events?

| Outcomes (Name + Summary) | Author, year, RefID | Study type | Duration of follow up | Population (number and description) | Intervention used in relevant population (Describe the intervention) | Results | Comments |
|---|---|---|---|---|---|---|---|
| Outcome1 Coronary Artery Abnormality at week 1-2 | 18568 | Randomized placebo controlled trial | Echoes done at baseline,1 week from enrollment (mean 7.8 days) and 5 weeks (mean 36.5 days0 | 199 patients with KD Must be between day 4 and 10 of illness (starting from day 1 of fever). Randomization stratified on center and age <=1 year old<br><br>101 received methylpred+IVIG, 98 received IVIG/ASA alone<br><br>17 were identified as | IVIG 2g/kg x1 + 80-100 mg/kg/day of ASA until 48 hours afebrile then 3-5 mg/kg/day, vs IVIg +ASA+30mg/kg methylpred x1 (not abstracted | 6/66 patients without abnormalities at baseline and 28/93 of all patients in the placebo arm developed abnormalities | Single arm of RCT |

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| | | | | likely to be IVIG resistance | | | |
| | 18717 | Randomized Control Trial | Not specified. 37/39 kids got echos at 2 weeks and 36/39 got 6 week echo (based on day of illness, not from treatment) | 41 patients with KD randomized to receive IVIG+ASA with or without IV methylpred<br>21 in IVIG alone group | IVIG 2 g/kg given over 10 hours, Aspirin 100 mg/kg/day.<br>The not abstracted group for this PICO also received 30 mg/kg IVmethylpred x1 | 2/21 had at least one coronary with a z score btw 2-3 and 1 with a z score of >3 | Single arm from RCT |
| Outcome 2 Coronary artery lesion at 4-6 weeks | 17914 | Retrospective study- record review | Variable, about ½ to 6 months, and 1/3 to 1 year | 930 patients with KD admitted to single center in China, included complete and incomplete KD per clinical definitions. 578 with 6 month follow up, 332 with 1 year follow up | All patients received IVIG, some early and some after day 10.<br>Some of the patients were reported to have received steroids before diagnosis (and then subsequently went on to get IVIG) | Odds ratio 1.22, 95% CI 0.81, 1.84 | Using steroids before diagnosis as a surrogate for steroids alone as initial treatment, however it is important to note that all of these patients subsequently got IVIG as well |
| | 18322 | Randomized open-label blind endpoints trial multicentre | Last echo at week 4 (from enrollment, not diagnosis) | 248 high risk KD patients (defined by Kobayashi score randomized to IVIG vs IVIg+ prednisolone. 121 received IVIG alone and included in analysis | IVIg 2g/kg over 24 hours, ASA 30 mg/kg/day until afebrile the 3-5 mg/kg/day | 15/120 (none of whom had an abnormality at baseline) | Single arm of an RCT |
| | 18340 | Randomized control trial | 1 month | 74 patients predicted to be IVIG responsive by egami score and 48 predicted to be | IVIg 2g/kg over 24 hours ASA 90mg/kg/d until 36 hours afebrile, then 5mg/kg/day | 10/26 high risk score patients on IVIG alone developed coronary artery with score of >2.5. this is not reported in those with | Single arm only |

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| | | | | IVIg non-responsive. The 48 high egami score patients were randomized to get IVIG+ ASA (26) vs IVIG+ASA+pulse methylpred+heparin (22). The 74 low risk received IVIG(68)+ASA(6) or ASA alone (not randomized, done as standard of care) | Data not abstracted for this on those receiving 30mg/kg methylpredx1 + heparin in addition to IVIG+ASA | low risk scores. All other coronary outcomes reported were z scores of various arteries | |
| | 18568 | Randomized placebo controlled trial | Echoes done at baseline,1 week from enrollment (mean 7.8 days) and 5 weeks (mean 36.5 days0 | 199 patients with KD Must be between day 4 and 10 of illness (starting from day 1 of fever). Randomization stratified on center and age <=1 year old<br><br>101 received methylpred+IVIG, 98 received IVIG/ASA alone<br><br>17 were identified as | IVIG 2g/kg x1 + 80-100 mg/kg/day of ASA until 48 hours afebrile then 3-5 mg/kg/day, vs IVIg +ASA+30mg/kg methylpred x1 (not abstracted | 5/67 patients without abnormalities at baseline and 18/95 of all patients in the placebo arm developed abnormalities | Single arm of RCT |

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|---|---|---|---|---|---|---|---|
| | | | | likely to be IVIG resistance | | | |
| | 18585 | Randomized control trial | Last echo at day 25-30 | 178 KD patients, 88 in the IVIG alone arm | IVIG (1g/kg/day x2) vs IVIG + Prednisolone (not included for this study)<br><br>All subjects received Aspirin 30mg/kg/day (decreased to 5 mg/kg/day after CRP normalized), all also received dipyridamole 2mg/kg/day. | 3/88 | Single arm from RCT |
| | 18717 | Randomized Control Trial | Not specified. 37/39 kids got echos at 2 weeks and 36/39 got 6 week echo (based on day of illness, not from treatment) | 41 patients with KD randomized to receive IVIG+ASA with or without IV methylpred<br>21 in IVIG alone group | IVIG 2 g/kg given over 10 hours, Aspirin 100 mg/kg/day.<br>The not abstracted group for this PICO also received 30 mg/kg IVmethylpred x1 | 1/21 had at least one coronary with a z score btw 2-3 and 0 with a z score of >3 | Single arm from RCT |
| Outcome 3 Coronary artery lesion at 6 months | 17914 | Retrospective study- record review | Variable, about ½ to 6 months, and 1/3 to 1 year | 930 patients with KD admitted to single center in China, included complete and incomplete KD per clinical definitions. 578 with 6 month follow up, 332 | All patients received IVIG, some early and some after day 10.<br>Some of the patients were reported to have received steroids before diagnosis (and then subsequently went on to get IVIG) | Odds ratio 1.19, 95% CI 0.57, 2.46 | Using steroids before diagnosis as a surrogate for steroids alone as initial treatment, however it is important to note that all of these patients subsequently got IVIG as well |

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| | | | | with 1 year follow up | | | |
| Outcome 4 Coronary artery Lesion at 1 year | 17914 | Retrospective study- record review | Variable, about ½ to 6 months, and 1/3 to 1 year | 930 patients with KD admitted to single center in China, included complete and incomplete KD per clinical definitions. 578 with 6 month follow up, 332 with 1 year follow up | All patients received IVIG, some early and some after day 10.<br>Some of the patients were reported to have received steroids before diagnosis (and then subsequently went on to get IVIG) | Odds ratio 1.12, 95% CI 0.31, 4.06 | Using steroids before diagnosis as a surrogate for steroids alone as initial treatment, however it is important to note that all of these patients subsequently got IVIG as well |
| Outcome 5 Coronary Artery aneurysm at any point | 18322 | Randomized open-label blind endpoints trial multicentre | Last echo at week 4 (from enrollment, not diagnosis) | 248 high risk KD patients (defined by Kobayashi score randomized to IVIG vs IVIg+ prednisolone. 121 received IVIG alone and included in analysis | IVIg 2g/kg over 24 hours, ASA 30 mg/kg/day until afebrile the 3-5 mg/kg/day | 28/121 (none of whom had an abnormality at baseline) | Single arm of an RCT |
| | 18585 | Randomized control trial | Last echo at day 25-30 | 178 KD patients, 88 in the IVIG alone arm | IVIG (1g/kg/day x2) vs IVIG + Prednisolone (not included for this study)<br><br>All subjects received Aspirin 30mg/kg/day (decreased to 5 mg/kg/day after CRP normalized), all also received dipyridamole 2mg/kg/day. | 10/88 | Single arm from RCT |
| | 23919 | Multicenter RCT | Echoes on enrollment, | 32 Kawasaki patients | IVIG 1g/kg/day x2 doses | 0/18 | Single arm of RCT |

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| | | | day 6-8 of illness, day 12-16 of illness, day 25-30 of illness | (complete KD), 18 got IVIG alone<br>All enrolled by day 9 of illness | Aspirin 30 mg/kg (not specified if this was total daily dose or doses TID) and dipyridamole 2mg/kg/d | | |
| Outcome 6 Refractory/Recurrent disease | 18322 | Randomized open-label blind endpoints trial multicentre | Last echo at week 4 (from enrollment, not diagnosis) | 248 high risk KD patients (defined by Kobayashi score randomized to IVIG vs IVIg+ prednisolone. 121 received IVIG alone and included in analysis | IVIg 2g/kg over 24 hours, ASA 30 mg/kg/day until afebrile the 3-5 mg/kg/day | 48/121 | Single arm of an RCT |
| | 18340 | Randomized control trial | 1 month | 74 patients predicted to be IVIG responsive by egami score and 48 predicted to be IVIg non-responsive. The 48 high egami score patients were randomized to get IVIG+ ASA (26) vs IVIG+ASA+pulse methylpred+heparin (22). The 74 low risk received IVIG(68)+ASA(6) or ASA alone (not randomized, done as standard of care) | IVIg 2g/kg over 24 hours ASA 90mg/kg/d until 36 hours afebrile, then 5mg/kg/day<br>Data not abstracted for this on those receiving 30mg/kg methylpredx1 + heparin in addition to IVIG+ASA | 6/68 predicted to be responders, and 20/26 predicted to be non-responders were resistant to the initial IVIG | Single arm only |
| | 18568 | Randomized placebo controlled trial | Echoes done at baseline,1 week from enrollment | 199 patients with KD Must be between day 4 and 10 of | IVIG 2g/kg x1 + 80-100 mg/kg/day of ASA until 48 hours afebrile then 3-5 mg/kg/day, vs IVIg | 15/97 were retreated with IVIG | Single arm of RCT |

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| | | | (mean 7.8 days) and 5 weeks (mean 36.5 days0 | illness (starting from day 1 of fever). Randomization stratified on center and age <=1 year old<br><br>101 received methylpred+IVIG, 98 received IVIG/ASA alone<br><br>17 were identified as likely to be IVIG resistance | +ASA+30mg/kg methylpred x1 (not abstracted | | |
| | 18585 | Randomized control trial | Last echo at day 25-30 | 178 KD patients, 88 in the IVIG alone arm | IVIG (1g/kg/day x2) vs IVIG + Prednisolone (not included for this study)<br><br>All subjects received Aspirin 30mg/kg/day (decreased to 5 mg/kg/day after CRP normalized), all also received dipyridamole 2mg/kg/day. | 16/88 | Single arm from RCT |

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|---|---|---|---|---|---|---|---|
| | 18717 | Randomized Control Trial | Not specified. 37/39 kids got echos at 2 weeks and 36/39 got 6 week echo (based on day of illness, not from treatment) | 41 patients with KD randomized to receive IVIG+ASA with or without IV methylpred<br>21 in IVIG alone group | IVIG 2 g/kg given over 10 hours, Aspirin 100 mg/kg/day.<br>The not abstracted group for this PICO also received 30 mg/kg IV methylpred x1 | 5/21 | Single arm from RCT |
| Outcome 7 Serious adverse events | 18322 | Randomized open-label blind endpoints trial multicentre | Last echo at week 4 (from enrollment, not diagnosis) | 248 high risk KD patients (defined by Kobayashi score randomized to IVIG vs IVIg+ prednisolone. 121 received IVIG alone and included in analysis | IVIg 2g/kg over 24 hours, ASA 30 mg/kg/day until afebrile the 3-5 mg/kg/day | 2/121 | Single arm of an RCT<br>Adverse events were high total cholesterol and a non-occlusive thrombus in left coronary, both events resolved spontaneously |
| | 18568 | Randomized placebo controlled trial | Echoes done at baseline,1 week from enrollment (mean 7.8 days) and 5 weeks (mean 36.5 days0 | 199 patients with KD Must be between day 4 and 10 of illness (starting from day 1 of fever). Randomization stratified on center and age <=1 year old<br><br>101 received methylpred+IVIG, 98 received IVIG/ASA alone | IVIG 2g/kg x1 + 80-100 mg/kg/day of ASA until 48 hours afebrile then 3-5 mg/kg/day, vs IVIg +ASA+30mg/kg methylpred x1 (not abstracted | 2/97 had serious adverse events- possible nonocclusive thrombus in the right coronary and anaphylaxis to IVIG. 22/97 had an adverse event | Single arm of RCT |

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| | | | | 17 were identified as likely to be IVIG resistance | | | |
| | 18585 | Randomized control trial | Last echo at day 25-30 | 178 KD patients, 88 in the IVIG alone arm | IVIG (1g/kg/day x2) vs IVIG + Prednisolone (not included for this study)<br><br>All subjects received Aspirin 30mg/kg/day (decreased to 5 mg/kg/day after CRP normalized), all also received dipyridamole 2mg/kg/day. | 1/88- shock developed shortly after IVIg administration | Single arm from RCT |
| Outcome 8 Duration of Fevers | 18322 | Randomized open-label blind endpoints trial multicentre | Last echo at week 4 (from enrollment, not diagnosis) | 248 high risk KD patients (defined by Kobayashi score randomized to IVIG vs IVIg+ prednisolone. 121 received IVIG alone and included in analysis | IVIg 2g/kg over 24 hours, ASA 30 mg/kg/day until afebrile the 3-5 mg/kg/day | Median 2 days, IQR 1,4 | Single arm of an RCT |
| | 18340 | Randomized control trial | 1 month | 74 patients predicted to be IVIG responsive by egami score and 48 predicted to be IVIg non-responsive. The 48 high egami | IVIg 2g/kg over 24 hours ASA 90mg/kg/d until 36 hours afebrile, then 5mg/kg/day<br>Data not abstracted for this on those receiving 30mg/kg methylpredx1 + heparin in addition to IVIG+ASA. | Duration of fevers (days after initial treatment) in those predicted to be IVIG resistant was a median of 7 days +/-3.3 days (this is how it reports the IQR) | Single arm only of RCT<br>There is no mention of additional therapies given after failing first line- this duration of fever post initial treatment is quite long if someone were to get additional treatments and |

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| | | | | score patients were randomized to get IVIG+ ASA (26) vs IVIG+ASA+pulse methylpred+heparin (22). The 74 low risk received IVIG(68)+ASA(6) or ASA alone (not randomized, done as standard of care) | | | makes me wonder if no additional treatments were given |
| | 18568 | Randomized placebo controlled trial | Echoes done at baseline,1 week from enrollment (mean 7.8 days) and 5 weeks (mean 36.5 days0 | 199 patients with KD Must be between day 4 and 10 of illness (starting from day 1 of fever). Randomization stratified on center and age <=1 year old<br><br>101 received methylpred+IVIG, 98 received IVIG/ASA alone<br><br>17 were identified as likely to be IVIG resistance | IVIG 2g/kg x1 + 80-100 mg/kg/day of ASA until 48 hours afebrile then 3-5 mg/kg/day, vs IVIg +ASA+30mg/kg methylpred x1 (not abstracted | Median 1 day (IQR 0-1) from randomization | Single arm of RCT |

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| | 18585 | Randomized control trial | Last echo at day 25-30 | 178 KD patients, 88 in the IVIG alone arm | IVIG (1g/kg/day x2) vs IVIG + Prednisolone (not included for this study)<br><br>All subjects received Aspirin 30mg/kg/day (decreased to 5 mg/kg/day after CRP normalized), all also received dipyridamole 2mg/kg/day. | Median 1 day, range 0-15, Mean 1.5, SD 1.0. Does not state if this was from start of first treatment or completion of first treatment. | Single arm from RCT |
| | 18717 | Randomized Control Trial | Not specified. 37/39 kids got echos at 2 weeks and 36/39 got 6 week echo (based on day of illness, not from treatment) | 41 patients with KD randomized to receive IVIG+ASA with or without IV methylpred<br>21 in IVIG alone group | IVIG 2 g/kg given over 10 hours, Aspirin 100 mg/kg/day.<br>The not abstracted group for this PICO also received 30 mg/kg IV methylpred x1 | 2 days from initiation of fever (range 0-8 days) | Single arm from RCT |
| | 23919 | Multicenter RCT | Echoes on enrollment, day 6-8 of illness, day 12-16 of illness, day 25-30 of illness | 32 Kawasaki patients (complete KD), 18 got IVIG alone<br>All enrolled by day 9 of illness | IVIG 1g/kg/day x2 doses<br>Aspirin 30 mg/kg (not specified if this was total daily dose or doses TID) and dipyridamole 2mg/kg/d | 2.9+/-2.4 days (presumably mean and standard deviation, but not explicitly stated) | Single arm of RCT |

- **References:**

- Randomized controlled trials:

  None

- Comparative observational studies:
  None

- Single arm studies:

| Refid | Author | Year | Title |
|---|---|---|---|
| 17914 | Qiu | 2018 | Delayed intravenous immunoglobulin treatment increased the risk of coronary artery lesions in children with Kawasaki disease at different status |
| 18322 | T. Kobayashi | 2012 | Efficacy of immunoglobulin plus prednisolone for prevention of coronary artery abnormalities in severe Kawasaki disease (RAISE study): a randomised, open-label, blinded-endpoints trial |
| 18340 | S. Ogata | 2012 | Corticosteroid pulse combination therapy for refractory Kawasaki disease: a randomized trial |
| 18568 | J. W. Newburger | 2007 | Randomized trial of pulsed corticosteroid therapy for primary treatment of Kawasaki disease |
| 18585 | Y. Inoue | 2006 | A multicenter prospective randomized trial of corticosteroids in primary therapy for Kawasaki disease: clinical course and coronary artery outcome |
| 18717 | R. P. Sundel | 2003 | Corticosteroids in the initial treatment of Kawasaki disease: report of a randomized trial |
| 23919 | Okada | 2003 | Effect of corticosteroids in addition to intravenous gamma globulin therapy on serum cytokine levels in the acute phase of Kawasaki disease in children |
| 18322 | T. Kobayashi | 2012 | Efficacy of immunoglobulin plus prednisolone for prevention of coronary artery abnormalities in severe Kawasaki disease (RAISE study): a randomised, open-label, blinded-endpoints trial |

# Kawasaki Disease (KD)

## Treatment

- **PICO question 4:** In patients with acute KD with high risk scores, what is the impact of initial treatment with IVIG and glucocorticoids vs. IVIG alone on the development of disease-related outcomes and treatment-related adverse events?

- **Critical Outcomes:** coronary artery abnormalities, myocardial infarction, relapse, infection, serious adverse events, toxicity leading to discontinuation of therapy (e.g., hyperglycemia, hemolysis, adverse reaction to IVIG, headache)

9. In patients with acute KD with high risk scores, what is the impact of initial treatment with IVIG and glucocorticoids vs. IVIG alone on the development of disease-related outcomes and treatment-related adverse events?

| 10. Certainty assessment | | | | | | | № of patients | | Effect | | Certainty | Importance |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| № of studies | Study design | Risk of bias | Inconsistency | Indirectness | Imprecision | Other considerations | initial treatment with IVIG and glucocorticoids | IVIG alone | Relative (95% CI) | Absolute (95% CI) | | |
| **Any coronary abnormality (any point), none at baseline** | | | | | | | | | | | | |
| 2 [1,2] | randomised trials | serious [a] | not serious | not serious | serious [b] | none | 4/135 (3.0%) | 28/139 (20.1%) | **OR 0.11** (0.04 to 0.34) | **174 fewer per 1,000** (from 191 fewer to 122 fewer) | ⨁⨁◯◯ LOW | |
| **Any coronary Abnormality week 4-6, none at baseline** | | | | | | | | | | | | |
| 2 [1,3] | randomised trials | serious [a] | not serious | not serious | serious [b] | none | 5/137 (3.6%) | 16/139 (11.5%) | **OR 0.30** (0.10 to 0.85) | **78 fewer per 1,000** (from 102 fewer to 16 fewer) | ⨁⨁◯◯ LOW | |
| **Serious Adverse Events** | | | | | | | | | | | | |
| 3 [1,4,5] | randomised trials | serious [a] | not serious | not serious | very serious [b] | none | 6/233 (2.6%) | 3/235 (1.3%) | **OR 2.00** (0.49 to 8.27) | **12 more per 1,000** (from 6 fewer to 84 more) | ⨁◯◯◯ VERY LOW | |
| **duration of fevers** | | | | | | | | | | | | |
| 6 [1,2,3,4,5,6] | randomised trials | serious [a] | not serious | not serious | serious [b] | none | 366 | 371 | - | SMD **0.97 lower** (1.64 lower to 0.31 lower) | ⨁⨁◯◯ LOW | |
| **Duration of hospital stay** | | | | | | | | | | | | |
| 1 [3] | randomised trials | serious [a] | not serious | not serious | serious [b] | none | 18 | 21 | - | MD **1.4 lower** (2.35 lower to 0.45 lower) | ⨁⨁◯◯ LOW | |

| 10. Certainty assessment | | | | | | | № of patients | | Effect | | Certainty | Importance |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| № of studies | Study design | Risk of bias | Inconsistency | Indirectness | Imprecision | Other considerations | initial treatment with IVIG and glucocorticoids | IVIG alone | Relative (95% CI) | Absolute (95% CI) | | |
| **complete regression of aneurysm** | | | | | | | | | | | | |
| 1 [7] | observational studies | not serious | not serious | not serious | serious [b] | none | 24/30 (80.0%) | 26/33 (78.8%) | **OR 1.08** (0.32 to 3.66) | **13 more per 1,000** (from 245 fewer to 144 more) | ⨁◯◯◯ VERY LOW | |
| **Refractory disease (requiring additional treatment)** | | | | | | | | | | | | |
| 1 [8] | observational studies | not serious | not serious | not serious | not serious | strong association | 132/724 (18.2%) | 59/147 (40.1%) | **OR 0.33** (0.23 to 0.49) | **220 fewer per 1,000** (from 268 fewer to 154 fewer) | ⨁⨁⨁◯ MODERATE | |
| **Serious Adverse Events - 2 mg/kg prednisolone high risk KD** | | | | | | | | | | | | |
| 1 [8] | observational studies | not serious | not serious | not serious | very serious [b] | strong association | 12/724 (1.7%) | 0/147 (0.0%) | **OR 5.18** (0.30 to 87.90) | **0 fewer per 1,000** (from 0 fewer to 0 fewer) | ⨁◯◯◯ VERY LOW | |

**CI:** Confidence interval; **OR:** Odds ratio; **SMD:** Standardised mean difference; **MD:** Mean difference

## Explanations

a. Patients and treating providers were not blinded in some studies, Patients and investigators not blinded to treatment in some studies

b. Clinical action would differ if the upper versus the lower boundary of the CI represented the truth

## References


1. Kobayashi, . . 2013.

2. Okada, . . 2003.

3. Sundel, . . 2003.

4. Ogata, . . 2012.

5. Inoue, . . 2006.

6. Newburger, . . 2007.

7. Dionne, . . 2019.

8. Miyata, . . 2018.

- **References:**

- Randomized controlled trials:

| Refid | Author | Year | Title |
|---|---|---|---|
| 18322 | T. Kobayashi | 2012 | Efficacy of immunoglobulin plus prednisolone for prevention of coronary artery abnormalities in severe Kawasaki disease (RAISE study): a randomised, open-label, blinded-endpoints trial |
| 18340 | S. Ogata | 2012 | Corticosteroid pulse combination therapy for refractory Kawasaki disease: a randomized trial |
| 18568 | J. W. Newburger | 2007 | Randomized trial of pulsed corticosteroid therapy for primary treatment of Kawasaki disease |
| 18585 | Y. Inoue | 2006 | A multicenter prospective randomized trial of corticosteroids in primary therapy for Kawasaki disease: clinical course and coronary artery outcome |
| 18717 | R. P. Sundel | 2003 | Corticosteroids in the initial treatment of Kawasaki disease: report of a randomized trial |
| 23919 | Okada | 2003 | Effect of corticosteroids in addition to intravenous gamma globulin therapy on serum cytokine levels in the acute phase of Kawasaki disease in children |
| 25062 | Dionne | 2019 | Treatment Intensification in Patients With Kawasaki Disease and Coronary Aneurysm at Diagnosis. |
| 18791 | Miyata | 2018 | Efficacy and safety of intravenous immunoglobulin plus prednisolone therapy in patients with Kawasaki disease (Post RAISE): a multicentre, prospective cohort study. |

# Kawasaki Disease (KD)

## Treatment

- **PICO question 5:** patients with acute KD with high risk scores, what is the impact of initial therapy with IVIG and other non-glucocorticoid immunosuppressive agents vs. IVIG alone on the development of disease-related outcomes and treatment-related adverse events?

- **Critical Outcomes:** coronary artery abnormalities, myocardial infarction, relapse, infection, malignancy, serious adverse events, toxicity leading to discontinuation of therapy (e.g., hemolysis, adverse reaction to IVIG, headache)

11. In patients with acute KD with high risk scores, what is the impact of initial therapy with IVIG and other non-glucocorticoid immunosuppressive agents vs. IVIG alone on the development of disease-related outcomes and treatment-related adverse events?
    - **Randomized controlled trials:**

| 12. Certainty assessment | | | | | | | № of patients | | Effect | | Certainty | Importance |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| № of studies | Study design | Risk of bias | Inconsistency | Indirectness | Imprecision | Other considerations | initial therapy with IVIG and other non-glucocorticoid immunosuppressive agents | IVIG alone | Relative (95% CI) | Absolute (95% CI) | | |
| **Duration of fever** | | | | | | | | | | | | |
| 2 [1,2] | randomised trials | not serious | not serious | not serious | very serious [a] | none | 138 | 136 | - | SMD **0.68 lower** (1.61 lower to 0.25 higher) | ⨁⨁◯◯ LOW | |
| **Treatment resistance** | | | | | | | | | | | | |
| 1 [2] | randomised trials | not serious | not serious | not serious | very serious [a] | none | 11/98 (11.2%) | 11/97 (11.3%) | **OR 0.99** (0.41 to 2.40) | **1 fewer per 1,000** (from 64 fewer to 121 more) | ⨁⨁◯◯ LOW | |
| **Any coronary abnormality** | | | | | | | | | | | | |
| 2 [1,2] | randomised trials | not serious | not serious | not serious | very serious [a] | none | 28/136 (20.6%) | 33/136 (24.3%) | **OR 0.85** (0.47 to 1.54) | **29 fewer per 1,000** (from 112 fewer to 88 more) | ⨁⨁◯◯ LOW | |
| **giant aneurysm** | | | | | | | | | | | | |
| 1 [2] | randomised trials | not serious | not serious | very serious [a] | very serious [a] | none | 1/96 (1.0%) | 1/97 (1.0%) | **OR 1.01** (0.06 to 16.39) | **0 fewer per 1,000** (from 10 fewer to 136 more) | ⨁◯◯◯ VERY LOW | |

| 12. Certainty assessment | | | | | | | № of patients | | Effect | | Certainty | Importance |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| № of studies | Study design | Risk of bias | Inconsistency | Indirectness | Imprecision | Other considerations | initial therapy with IVIG and other non-glucocorticoid immunosuppressive agents | IVIG alone | Relative (95% CI) | Absolute (95% CI) | | |
| **serious adverse events** | | | | | | | | | | | | |
| 1 [2] | randomised trials | not serious | not serious | not serious | very serious [a] | none | 23/98 (23.5%) | 22/98 (22.4%) | **OR 1.06** (0.54 to 2.06) | **10 more per 1,000** (from 89 fewer to 149 more) | ⨁⨁◯◯ LOW | |
| **IVIg infusion reaction** | | | | | | | | | | | | |
| 1 [2] | randomised trials | not serious | not serious | not serious | very serious [a] | none | 0/97 (0.0%) | 13/98 (13.3%) | **OR 0.03** (0.00 to 0.55) | **128 fewer per 1,000** (from 55 fewer to --) | ⨁⨁◯◯ LOW | |

**CI:** Confidence interval; **SMD:** Standardised mean difference; **OR:** Odds ratio

## Explanations

a. Clinical action would differ if the upper versus the lower boundary of the CI represented the truth

## References


1. Furukawa, . . 1994.

2. Tremoulet, . . 2014.


- **Observational studies:**

| - Certainty assessment | | | | | | | № of patients | | Effect | | Certainty | Importance |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| № of studies | Study design | Risk of bias | Inconsistency | Indirectness | Imprecision | Other considerations | initial therapy with IVIG and other non-glucocorticoid immunosuppressive agents | IVIG alone | Relative (95% CI) | Absolute (95% CI) | | |
| **complete regression of aneurysm** | | | | | | | | | | | | |
| 1 | observational studies | not serious | not serious | not serious | very serious [a] | none | 43/58 (74.1%) | 26/33 (78.8%) | **OR 0.77** (0.28 to 2.14) | **47 fewer per 1,000** (from 278 fewer to 100 more) | ⨁◯◯◯ VERY LOW | |
| **maximum coronary z score within 12 months of onset (worst z score)** | | | | | | | | | | | | |
| 1 | observational studies | not serious | not serious | not serious | very serious [a] | none | 30 | 33 | - | SMD **0.09 lower** (0.59 lower to 0.4 higher) | ⨁◯◯◯ VERY LOW | |
| **Giant aneurysm** | | | | | | | | | | | | |
| 1 | observational studies | not serious | not serious | not serious | very serious [a] | none | 5/58 (8.6%) | 4/33 (12.1%) | **OR 0.68** (0.17 to 2.75) | **35 fewer per 1,000** (from 98 fewer to 154 more) | ⨁◯◯◯ VERY LOW | |
| **Maximum increase in z score** | | | | | | | | | | | | |
| 1 | observational studies | not serious | not serious | not serious | very serious [a] | none | 58 | 33 | - | MD **1.2 lower** (2.08 lower to 0.32 lower) | ⨁◯◯◯ VERY LOW | |

**CI:** Confidence interval; **OR:** Odds ratio; **SMD:** Standardised mean difference; **MD:** Mean difference

## Explanations

a. Clinical action would differ if the upper versus the lower boundary of the CI represented the truth

- **References:**

- Randomized controlled trials:

| Refid | Author | Year | Title |
|---|---|---|---|
| 18222 | A. H. Tremoulet | 2014 | Infliximab for intensification of primary therapy for Kawasaki disease: a phase 3 randomised, double-blind, placebo-controlled trial |
| 18901 | S. Furukawa | 1994 | Pentoxifylline and intravenous gamma globulin combination therapy for acute Kawasaki disease |

- Comparative observational studies:

| Refid | Author | Year | Title |
|---|---|---|---|
| 25062 | Dionne | 2019 | Treatment Intensification in Patients With Kawasaki Disease and Coronary Aneurysm at Diagnosis |

# Kawasaki Disease (KD)

## Treatment

- **PICO question 6:** In patients with acute KD, what is the impact of treatment with any dose of aspirin vs. no aspirin on the development of disease-related outcomes and treatment-related adverse events?

- **Critical Outcomes:** coronary artery abnormalities, myocardial infarction, relapse, serious adverse events, toxicity leading to discontinuation of therapy (e.g., bleeding, renal dysfunction)

13. In patients with acute KD, what is the impact of treatment with any dose of aspirin vs. no aspirin on the development of disease-related outcomes and treatment-related adverse events?

| 14. Certainty assessment | | | | | | | № of patients | | Effect | | Certainty | Importance |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| № of studies | Study design | Risk of bias | Inconsistency | Indirectness | Imprecision | Other considerations | No Aspirin | Any dose of Aspirin | Relative (95% CI) | Absolute (95% CI) | | |
| Duration of Fever to IVIG | | | | | | | | | | | | |

| 14. Certainty assessment | | | | | | | № of patients | | Effect | | Certainty | Importance |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| № of studies | Study design | Risk of bias | Inconsistency | Indirectness | Imprecision | Other considerations | No Aspirin | Any dose of Aspirin | Relative (95% CI) | Absolute (95% CI) | | |
| 1 | observational studies | not serious | not serious | not serious | very serious [a] | none | 51 | 129 | - | MD **0.2 higher** (0.6 lower to 1 higher) | ⨁◯◯◯ VERY LOW | |

**Incidence of Coronary Artery Lesion**

| | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 1 | observational studies | not serious | not serious | not serious | very serious [a] | none | 2/51 (3.9%) | 10/129 (7.8%) | **OR 0.49** (0.10 to 2.30) | **38 fewer per 1,000** (from 69 fewer to 84 more) | ⨁◯◯◯ VERY LOW | |

**Response to IVIG**

| | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 1 | observational studies | not serious | not serious | not serious | very serious [a] | none | 43/51 (84.3%) | 107/129 (82.9%) | **OR 1.11** (0.46 to 2.67) | **14 more per 1,000** (from 138 fewer to 99 more) | ⨁◯◯◯ VERY LOW | |

**CI:** Confidence interval; **MD:** Mean difference; **OR:** Odds ratio

## Explanations

a. Clinical action would differ if the upper versus the lower boundary of the CI represented the truth

- **References:**

- Randomized controlled trials:

  None

- Comparative observational studies:

| Refid | Author | Year | Title |
|---|---|---|---|
| 18268 | G. Lee | 2013 | Is high-dose aspirin necessary in the acute phase of Kawasaki disease? |

# Kawasaki Disease (KD)

## Treatment

- **PICO question 7:** patients with acute KD, what is the impact of initial treatment with high-dose or moderate dose aspirin vs. low-dose aspirin on the development of disease-related outcomes and treatment-related adverse events?

- **Critical Outcomes:** coronary artery abnormalities, myocardial infarction, relapse, serious adverse events, toxicity leading to discontinuation of therapy (e.g., bleeding, renal dysfunction)

15. In patients with acute KD, what is the impact of initial treatment with high-dose or moderate dose aspirin vs. low-dose aspirin on the development of disease-related outcomes and treatment-related adverse events?

| Certainty assessment | | | | | | | № of patients | | Effect | | Certainty | Importance |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| № of studies | Study design | Risk of bias | Inconsistency | Indirectness | Imprecision | Other considerations | low-dose aspirin | high-dose or moderate dose aspirin | Relative (95% CI) | Absolute (95% CI) | | |
| **Any coronary abnormality** | | | | | | | | | | | | |
| 3 [1,2,3] | observational studies | not serious | not serious | not serious | serious [a] | none | 287/1546 (18.6%) | 2157/8881 (24.3%) | **OR 0.88** (0.61 to 1.26) | **23 fewer per 1,000** (from 79 fewer to 45 more) | ⨁◯◯◯ VERY LOW | |
| **coronary artery aneurysm subacute phase (6-8 weeks)** | | | | | | | | | | | | |
| 2 [4,5] | observational studies | not serious | not serious | not serious | serious [a] | strong association | 3/141 (2.1%) | 26/321 (8.1%) | **OR 0.36** (0.10 to 1.28) | **50 fewer per 1,000** (from 72 fewer to 20 more) | ⨁⨁◯◯ LOW | |
| **Giant Aneurysm** | | | | | | | | | | | | |
| 2 [2,3] | observational studies | not serious | not serious | not serious | serious [a] | none | 9/874 (1.0%) | 76/8795 (0.9%) | **OR 0.71** (0.34 to 1.46) | **2 fewer per 1,000** (from 6 fewer to 4 more) | ⨁◯◯◯ VERY LOW | |

| Certainty assessment | | | | | | | № of patients | | Effect | | Certainty | Importance |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| № of studies | Study design | Risk of bias | Inconsistency | Indirectness | Imprecision | Other considerations | low-dose aspirin | high-dose or moderate dose aspirin | Relative (95% CI) | Absolute (95% CI) | | |
| **Total Duration of Fever (D)** | | | | | | | | | | | | |
| 2 [3,6] | observational studies | not serious | not serious | not serious | serious [a] | none | 539 | 7977 | - | SMD **0.2 lower** (1.02 lower to 0.62 higher) | ⨁◯◯◯ VERY LOW | |
| **Refractory disease (requiring retreatment)** | | | | | | | | | | | | |
| 1 [5] | observational studies | not serious | not serious | not serious | serious [a] | strong association | 28/122 (23.0%) | 11/127 (8.7%) | **OR 3.14** (1.49 to 6.64) | **143 more per 1,000** (from 37 more to 300 more) | ⨁⨁◯◯ LOW | |

**CI:** Confidence interval; **OR:** Odds ratio; **SMD:** Standardised mean difference

## Explanations

a. Clinical action would differ if the upper versus the lower boundary of the CI represented the truth

## References


1. Huang, . 17945. 2018.

2. Dallaire, . 17985. 2017.

3. Kim, . 18023. 2017.

4. Amarilyo, . 18019. 2017.

5. Dhanjarani, . . 2018.

6. Akagi, . . 1990.


- **References:**

- Randomized controlled trials:

  None

- Comparative observational studies:

| Refid | Author | Year | Title |
|---|---|---|---|
| 18986 | T. Akagi | 1990 | A study on the optimal dose of aspirin therapy in Kawasaki disease--clinical evaluation and arachidonic acid metabolism |
| 24483 | A.Dhanrajani | 2018 | Aspirin Dose in Kawasaki Disease: The Ongoing Battle |
| 17985 | Dallaire | 2017 | Aspirin dose and prevention of coronary abnormalities in Kawasaki disease. |
| 18019 | Amarilyo G | 2017 | High-dose aspirin for Kawasaki disease: outdated myth or effective aid? |
| 18023 | Kim | 2017 | Medium- or higher-dose acetylsalicylic acid for acute Kawasaki disease and patient outcomes |
| 17945 | Huang X | 2018 | Is aspirin necessary in the acute phase of Kawasaki disease? |

- Comments:

| Author | Year | Title | Comments |
|---|---|---|---|
| Zheng | 2019 | Efficacy between low and high dose aspirin for the initial treatment of Kawasaki disease: Current evidence based on a meta-analysis. | Exclude – Meta analysis – Used for cross referencing |
| Migally | 2018 | Duration of high-dose aspirin therapy does not affect long-term coronary artery outcomes in Kawasaki disease | Does not compare dose but duration, exclude |
| Rahbarimanesh | 2014 | Comparison of high-dose versus low-dose aspirin in the management of Kawasaki disease | Exclude- Scientific letter, irrelevant study design. |

# Kawasaki Disease (KD)

## Treatment

- **PICO question 8:** In patients with KD and coronary artery aneurysms, what is the impact of treatment with anti-coagulation vs. no anti-coagulation on the development of disease-related outcomes and treatment-related adverse events?

- **Critical Outcomes:** myocardial infarction, death, serious adverse events, toxicity leading to discontinuation of therapy (e.g., hemorrhage)

16. In patients with KD and coronary artery aneurysms, what is the impact of treatment with anti-coagulation vs. no anti-coagulation on the development of disease-related outcomes and treatment-related adverse events?

| 17. Certainty assessment | | | | | | | № of patients | | Effect | | Certainty | Importance |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| № of studies | Study design | Risk of bias | Inconsistency | Indirectness | Imprecision | Other considerations | anti-coagulation | no anti-coagulation | Relative (95% CI) | Absolute (95% CI) | | |
| **Coronary artery lesion at 1 month** | | | | | | | | | | | | |
| 2 [1] | observational studies | not serious | not serious | not serious | not serious | none | 9/238 (3.8%) | 4490/44205 (10.2%) | **OR 0.34** (0.17 to 0.66) | **65 fewer per 1,000** (from 83 fewer to 32 fewer) | ⨁⨁◯◯ LOW | |
| **refractory disease (additional treatment needed)** | | | | | | | | | | | | |
| 2 [1] | observational studies | not serious | not serious | not serious | not serious | none | 19/238 (8.0%) | 6909/44205 (15.6%) | **OR 0.48** (0.30 to 0.76) | **75 fewer per 1,000** (from 104 fewer to 33 fewer) | ⨁⨁◯◯ LOW | |
| **Persistent Coronary Artery lesion** | | | | | | | | | | | | |
| 2 [1] | observational studies | not serious | not serious | not serious | serious [a] | strong association | 1/238 (0.4%) | 1468/44205 (3.3%) | **OR 0.21** (0.04 to 1.03) | **26 fewer per 1,000** (from 32 fewer to 1 more) | ⨁⨁◯◯ LOW | |

**CI:** Confidence interval; **OR:** Odds ratio

## Explanations

a. Clinical action would differ if the upper versus the lower boundary of the CI represented the truth

## References

1. Inamo, 2014, which includes 2 cohorts

- **References:**

- Randomized controlled trials:

  None

- Comparative observational studies:

| Refid | Author | Year | Title |
|---|---|---|---|
| 18228 | Inamo | 2014 | Effect of dalteparin, a low-molecular-weight heparin, as adjunctive therapy in patients with Kawasaki disease: a retrospective study |

# Kawasaki Disease (KD)

## Treatment

- **PICO question 9:** In patients with KD and coronary artery aneurysms, what is the impact of treatment with anti-platelet agents besides aspirin vs. low dose aspirin on the development of disease-related outcomes and adverse effects of anti-platelet therapy?

- **Critical Outcomes:** Myocardial infarction, death, serious adverse events, toxicity leading to discontinuation of therapy (e.g., hemorrhage, renal dysfunction)

18. In patients with KD and coronary artery aneurysms, what is the impact of treatment with anti-platelet agents besides aspirin vs. low dose aspirin on the development of disease-related outcomes and adverse effects of anti-platelet therapy?

| 19. Certainty assessment | | | | | | | № of patients | | Effect | | Certainty | Importance |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| № of studies | Study design | Risk of bias | Inconsistency | Indirectness | Imprecision | Other considerations | treatment with anti-platelet agents besides Aspirin | Aspirin alone | Relative (95% CI) | Absolute (95% CI) | | |
| **Myocardial ischemia** | | | | | | | | | | | | |
| 1 | observational studies | serious [a] | not serious | not serious | very serious [b] | none | 1/5 (20.0%) | 3/17 (17.6%) | **OR 1.17** (0.09 to 14.52) | **24 more per 1,000** (from 158 fewer to 580 more) | ⨁◯◯◯ VERY LOW | |

| 19. Certainty assessment | | | | | | | № of patients | | Effect | | Certainty | Importance |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| № of studies | Study design | Risk of bias | Inconsistency | Indirectness | Imprecision | Other considerations | treatment with anti-platelet agents besides Aspirin | Aspirin alone | Relative (95% CI) | Absolute (95% CI) | | |
| **Stroke** | | | | | | | | | | | | |
| 1 | observational studies | serious [a] | not serious | not serious | very serious [b] | none | 0/5 (0.0%) | 1/17 (5.9%) | **OR 1.00** (0.04 to 28.30) | **0 fewer per 1,000** (from 56 fewer to 580 more) | ⨁◯◯◯ VERY LOW | |
| **coronary stenosis** | | | | | | | | | | | | |
| 1 | observational studies | serious [a] | not serious | not serious | very serious [b] | strong association | 2/5 (40.0%) | 3/17 (17.6%) | **OR 3.11** (0.35 to 27.55) | **223 more per 1,000** (from 107 fewer to 679 more) | ⨁◯◯◯ VERY LOW | |

**CI:** Confidence interval; **OR:** Odds ratio

## Explanations

a. The choice for dipyridamole vs not was left entirely to the discretion of treating physician, so was likely influenced by disease severity factors. variable follow up, minimum 1 year, which likely is not long enough to see ischemic events

b. Clinical action would differ if the upper versus the lower boundary of the CI represented the truth

- **References:**

- Randomized controlled trials:

  None

- Comparative observational studies:

| Refid | Author | Year | Title |
|---|---|---|---|
| 18654 | Levy | 2005 | Longterm outcomes in patients with giant aneurysms secondary to Kawasaki disease |

# Kawasaki Disease (KD)

## Treatment

- **PICO question 10:** In patients with acute KD and persistent fevers after initial treatment with IVIG, what is the impact of treatment with glucocorticoids vs. another course of IVIG on the development of disease-related outcomes and treatment-related adverse events?

- **Critical Outcomes:** coronary artery abnormalities, myocardial infarction, relapse, serious adverse events, toxicity leading to discontinuation (e.g., hyperglycemia, hemolysis, adverse reaction to IVIG, headache)

20. In patients with acute KD and persistent fevers after initial treatment with IVIG, what is the impact of treatment with glucocorticoids vs. another course of IVIG on the development of disease-related outcomes and treatment-related adverse events?

| 21. Certainty assessment | | | | | | | № of patients | | Effect | | Certainty | Importance |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| № of studies | Study design | Risk of bias | Inconsistency | Indirectness | Imprecision | Other considerations | treatment with glucocorticoids | another course of IVIG | Relative (95% CI) | Absolute (95% CI) | | |
| **clinical response to therapy** | | | | | | | | | | | | |
| 3 [1,2,3] | observational studies | not serious | serious [a] | not serious | serious [b] | none | 42/61 (68.9%) | 50/81 (61.7%) | **OR 0.83** (0.37 to 1.87) | **45 fewer per 1,000** (from 244 fewer to 134 more) | ⨁◯◯◯ VERY LOW | |
| **Failure to respond to rescue therapy** | | | | | | | | | | | | |
| 1 [4] | observational studies | not serious | not serious | not serious | serious [b] | none | 23/72 (31.9%) | 51/136 (37.5%) | **OR 0.78** (0.43 to 1.43) | **56 fewer per 1,000** (from 170 fewer to 87 more) | ⨁◯◯◯ VERY LOW | |
| **coronary aneurysms until 1 month** | | | | | | | | | | | | |
| 1 [4] | observational studies | not serious | not serious | not serious | serious [b] | none | 22/72 (30.6%) | 39/136 (28.7%) | **OR 1.09** (0.59 to 2.04) | **18 more per 1,000** (from 95 fewer to 164 more) | ⨁◯◯◯ VERY LOW | |

**CI:** Confidence interval; **OR:** Odds ratio

## Explanations

a. the effect estimate (OR) in Teraguchi, 2012 does not meet with the confidence interval of the OR in Furukawa, 2007

b. Clinical action would differ if the upper versus the lower boundary of the CI represented the truth

## References


1. Kim, . . 2016.

2. Teraguchi, . . 2012.

3. Furukawa, . . 2007.

4. Kobayashi, . . 2013.


- **References:**

- Randomized controlled trials:

  None

- Comparative observational studies:

| Refid | Author | Year | Title |
|---|---|---|---|
| 18045 | Kim | 2016 | Clinical outcome of patients with refractory Kawasaki disease based on treatment modalities |
| 18287 | Teraguchi | 2012 | Steroid pulse therapy for children with intravenous immunoglobulin therapy-resistant Kawasaki disease: a prospective study |
| 18541 | Furukawa | 2007 | Effects of steroid pulse therapy on immunoglobulin-resistant Kawasaki disease |
| 18275 | Kobayashi | 2013 | Efficacy of intravenous immunoglobulin combined with prednisolone following resistance to initial intravenous immunoglobulin treatment of acute Kawasaki disease |

# Kawasaki Disease (KD)

## Treatment

- **PICO question 11:** In patients with acute KD and persistent fevers after initial treatment with IVIG, what is the impact of treatment with glucocorticoids in combination with non-glucocorticoid immunosuppressive therapy vs. treatment with glucocorticoids alone on the development of disease-related outcomes and treatment-related adverse events?

- **Critical Outcomes:** coronary artery abnormalities, myocardial infarction, relapse, infection, malignancy, serious adverse events, toxicity leading to discontinuation of therapy (e.g., hyperglycemia)

22. In patients with acute KD and persistent fevers after initial treatment with IVIG, what is the impact of treatment with glucocorticoids in combination with non-glucocorticoid immunosuppressive therapy vs. treatment with glucocorticoids alone on the development of disease-related outcomes and treatment-related adverse events?

| 23. Certainty assessment | | | | | | | № of patients | | Effect | | Certainty | Importance |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| № of studies | Study design | Risk of bias | Inconsistency | Indirectness | Imprecision | Other considerations | treatment with glucocorticoids alone | treatment with glucocorticoids in combination with non-glucocorticoid immunosuppressive therapy | Relative (95% CI) | Absolute (95% CI) | | |
| **Giant Coronary Aneuryms** | | | | | | | | | | | | |
| 1 | observational studies | serious [a] | not serious | not serious | serious [b] | none | 6/22 (27.3%) | 0.0% | **OR 0.65** (0.22 to 1.86) | **0 fewer per 1,000** (from 0 fewer to 0 fewer) | ⨁◯◯◯ VERY LOW | |

**CI:** Confidence interval; **OR:** Odds ratio

### Explanations

a. Confounding by indication is a big issue- it is not stated whether or not aneurysms or coronary abnormalities were absent before additional steroids were given- patients with abnormalities may be more likely to get more aggressive therapy, and are also more likely to go on to get giant coronary aneurysms

24. In patients with acute KD and persistent fevers after initial treatment with IVIG, what is the impact of treatment with glucocorticoids in combination with non-glucocorticoid immunosuppressive therapy on the development of disease-related outcomes and treatment-related adverse events?

- **Patient important outcomes:**

| Outcomes (Name + Summary) | Author, year, RefID | Study type | Duration of follow up | Population (number and description) | Intervention used in relevant population (Describe the intervention) | Results | Comments |
|---|---|---|---|---|---|---|---|
| Coronary aneurysm (any point) | 18072 Zhao 2016 | Retrospective cohort study chart review of single center from 1/2005-12/2014 | Coronary artery outcome noted at 1 month | This study includes children with KD and incomplete KD.2467 children total, 136 excluded. 2331 cases analyzed age 1 month to 17.6 years. 2294 got IVIG. 523 children refractory to initial IVIG (fever 36h-7 days post IVIG), 509 were retreated with IVIG, 39 received corticosteroids for continuing fever | Corticosteroid therapy was IV methypred (2mg/kg/d) or oral prednisolone (2 mg/kg/day)- the timing of steroids is not clearly stated (ie could have been after 1 or more failed IVIg) and it is unclear how many got it with IVIG vs steroids alone vs with another agent. (509/523 refractory patients got more IVIg, and 39 got steroids, so some at least got both) It's not entirely clear from the wording in the article but some may have gotten steroids up front | 23/39 kids receiving steroids had Coronary abnormalities at 1 month (13 dilations, 2 small 3 medium, and 3 giant CAA) 7/8 with aneurysms had dilations before receiving corticosteroids. 197/484 of the refractory patients that did not receive steroids had coronary artery abnormalities (142 dilations, 26 small, 21 medium, 8 giant aneurysms) Steroid use was not associated with coronary dilation in multivariate logistic regression. It was associated with coronary artery aneurysm (univariate OR 3.511, 95% CI 1.687, 7.306 multivariate OR 2.864 CI 1.210, 6.777)- Final model steroids, sex, incomplete KD, days of illness at first treatment, total fever duration, IVIG resistance, sodium, albumin. Giant coronary artery aneurysm (univariate OR 7.557, 95% CI 2.182, 26.165, multivariate OR 8.315 95% CI 2.024, 34.158)- Model includes sex, | This article does not adequately adjust for confounding by indication-model adjusts for pretreatment WBC, CRP, PLT, sodium, and albumin (labs all dichotomous cutoffs), duration of illness prior to treatment, total duration of fever, incomplete KD, and refractory disease. Furthermore, it is not stated whether the regression analysis took into account if patients were aneurysm/ abnormality free before receiving steroids. The giant CAA model is overfit- there are only 11 giant aneurysms, and 6 factors in their multivariate model, Also, not addressed if there is |

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| | | | | | | incomplete KD, steroids, total fever duration, days of illness at initial treatment, albumin | |
| Refractory (requiring additional treatment) | 18033 Seo E 2016 | Retrospective cohort study chart review from single center | Not stated | 588 patients with complete KD treated with IVIG initially. 80 did not respond to initial IVIG. Per hospital protocol prior to 2009, retreated with 2nd dose of IVIg alone (42 subjects), after 2009 per policy got 2nd dose of IVIG+MP (38 subjects) | 2nd dose of IVIg with pulse methylpred (30mg/kg/day) for 2-3 days | 4/38 were refractory to the second line treatment and required further treatment | |

25. In patients with acute KD and persistent fevers after initial treatment with IVIG, what is the impact of treatment with glucocorticoids alone on the development of disease-related outcomes and treatment-related adverse events?
    - **Patient important outcomes:**

| Outcomes (Name + Summary) | Author, year, RefID | Study type | Duration of follow up | Population (number and description) | Intervention used in relevant population (Describe the intervention) | Results | Comments |
|---|---|---|---|---|---|---|---|
| Coronary aneurysm | 18071 Kibata 2016 | Retrospective cohort study from all 14 hospitals in a single prefecture in Japan. | | 1487 children with KD according to 5th revision of the diagnostic guidelines, 2003-2014. Complete KD ≥5 cardinal features or ≥4 and coronary aneurysm. Incomplete is suspected KD (not defined) and not meeting criteria. | 100% got aspirin, 1309/1487 IVIG (1087 of whom responded to first dose). 34 got infliximab, 6 got plasma exchange, 37 got corticosteroids 25 patients got steroids after failure to respond to "repeated" IVIG, 6 patients received steroids via RAISE protocol (so up front steroids), and 6 patients for suspected allergic conditions- unclear if this was | 10/37 who received steroids at any point developed coronary artery lesions vs 14/1450 who never received steroids. Of the 1087 IVIG responders, the 9 who received steroids prior to/with initial IVIG (4 raise protocol) none developed coronary artery lesions. In the 222 initial IVIG resistant patients (including 2 RAISE nonresponders) | This article does not differentiate the timing of the corticosteroids (i.e., first line, second line, third line) in the entire group (i.e., initially with first dose of IVIG vs later). It does outline the timing of corticosteroids only in those with coronary artery lesions, however none of those got steroids second line- they were all either with the Initial IVIg or 3rd or |

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| | | | | | pre/concurrent 1st IVIg, and whether or not they were used alone or in combination with other agents, however all the patients with coronary artery aneurysms who received steroids, the steroids were given alone as 3rd or th line | 10/28 who received steroids ever developed coronary lesions vs 5/194 Of 24 patients with coronary lesions for more than 1 month, 3 received steroids as part of 1st line, 7 received it as 3rd or 4th line after more IVIG, and 1 PLEX, 1 infliximab | fourth line after failing second IVIG and in some cases as subsequent 3rd agent |
| | 18293 Miura 2011 | Prospective cohort study from single center using a protocol for all patients. | 1 year | All patients had KD (not defined) and were treated with IVIG within 9 days or less from the start of fever.<br>21 did not respond to second IVIG and got steroids (11 male, 10 female)<br><br>Excluded incomplete KD, and those who got IVIG or steroid within 2 weeks before hospitalization.<br>461 children with 469 cases of KD (8 recurrent). 35 excluded for incomplete, 7 excluded because received aspirin alone, 3 excluded because IVIG 10 days or later, 12 excluded because of IVIG prior to transfer to hospital.<br>412 cases (8 recurrent) for 227 male, 177 females. | All patients initially got IVIG 2g/kg over 24 hours with 30-50 mg/kg/day of aspirin until 2-3 days post fever, then 5 mg/kg/day until no Coronary lesions were evident as of 8 weeks of illness. If fever persisted/recurred 48 hours after IVIG completion, IVIG was redosed. If fever did not resolve within 24 h of second IVIg, patients received IV methylpred 30mg/kg/day for 3 days with a continuous heparin infusion. The oral prednisolone 1-2 mg/kg/day was given for 1 week, and then tapered to off over a second week. IF fever recurred on oral pred, pred dose was increased and re-tapered. All patients got oral famotidine while on steroids. Median time on steroids 15 days (IQR 13-24) | At 4 weeks after disease onset 2/21 had coronary artery lesions by both the American heart association and Japanese ministry of health, labor and welfare definitions, at 1 year, no children had aneurysms by either definition. | Steroids are actually third line agent after 2 failed courses of IVIG.<br>It is not stated if the coronary lesions were present before the initiation of steroids. |

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| | | | | 74 did not respond to initial IVIG and got second IVIG, | | | |
| | 18317 Tremoulet 2013 | Retrospective cohort study | Not stated | 10 patients with treatment resistant KD who were treated with calcineurin inhibitors between 2007-2010, and had failed at least 2 courses of IVIG. 4 patients were in an RCT of infliximab vs placebo for initial treatment intensification. 8 from one center (out of 269 KD patients seen there over that time period), and 2 from 2 other centers. All met AHA definition of KD 4 days of fever and at least 4/5 clinical features | 9 received cyclosporine1 tacrolimus. Prior to calcineurin inhibitor 3 received methylprednisolone after at least two doses of IVIg + aspirin. (dose not listed). 2/3 also received infliximab (not as part of the ongoing study)- unclear if this was concurrent with or before methylpred | All 3 developed coronary artery aneurysm at some point, 2 giant (max z scores of 21.9 and 15.2 - one with inflix, one without infliximab) | This is a highly refractory population who failed several agents. Unclear when in time course of treatment steroids were actually given. Confounding by indication is not addressed in this study, it is just a sample of patients who were so refractory they went on to get cyclosporine, most at a single center |
| | 18380 Iwashima 2011 | Retrospective cohort study | Not clearly stated, however persistent coronary abnormality had to be present at least 1 month out | 433 KD patients from 13 centers from april 2005-july 2009 325 responded to initial IVIG, 108 did not. 91/108 got a second round of IVIG, 17 got nothing else. Of 91 receiving second IVIG 25 were non-responders and went on to get additional therapy. | All steroid receiving patients failed 2 rounds of IVIg (2g/kg) with aspirin (30 mg/kg/day)-the initial treatment sounds protocolized. Patients refractory to second IVIG received steroids, plasma exchange, and/or ulinastatin. Steroids were IVI prednisolone 2 mg/kg/day div TID until afebrile, then orally until CRP normalized. 21/25 received steroids, 4 received PLEX. It is not clearly stated if those | 11/21 who received steroids after failing 2nd IVIg developed coronary artery lesions (not stated persistent vs transient).3/4 receiving PLEX developed coronary artery lesions. (not stated persistent or transient)<br>For context 53/433 patients in overall had coronary artery lesions. 14/25 patients who did not respond to 2nd IVIG and got something else (21 of whom got steroids) | Steroids are used as 3rd line. Unable to tell if some, none or all of PLEX patients got steroids with PLEX. It is reported that no coronary lesions were present before IVIG. Confounding by indication is a problem in this study. |

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| | | | | | receiving PLEX also got corticosterois | developed coronary artery lesions, 8 were transient, 6 persistent at 1 month. | |
| | 18604 Lang 2006 | Retrospective multicenter cohort study – patients identified by chart review, through KD databases and records of consultations | Varied. Median follow up 14 months, range 3 months to 5 years | 26 KD patients refractory (recurrent or persistent fever) to initial IVIG and treated subsequently with steroids<br><br>All patients had at least one 2g/kg dose of IVIg before steroids, 21/26 got this within 10 days of disease onset. 25/26 received high dose<br>4 had coronary aneurysms on baseline echo and 6 had coronary dilations at baseline, with 2 with no baseline available | 17 received 2 prior doses, 5 received 1 prior dose, and 4 received 3 or more prior doses of IVIG.<br>25/26 received pulse IV methylpred (Varying doses, all but 2 got 30 mg/kg, 1 got 25 mg/kg, 1 20mg/kg) for 1-6 doses, and 1 received 2 mg/kg IV methylpred. 8 received oral steroids as well | Overall, 8 of 26 patients developed coronary artery aneurysms at any point, 4 first noted after methylpred, including 3 giant. 9 patients developed dilations at some point without aneurysm, persisting as dilations in 3 at a median 3 months f/u (range 2.5-10 months)<br>7 patients had coronary abnormalities detected for the first time after steroids, with 2/7 not having an echo prior to steroids- these 2 patients got IVMP on day 10 and 12 respectively, for 3 days pulses, coronary dilations found on day 13, both progressed to aneurysms present at last follow up 1-3 years later. In the other 5 with coronary abnormalities first detected post steroids, with a baseline echo, 2 developed aneurysms, 3 only developed dilations.<br><br>10/24 had coronary artery abnormalities on baseline echo prior to steroids<br><br>5/26 had coronary artery aneurysms at last follow | Steroids were frequently 3rd or 4th line in this cohort. Confounding by indication is a problem in this case series, however this article does a better job of addressing the timing of the medication in relation to the outcome. They note a high prevalence (42%) of coronary abnormalities prior to first steroids |

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| | | | | | | up. 1 had no baseline coronary abnormality, 2 had aneurysms at baseline, one of which was giant and 2 had no baseline echo. 3/26 had coronary dilations without aneurysm at last follow up- 1 had baseline aneurysm, 1 had baseline dilation, 1 with no abnormality. | |
| Adverse events | 18293 Miura 2011 | Prospective cohort study from single center using a protocol for all patients. | 1 year | All patients had KD (not defined) and were treated with IVIG within 9 days or less from the start of fever. Excluded incomplete KD, and those who got IVIG or steroid within 2 weeks before hospitalization. 461 children with 469 cases of KD (8 recurrent). 35 excluded for incomplete, 7 excluded because received aspirin alone, 3 excluded because IVIG 10 days or later, 12 excluded because of IVIG prior to transfer to hospital. 412 cases (8 recurrent) for 227 male, 177 females. 74 did not respond to initial IVIG and | All patients initially got IVIG 2g/kg over 24 hours with 30-50 mg/kg/day of aspirin until 2-3 days post fever, then 5 mg/kg/day until no Coronary lesions were evident as of 8 weeks of illness. If fever persisted/recurred 48 hours after IVIG completion, IVIG was redosed. If fever did not resolve within 24 h of second IVIg, patients received IV methylpred 30mg/kg/day for 3 days with a continuous heparin infusion. The oral prednisolone 1-2 mg/kg/day was given for 1 week, and then tapered to off over a second week. IF fever recurred on oral pred, pred dose was increased and re-tapered. All patients got oral famotidine while on steroids. Median time on steroids 15 days (IQR 13-24) | While on IV methylpred 17/21 sinus bradycardia, 17/21 hypertension, 7/21 hyperglycemia, 4/21 hyponatremia, 3/21 hypothermia, no hyperkalemia. While on oral prednisolone 13/21 sinus bradycardia, 11/21 hypertension, 3/21 hyponatremia, 1/21 hyperglycemia, 1/21 hyperkalemia, no hypothermia. All resolved without intervention.<br>No thrombosis, femoral head necrosis, convulsions, secondary infection, GI bleed, or severe arrhythmias in any patients | Steroids are actually third line agent after 2 failed courses of IVIG. |

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| | | | | got second IVIG, 21 did not respond to second IVIG and got steroids (11 male, 10 female) | | | |
| Refractory disease | 18604 Lang 2006 | Retrospective multicenter cohort study – patients identified by chart review, through KD databases and records of consultations | Varied. Median follow up 14 months, range 3 months to 5 years | 26 KD patients refractory (recurrent or persistent fever) to initial IVIG and treated subsequently with steroids<br><br>All patients had at least one 2g/kg dose of IVIg before steroids, 21/26 got this within 10 days of disease onset. 25/26 received high dose<br>4 had coronary aneurysms on baseline echo and 6 had coronary dilations at baseline, with 2 with no baseline available | 17 received 2 prior doses, 5 received 1 prior dose, and 4 received 3 or more prior doses of IVIG.<br>25/26 received pulse IV methylpred (Varying doses, all but 2 got 30 mg/kg, 1 got 25 mg/kg, 1 20mg/kg) for 1-6 doses, and 1 received 2 mg/kg IV methylpred. 8 received oral steroids as well | 22 patients had resolution of fever within 48 hours of steroids<br>Of the 7 who were found to have coronary aneurysms post steroids (including the 2 with no baseline echo), 4 had fever for 3 or more days post steroids, 2 had fever for 1 day post steroid initiation, and 1 had no more fever. | Steroids were frequently 3rd or 4th line in this cohort. Confounding by indication is a problem in this case series, however this article does a better job of addressing the timing of the medication in relation to the outcome. They note a high prevalence (42%) of coronary abnormalities prior to first steroids |

- **References:**

- Randomized controlled trials:

  None

- Comparative observational studies:

| Refid | Author | Year | Title |
|---|---|---|---|
| 18428 | Sudo D | 2010 | Case-control study of giant coronary aneurysms due to Kawasaki disease: the 19th nationwide survey |

- Single arm studies and test accuracy studies:

| Refid | Author | Year | Title | Comments |
|---|---|---|---|---|
| 18033 | E. Seo, J. J. Yu, H. O. Jun, E. J. Shin, J. S. Baek, Y. H. Kim, J. K. Ko | 2016 | Prediction of unresponsiveness to second intravenous immunoglobulin treatment in patients with Kawasaki disease refractory to initial treatment | Cannot ascertain coronary outcomes in specifically those who received IVIg+ steroids as they are pooled with those who received IVIG alone as second line. Could ascertain if disease was refractory |
| 18071 | T. Kibata, Y. Suzuki, S. Hasegawa, T. Matsushige, T. Kusuda, M. Hoshide, K. Takahashi, S. Okada, H. Wakiguchi, T. | 2016 | Coronary artery lesions and the increasing incidence of Kawasaki disease resistant to initial immunoglobulin | This article does not differentiate the timing of the corticosteroids (i.e., first line, second line, third line) in the entire group (i.e., initially with first dose of IVIG vs later). It does outline the timing of corticosteroids only in those with coronary artery lesions, however none of those got steroids second line- they were all either with the Initial IVIg or 3rd or fourth line after failing second IVIG and in some cases as subsequent 3rd agent |
| 18072 | C. N. Zhao, Z. D. Du, L. L. Gao | 2016 | Corticosteroid Therapy Might be Associated with the Development of Coronary Aneurysm in Children with Kawasaki Disease | this article does not differentiate the outcomes after the first IVIG- 37 got steroids after one or more additional IVIg, only 2 received it after the failed first dose, however outcomes are from the pooled group of 39. |
| 18293 | M. Miura, T. Tamame, T. Naganuma, S. Chinen, M. Matsuoka, H. Ohki | 2011 | Steroid pulse therapy for Kawasaki disease unresponsive to additional immunoglobulin therapy | Steroids are 3rd line agent after 2 failed IVIg |
| 18317 | A. H. Tremoulet, P. Pancoast, A. Franco, M. Bujold, C. Shimizu, Y. | 2012 | Calcineurin inhibitor treatment of intravenous immunoglobulin-resistant Kawasaki disease | Not abstracted- only 3 patients got corticosteroids (in combination with other agents). This study is focused on cyclosporine for refractory disease. While it is noted that 3 patients received at least 2 doses of pulse methylpred, |
| 18380 | S. Iwashima, M. Kimura, T. Ishikawa, T. Ohzeki | 2011 | Importance of C-reactive protein level in predicting non-response to additional intravenous immunoglobulin treatment in children with Kawasaki disease: a retrospective study | Focus is not on treatment, rather on lab Steroids are used as 3rd line. Unable to tell if some, none or all of PLEX patients got steroids with PLEX. It is reported that no coronary lesions were present before IVIG. Confounding by indication is a problem in this study. |
| 18604 | B. A. Lang, R. S. Yeung, K. G. Oen, P. N. Malleson, A. M. Huber, M. Riley, R. Ebbeson, | 2006 | Corticosteroid treatment of refractory Kawasaki disease | This article pools together all patients receiving steroids after failing at least one IVIG, however several failed more2 or more IVIG doses before steroids. The authors also note a high prevalence of coronary artery abnormalities prior to steroid use |

- Studies reviewed and excluded:

| Refid | Author | Year | Title | Comments |
|---|---|---|---|---|
| 17949 | T. Ebato, S. Ogata, Y. Ogihara, M. Fujimoto, | 2017 | The Clinical Utility and Safety of a New Strategy for the Treatment of Refractory Kawasaki Disease | Not abstracted- the second line treatment for true refractory KD is IVIG alone, which is neither arm of this question. 3rd line is IVIg, infliximab or plasma exchange without GC- also neither arm. |

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| | A. Kitagawa, M. Takanashi, M. Ishii | | | Note: They use the term refractory to refer to those who actually are predicted to be refractory based on the egami score, not actual refractory patients. Difficult to obtain coronary artery outcomes for those who are actually refractory to their first line treatment, as they aren't well reported for the truly refractory subset<br>First line treatment is IVIG+ steroids, not IVIg alone |
| 17960 | M. Yoshida, S. Oana, H. Masuda, A. Ishiguro, H. Kato, S. Ito, T. Kobayashi, J. Abe | 2018 | Recurrence of Fever After Initial Intravenous Immunoglobulin Treatment in Children With Kawasaki Disease | Not abstracted-patients with refractory disease were retreated with IVIG without glucocorticoids. A few after failing second IVIG got plasma exchange or infliximab, but not in combination with steroids, and there is no way to differentiate outcomes in those specific patients |
| 18034 | M. C. Maggio, G. Corsello, E. Prinzi, R. Cimaz | 2016 | Kawasaki disease in Sicily: clinical description and markers of disease severity | Not abstracted- second line treatment used was IVIG alone. GC and infliximab only used in 1 patient after 3 doses of IVIG |
| 18043 | M. L. Downie, C. Manlhiot, G. A. Latino, T. H. Collins, N. Chahal, R. S. Yeung, B. W. McCrindle | 2016 | Variability in Response to Intravenous Immunoglobulin in the Treatment of Kawasaki Disease | Not abstracted- This article does not go into the outcomes based on second line treatment- its focused on comparing responders and non-responders to IVIg as a first line treatment, so results of second line agents pooled under non-responders |
| 18069 | S. Singh, D. Sharma, D. Suri, A. Gupta, A. Rawat, M. K. Rohit | 2016 | Infliximab is the new kid on the block in Kawasaki disease: a single-centre study over 8 years from North India | Not abstracted- the only arm is infliximab alone, not infliximab with gc in refractory KD. |
| 18089 | Y. Youn, J. Kim, Y. M. Hong, S. Sohn | 2016 | Infliximab as the First Retreatment in Patients with Kawasaki Disease Resistant to Initial Intravenous Immunoglobulin | Not abstracted- there is no treatment arm that is GC alone or GC+ another immunosuppressant. The arms are second IVIG vs infliximab, no GC. There are seven subjects who received methylpred after failing 2 doses of IVIG |
| 18099 | M. Goto, N. Miyagawa, K. Kikunaga, M. Miura, Y. Hasegawa | 2015 | Single serum cortisol values at 09:00 h can be indices of adrenocortical function in children with Kawasaki disease treated with intravenous immunoglobulin plus prednisolone | Not abstracted- this study looks specifically at children treated with steroids and IVIG up front, and excluded any children who had to get additional steroids due to refractory disease |
| 18223 | K. Sonoda, M. Mori, T. Hokosaki, S. Yokota | 2014 | Infliximab plus plasma exchange rescue therapy in Kawasaki disease | Not abstracted. Patients did not receive any glucocorticoids, and so fit neither arm |
| 18297 | H. Hamada, H. Suzuki, J. Abe, Y. Suzuki, T. | 2012 | Inflammatory cytokine profiles during Cyclosporin treatment for immunoglobulin-resistant Kawasaki disease | Not abstracted. Patients did not receive any glucocorticoids, and so fits neither arm |
| 18329 | M. Mori, T. Imagawa, R. Hara, M. Kikuchi, T. Hara, T. Nozawa, T. Miyamae, S. Yokota | 2012 | Efficacy and limitation of infliximab treatment for children with Kawasaki disease intractable to intravenous immunoglobulin therapy: report of an open-label case series | Not abstracted- none of the patients received steroids, just infliximab and so met neither arm. |

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| 18372 | H. Suzuki, M. Terai, H. Hamada, T. Honda, T. Suenaga, T. Takeuchi, N. Yoshikawa, S. Shibuta, M. Miyawaki, K. Oishi, H. Yamaga, N. Aoyagi, S. Iwahashi, R. Miyashita, Y. Onouchi, K. Sasago, Y. Suzuki, A. Hata | 2011 | Cyclosporin A treatment for Kawasaki disease refractory to initial and additional intravenous immunoglobulin | Not abstracted- none of the patients received steroids, just additional IVIg followed by cyclosporine and so met neither arm. |
| 18384 | T. Jibiki, I. Kato, T. Shiohama, K. Abe, S. Anzai, N. Takeda, K. I. Yamaguchi, M. Kanazawa, T. Kurosaki | 2011 | Intravenous immune globulin plus corticosteroids in refractory Kawasaki disease | Not abstracted- there are less than |
| 18395 | M. B. Son, K. Gauvreau, J. C. Burns, E. Corinaldesi, A. H. Tremoulet, V. E. Watson, A. Baker, D. R. Fulton, R. P. Sundel, J. W. Newburger | 2011 | Infliximab for intravenous immunoglobulin resistance in Kawasaki disease: a retrospective study | Not abstracted- the arms are infliximab vs IVIG- no one got steroids second line. A few did receive steroids 3rd line, however no outcomes are reported specific to those patients |
| 18488 | K. Hirono, Y. Kemmotsu, H. Wittkowski, D. Foell, K. Saito, K. Ibuki, K. Watanabe, S. Watanabe, K. Uese, H. Kanegane, H. Origasa, F. Ichida, J. Roth, T. Miyawaki, T. Saji | 2009 | Infliximab reduces the cytokine-mediated inflammation but does not suppress cellular infiltration of the vessel wall in refractory Kawasaki disease | Not abstracted- only 8 patients ultimately received methylpred, some in combination with infliximab |
| 18504 | T. J. Lee, K. H. Kim, J. K. Chun, D. S. Kim | 2008 | Low-dose methotrexate therapy for intravenous immunoglobulin-resistant Kawasaki disease | Not abstracted, no subjects received glucocorticoids |
| 18653 | J. C. Burns, W. H. Mason, S. B. Hauger, H. Janai, J. F. Bastian, J. D. Wohrley, I. Balfour, C. A. Shen, E. D. Michel, S. T. Shulman, M. E. Melish | 2005 | Infliximab treatment for refractory Kawasaki syndrome | Not abstracted- This study focuses on patients who failed several therapies (including steroids) and ultimately went on to get infliximab, and so only includes those who failed steroids. Fewer than 10 patients received steroids. Outcomes not reported specifically for the subset of patients who did receive steroids. |

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|---|---|---|---|---|
| 18677 | R. L. Ebbeson, M. R. Riley, J. E. Potts, D. G. Human, P. N. Malleson | 2004 | Kawasaki disease at British Columbia's Children's Hospital | Not abstracted- Only 8 patients received steroids |
| 18793 | R. K. Han, E. D. Silverman, A. Newman, B. W. McCrindle | 2000 | Management and outcome of persistent or recurrent fever after initial intravenous gamma globulin therapy in acute Kawasaki disease | Not abstracted- only 6 patients received corticosteroids |
| 18794 | C. A. Wallace, J. W. French, S. J. Kahn, D. D. Sherry | 2000 | Initial intravenous gammaglobulin treatment failure in Kawasaki disease | Not abstracted- only 4 patients received steroids |
| 22396 | H. Kobayashi T. Hachiya A. Nakashima Y. Shimizu H. Nozawa T. | 2018 | Infliximab for the Treatment of Refractory Kawasaki Disease: A Nationwide Survey in Japan | Not abstracted- this article focuses on infliximab. While 23/363 patients who received infliximab went on to get steroids, it is unclear if this is concurrent or consecutive, and outcomes are not reported specifically in this small subset |

# Kawasaki Disease (KD)

## Treatment

- **PICO question:** In patients on treatment for acute KD with resolution of fevers, what is the impact of continued daily monitoring for fevers for 2 weeks vs. no monitoring for fevers on the development of disease-related outcomes?

- **Critical Outcomes:** coronary artery abnormalities, myocardial infarction, relapse

26. In patients on treatment for acute KD with resolution of fevers, what is the impact of continued daily monitoring for fevers for 2 weeks vs. no monitoring for fevers on the development of disease-related outcomes?
    No comparative data available

27. In patients on treatment for acute KD with resolution of fevers, what is the impact of continued daily monitoring for fevers for 2 weeks on the development of disease-related outcomes?
    - **Patient important outcomes:**

| Outcomes (Name + Summary) | Author, year, RefID | Study type | Duration of follow up | Population (number and description) | Intervention used in relevant population (Describe the intervention) | Results | Comments |
|---|---|---|---|---|---|---|---|
| Outcome 1 Coronary Artery | Jaggi 2015 18119 | Post hoc analysis of subjects from | 5 weeks | Patients with KD as defined by AHA guidelines. | Body temperature measured by both axillary and either oral or rectal, | 18/190 had fever 0-12 hours after IVIg, 37/190 had fever 12-24 hours | |

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| abnormalities | | double blind placebo controlled RCT (Tremoulet et al 2014) | | Subjects were participants in an RCT comparing IVIG + placebo vs IVIG+infliximab as primary treatment of KD<br>96 got IVIg+infliximab, 94 IVIg+placebo<br>If fever without other source recurred/persisted ≥36 hours after IVIG ended received a second dose of IVIg<br>1 withdrew from study, 2 had >50% missing temperature points, and 3 got an early second IVIg and were excluded from analysis | every 6 hours just prior to scheduled Aspirin. Every 6 hours, and then families instructed to check once daily at home for 72 hours after discharge (a varying timepoint for each patient), and call for any fevers within a week of discharge | after IVIG, 29 had fever 24-36 hours after IVIG (59 total in the 36 hours post IVIg). There was no difference in Coronary Artery abnormalities in those who had a fever in the first 36 hours after IVIG completion (12/59 vs 39/131) and those who did not.<br>43 had coronary artery abnormalities first noted prior to discharge, with only 8 developing abnormalities after discharge (all of which were dilation, not aneurysm). 33/43 had baseline coronary dilation with none progressing to aneurysm, 9/43 with baseline aneurysm, and 1/43 with baseline aneurysm that progressed to to aneurysm. | |

28. In patients on treatment for acute KD with resolution of fevers, what is the impact of no monitoring for fevers on the development of disease-related outcomes?
    No single arm data available

- **References:**

- Randomized controlled trials:
    None

- Comparative observational studies:
    None

- Single arm studies and test accuracy studies:

| Refid | Author | Year | Title | Comments |
|---|---|---|---|---|
| 18119 | P. Jaggi, W. Wang, I. Dvorchik, B. Printz, E. Berry, J. P. Kovalchin | 2015 | Patterns of Fever in Children After Primary Treatment for Kawasaki Disease | This study does not address the question well- it focuses on fever in the 36 hours post IVIg, although all patients were instructed to check temperature once daily for 72 hours post discharge and report any fever within a week of discharge. |

- Studies reviewed and excluded:

| Refid | Author | Year | Title | Comments |
|---|---|---|---|---|
| 18107 | T. Takahashi, H. Sakakibara, Y. Morikawa, M. Miura | 2015 | Development of coronary artery lesions in indolent Kawasaki disease following initial spontaneous defervescence: a retrospective cohort study | Not abstracted- There is no mention of whether or not patients had daily monitoring of fevers after resolution of fevers, it just talks about coronary outcomes in patients with KD who defervesced before treatment (some of whom were never treated, some of whom got treated regardless) |

# Kawasaki Disease (KD)

## Treatment

- **PICO question 13:** In patients with KD and arthritis that persists after IVIG treatment, what is the impact of treatment with NSAIDs vs. no NSAIDS on the persistence of arthritis, development of disease-related outcomes, and development of treatment-related adverse events?

- **Critical Outcomes:** persistence of arthritis, coronary artery abnormalities, myocardial infarction, relapse, serious adverse events, toxicity leading to discontinuation of therapy (e.g., renal insufficiency, hemorrhage)

29. In patients with KD and arthritis that persists after IVIG treatment, what is the impact of treatment with NSAIDs vs. no NSAIDS on the persistence of arthritis, development of disease-related outcomes, and development of treatment-related adverse events?
    No comparative data available

30. In patients with KD and arthritis that persists after IVIG treatment, what is the impact of treatment with NSAIDs on the persistence of arthritis, development of disease-related outcomes, and development of treatment-related adverse events?
No single arm data available

31. In patients with KD and arthritis that persists after IVIG treatment, what is the impact of no NSAIDS on the persistence of arthritis, development of disease-related outcomes, and development of treatment-related adverse events?
No single arm data available

- **References:**

- Randomized controlled trials:
None

- Comparative observational studies:
None

- Single arm studies and test accuracy studies:
None

- Studies reviewed and excluded:

| Refid | Author | Year | Title | Comments |
|---|---|---|---|---|
| 18653 | J. C. Burns, W. H. Mason, | 2005 | Infliximab treatment for refractory Kawasaki syndrome | Not abstracted. While the indication for retreatment with infliximab in several patients was fever and/or arthritis, they only report on the outcome of the arthritis in 2/15 patients with arthritis who got a higher dose than all the rest. Moreover, it is unknown if patients did or did not receive NSAIDS as this was not explicitly mentioned |

# Kawasaki Disease (KD)

**Additional diagnostic testing**

- **PICO question additional 1:** In patients with suspected incomplete KD and fever for over 7 days, what is the impact of obtaining an echocardiogram before day 10 of fever vs. not obtaining an echocardiogram on diagnostic accuracy of KD, development of disease-related outcomes, and development of treatment-related adverse events?

- **Critical Outcomes:** diagnostic accuracy measures, coronary artery abnormalities, myocardial infarction, adverse events related to diagnostic testing, toxicity leading to discontinuation of therapy (e.g., headache, adverse reaction to IVIG, hemolysis)

32. In patients with suspected incomplete KD and fever for over 7 days, what is the impact of obtaining an echocardiogram before day 10 of fever vs. not obtaining an echocardiogram on diagnostic accuracy of KD, development of disease-related outcomes, and development of treatment-related adverse events?
    No comparative data available

33. In patients with suspected incomplete KD and fever for over 7 days, what is the impact of obtaining an echocardiogram before day 10 of fever on diagnostic accuracy of KD, development of disease-related outcomes, and development of treatment-related adverse events?
    No single arm data available

34. In patients with suspected incomplete KD and fever for over 7 days, what is the impact of not obtaining an echocardiogram on diagnostic accuracy of KD, development of disease-related outcomes, and development of treatment-related adverse events?
    No single arm data available

- **References:**

- Randomized controlled trials:
  None

- Comparative observational studies:
  None

- Single arm studies and test accuracy studies:
  None

- Studies reviewed and excluded:

| Refid | Author | Year | Title | Comments |
|---|---|---|---|---|

| | | | | |
|---|---|---|---|---|
| 18790 | J. S. Chang | 1999 | The significance of early subtle coronary arterial lesions on echocardiogram in Kawasaki disease | echoes repeated serially over the first **12 days (acute phase)** not before day 10 |
| 19039 | M. Iwasa, K. Sugiyama, T. Ando, | 1987 | Selection of high-risk children for immunoglobulin therapy in Kawasaki disease | Not abstracted, does not apply to this question- No data on echo utility in diagnosis, no non KD group, everyone had echoes does not limit to suspected incomplete KD (just KD), not meeting 7day/10 day time cutoffs |
| 22345 | Y. M. Kang H. M. Lee S. C. Yu J. W. | 2018 | Clinical implications in laboratory parameter values in acute Kawasaki disease for early diagnosis and proper treatment | Not abstracted, this study is actually comparing KD vs non KD, however no results were reported on echo findings in the non KD group (although everyone got echoes). Not meeting 7 day/10 day (at least in terms of echo), not limited to incomplete KD |
| 22357 | N. Sastroasmoro S. Ontoseno T. Uiterwaal C. Advani | 2018 | Long-Term outcome of coronary artery dilatation in Kawasaki disease | Not abstracted- study looks at echoes only of kids with KD who had coronary dilations in the acute phase, not all patients with KD or suspected KD.<br>does not limit to suspected incomplete KD, not meeting 7day/10 day time cutoffs |
| 22649 | N. N. F. Mia | 2017 | Kawasaki disease hospitalization: Outcomes in two tertiary care hospitals in Bangladesh | Not abstracted- No non-KD does not limit to suspected incomplete KD, not meeting 7day/10 day time cutoffs |
| 22697 | V. Bhardwaj P. Sharma M. Yadav | 2016 | Clinical profile and Outcome of Kawasaki Disease in children in Himalayan Region of North India | Not abstracted-No patients without KD, everyone got echo, not meeting 7day/10 day time cutoffs |
| 23287 | B. Kalis N. N. Hassan | 2010 | Early compared to late presentation of Kawasaki disease | Not abstracted-No patients without KD, not meeting 7day/10 day time cutoffs |
| 23316 | W. Yousef N. Abuhammour | 2008 | Incomplete Kawasaki disease: Experience with 14 patients with cardiac complications | Not abstracted- no non-KD patients, not meeting &day/10 day time period |
| 23344 | H. Iino M. Hoshina M | 2007 | Intravenous immunoglobulin 1 g/kg as the initial treatment for Kawasaki disease | Not abstracted- no non-KD patients, not meeting &day/10 day time period |

# Kawasaki Disease (KD)

## Additional diagnostic testing

- **PICO question additional 2:** In patients with unexplained shock physiology, what is the impact of obtaining an echocardiogram vs. not obtaining an echocardiogram on the diagnostic accuracy of KD, development of disease-related outcomes, and development of treatment-related adverse events?

- **Critical Outcomes:** diagnostic accuracy measures, coronary artery abnormalities, myocardial infarction, death, adverse events related to diagnostic testing, toxicity leading to discontinuation of therapy (e.g., headache, adverse reaction to IVIG, hemolysis)

35. In patients with unexplained shock physiology, what is the impact of obtaining an echocardiogram vs. not obtaining an echocardiogram on the diagnostic accuracy of KD, development of disease-related outcomes, and development of treatment-related adverse events?
    No comparative data available

36. In patients with unexplained shock physiology, what is the impact of obtaining an echocardiogram on the diagnostic accuracy of KD, development of disease-related outcomes, and development of treatment-related adverse events?
    No single arm data available

37. In patients with unexplained shock physiology, what is the impact of not obtaining an echocardiogram on the diagnostic accuracy of KD, development of disease-related outcomes, and development of treatment-related adverse events?
    No single arm data available

- **References:**

- Randomized controlled trials:
  None

- Comparative observational studies:
  None

- Single arm studies and test accuracy studies:
  None

# Kawasaki Disease (KD)

## Additional diagnostic testing

- **PICO question additional 3:** In patients with fever and unexplained macrophage activation syndrome, what is the impact of obtaining an echocardiogram vs. not obtaining an echocardiogram on diagnostic accuracy of KD, development of disease-related outcomes, and development of treatment-related adverse events?

- **Critical Outcomes:** persistent macrophage activation syndrome, diagnostic accuracy measures, coronary artery abnormalities, myocardial infarction, relapse, death, adverse events related to diagnostic testing, toxicity leading to discontinuation of therapy (e.g., headache, adverse reaction to IVIG, hemolysis)

38. In patients with fever and unexplained macrophage activation syndrome, what is the impact of obtaining an echocardiogram vs. not obtaining an echocardiogram on diagnostic accuracy of KD, development of disease-related outcomes, and development of treatment-related adverse events?
    No comparative data available

39. In patients with fever and unexplained macrophage activation syndrome, what is the impact of obtaining an echocardiogram on diagnostic accuracy of KD, development of disease-related outcomes, and development of treatment-related adverse events?
    No single arm data available

40. In patients with fever and unexplained macrophage activation syndrome, what is the impact of not obtaining an echocardiogram on diagnostic accuracy of KD, development of disease-related outcomes, and development of treatment-related adverse events?
    No single arm data available

- **References:**

- Randomized controlled trials:
  None

- Comparative observational studies:
  None

- Single arm studies and test accuracy studies:
  None

- Studies reviewed and excluded:

| Refid | Author | Year | Title | Comments |
|---|---|---|---|---|
| 17906 | J. E. Choi, Y. Kwak, J. W. Huh, E. S. Yoo, K. H. Ryu, S. Sohn, Y. M. Hong | 2018 | Differentiation between incomplete Kawasaki disease and secondary hemophagocytic lymphohistiocytosis following Kawasaki disease using N-terminal pro-brain natriuretic peptide | There is no non-KD population in this study- it compares incomplete KD with MAS to incomplete KD without MAS |