Corticosteroid Treatment of Refractory Kawasaki Disease

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ABSTRACT. ***Objective.*** To review the indications for corticosteroids in patients with Kawasaki disease (KD) treated by pediatric rheumatologists in Canada and to determine their efficacy on fever in patients with refractory KD.

Methods. All practicing pediatric rheumatologists in Canada identified KD patients treated with corticosteroids and completed a standard data form that included demographics, clinical and laboratory features, imaging studies, and therapeutic interventions, by chart review.

Results. Thirty-two patients with KD (14 female; 18 male: mean age 4.6 years) were treated with corticosteroids. Corticosteroids were used in 26 patients (81%) for persistent fever despite treatment with intravenous immunoglobulin (IVIG) (refractory KD), 5 patients (19%) for congestive heart failure, and 1 patient for persistent acute phase symptoms other than fever. The 26 patients with refractory KD are the primary subject of this report. Twenty-two patients (85%) had rapid, sustained resolution of fever after corticosteroids. There were no serious reported adverse effects. Eight patients (31%) treated with corticosteroids developed coronary artery (CA) aneurysms and 9 (35%) developed CA dilatations without aneurysms. Of those who developed CA aneurysm, 4 had aneurysms detected prior to IV methylprednisolone (MP) on echocardiograms performed on days 6-27 (mean day 13) of illness. The remaining 4 patients had CA aneurysm detected after IVMP therapy, on echocardiograms performed on days 13-49 (mean day 23) of illness, 1-25 days (mean 9 days) after IVMP. In patients with one year or more of followup, 46% had resolution of CA abnormalities.

Conclusion. Corticosteroids are effective in the treatment of fever in most patients with IVIG-refractory KD. A multicenter prospective study is needed to determine the effect of corticosteroids on CA outcome in patients with refractory KD. (J Rheumatol 2006;33:803–9)

Key Indexing Terms:
KAWASAKI DISEASE
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INTRAVENOUS METHYLPREDNISOLONE

Kawasaki disease (KD) is a systemic vasculitis that predominantly affects young children. Its most serious complication is the development of coronary artery (CA) aneurysms[1-4], as a result of which KD has become the most common cause of acquired heart disease in children in North America[5]. Most children with KD respond to intravenous immunoglobulin (IVIG) and aspirin (ASA)[6-10], however, 10 to 20% of patients with KD fail to respond to this therapy[8,11-16] and have persistent fever, or fever that recurs 24 to 48 hours later. Although most of these patients will become afebrile after a subsequent IVIG infusion[11,12,14], up to one-third of retreated patients will not respond[11,14]. There are currently no generally accepted guidelines for the treatment of this subgroup of patients.

Although corticosteroids are used to treat most forms of vasculitis, their use in KD has been avoided because of concerns of inducing or exacerbating CA abnormalities[17]. Avoidance of corticosteroids in the treatment of KD has been based primarily on the results of an uncontrolled, nonrandomized study by Kato, *et al* reported in 1979, which found a high incidence of CA aneurysms (11/17;65%) in patients treated with oral prednisolone. In the same study, however, none of the 7 patients treated with oral prednisolone plus ASA developed coronary aneurysms[17]. Other early experience in Japan, prior to the regular use of IVIG in KD, also suggested that corticosteroids were not effective in preventing cardiac sequelae

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or reducing mortality in KD. However, none of these studies were controlled or blinded[18,19].

The first report of pulse IV corticosteroids in the treatment of KD was published in 1982 by Kijima, *et al*. This small, uncontrolled study showed no adverse effects of pulse IV methylprednisolone (IVMP 30 mg/kg/day for 3 days) plus heparin, and reported improvement or resolution of CA abnormalities in 8/15 (53%) of patients receiving this treatment[20].

Several more recent studies, performed since IVIG became standard therapy in KD, assessed the use of corticosteroids in the initial treatment of KD; all reported shorter duration of fever associated with corticosteroid therapy[21-24]. Moreover, use of corticosteroids in patients with KD refractory to initial treatment with IVIG has also been reported in small numbers of patients. Wright, *et al* and Wallace, *et al* each reported defervescence and no worsening of CA abnormalities in 4 patients with refractory KD who were treated with pulse IVMP[13,15]. Dale, *et al* also reported resolution of fever and no worsening of CA abnormalities in 8 patients who had failed IVIG and were treated with oral prednisolone and ASA[25]. In one small prospective study of patients with refractory KD, 9 patients treated with pulse corticosteroids had more rapid resolution of fever compared with 8 patients treated with additional IVIG. However, 3 patients treated with corticosteroids had CA dilatation detected for the first time during corticosteroid treatment[16].

The limited literature on corticosteroid use in patients with KD who have failed to respond to IVIG therapy, and the fact that treatment of this subgroup of patients is one of the major challenges in the current management of KD, led us to retrospectively review the use of corticosteroids in KD patients in Canada. The aims of this study were (1) to determine indications for the use of corticosteroids in patients with KD treated by pediatric rheumatologists in Canada; (2) to assess the efficacy of this therapy on fever in patients with refractory KD; and (3) to assess CA outcome in patients with KD treated with corticosteroids.

MATERIALS AND METHODS

Study design. This retrospective study captures the Canadian national experience in the corticosteroid treatment of KD between 1992 and 2000. In Canadian academic centers, all patients with acute KD are assessed by a pediatric rheumatologist, all of whom are members of the Canadian Pediatric Rheumatology Association (CPRA). This study was a multicenter collaboration of members of the CPRA. Patients with KD treated with corticosteroids between January 1992 and June 30, 2000 were identified by chart review, through KD databases, and records of consultations. Ethics approval was obtained at participating centers as required by local ethics boards.

A standardized data collection form completed for each child included: demographic data; clinical features of disease including complications, treatment, indications for, and effects of, corticosteroid treatment including adverse effects; and imaging data including the presence of CA lesions on echocardiography prior to and after corticosteroid treatment. The results of echocardiograms were accepted as documented in the medical record. Standard methods based on the American Heart Association guidelines were used to assess CA dilatation and CA aneurysms in all institutions[26]. Refractory KD was defined as failure to become afebrile 48 hours after receiving IVIG, or recurrence of fever after initial defervescence with one or more infusions of IVIG.

Statistical analysis. Summary data are presented as frequencies, medians, and means. Pearson's correlations were calculated to explore the relationship between risk factors and CA abnormalities. Logistic regression analysis was used to examine the contribution of a number of variables to the prediction of CA outcomes. The variables were age (< 12 mos or > 12 mos), duration of fever (as a continuous variable), gender, and IVIG treatment before day 10 of illness. When relevant, p values of < 0.05 were considered statistically significant. SPSS version 10 (SPSS Inc., Chicago, IL, USA) was used in data analysis.

RESULTS

Recruitment. In 3 of the 10 Canadian provinces (Quebec, Alberta, and Saskatchewan), no patients with KD were known to have received corticosteroids during the study period. In one province (Newfoundland), there was no pediatric rheumatologist and therefore no data were obtained. In the remaining 6 provinces, 32 patients with KD were treated with corticosteroids. Of these, 26 patients (81%) received corticosteroids because of refractory KD and are the primary subject of this report. A further 5 patients (16%) received corticosteroids because of clinical evidence of congestive heart failure. One patient received steroids because of persistent rash, conjunctivitis, and irritability despite defervescence following IVIG treatment. These 6 patients were not included in the subsequent analysis. All had normal CA at last followup.

Demographic and clinical features. Twenty-six patients with KD (9 female, 17 male; mean age 4.2 yrs ± 2.6; range 0.4 to 10.3) were treated with corticosteroids because of either persistent fever after treatment with IVIG, or recurrence of fever within 48 hours of IVIG treatment despite initial improvement. Three patients (11%) were under 12 months of age (one under 6 months), and 4 (15%) were 7 years of age or older. Seven patients (27%) were Caucasian, 6 (23%) Asian, and 2 (8%) were Black. In 11 patients (42%), ethnicity was not recorded. All patients met diagnostic criteria for definite KD[1,2]. The median duration of fever was 12 days (range 7-50 days). With the exception of 2 patients who had a very prolonged acute phase of their illness (50 and 35 days), and one patient in whom the exact duration of fever could not be determined by chart review, the duration of the acute phase of KD ranged from 7 to 18 days.

Treatment regimens. Treatment regimens of IVIG refractory patients who received corticosteroids are summarized in Table 1. All patients received IVIG 2 g/kg at the time of diagnosis. Twenty-one patients (81%) received IVIG within 10 days of disease onset. The mean time to receive IVIG was 7 days from onset of KD, with a median of 6 days (range 4-23 days). Prior to corticosteroid treatment, 17 patients (65%) received 2 doses of IVIG, 5 patients (19%) received a single dose of IVIG, and 4 patients (15%) received 3 or more doses of IVIG. Twenty-five patients (96%) received high-dose ASA (50-104 mg/kg/day) during the acute phase of KD. Data were available to determine the duration of high-dose ASA treatment in 19

Table 1. Summary of demographics, treatment regimens, and echocardiographic studies in patients with corticosteroid-treated IVIG-refractory KD.

Patient	Demographics		Treatment Regimen					Baseline Echo		Echo at Last Followup	
	Age (yrs)	Sex (M/F)	IVIG (2 g/kg) Doses Prior to CS	Illness Day at IVIG Rx	IVMP Dose (mg/kg)	IVMP Doses	Oral CS Y/N	CAA Y/N	CAD Y/N	CAA Y/N	CAD Y/N
1	4.4	F	2	4	30	1	N	N	N	N	N
2	10.3	M	2	11	30	2	N	N	Y	N	N
3	6.4	M	2	7	30	1	Y	N	N	Y*	N
4	3.8	M	2	6	30	1	N	N	Y	N	N
5	2.4	F	2	8	30	3	Y	N	N	N	N
6	0.7	M	2	5	30	3	N	Y	N	N	Y
7	3.2	F	2	12	30	3	Y	N	N	N	N
8	3.4	M	2	5	30	1	N	N	N	N	N
9	9.9	F	1	8	25	3	N	NA	NA	Y	N
10	4.4	F	2	NA	30	1	N	N	Y	N	N
11	4.4	M	2	4	30	3	Y	N	N	N	Y
12	0.7	M	1	6	30	3	N	NA	NA	Y	N
13	7.6	F	2	7	20	3	Y	N	N	N	N
14	7.3	M	3	5	30	3	N	N	N	N	N
15	5.5	F	2	7	2	6	Y	N	Y	N	N
16	4.0	M	2	5	30	1	N	N	Y	N	Y
17	1.1	M	2	5	30	3	N	N	Y	N	N
18	2.1	F	5	5	30	3	N	Y	N	Y	N
19	3.1	M	2	6	NA	3	N	N	N	N	N
20	0.4	M	3	23	30	3	Y	Y*	N	Y*	N
21	5.9	F	3	12	10 × 3; 30 × 3	6	Y	N	N	N	N
22	2.3	M	1	6	30	6	N	N	N	N	N
23	3.3	M	1	6	30	3	N	Y	N	N	N
24	4.8	M	2	5	30	1	N	N	N	N	N
25	3.1	M	1	5	30	3	N	N	N	N	N
26	5.4	M	2	7	30	1	N	N	N	N	N

NA: not available; M: male; F: female; Y: yes; N: no; IVMP: intravenous methylprednisolone; CS: corticosteroid; Rx: treatment; CAA: coronary artery aneurysm; CAD: coronary artery dilatation without CAA: * giant CA aneurysm.

patients. The mean duration was 7 days (range 2–22 days.) On average, patients discontinued high dose ASA 2.5 days after their last day of fever. In 4 patients, high dose ASA was replaced with low dose ASA at the onset of IVMP therapy, prior to the patients becoming afebrile. One patient received only low-dose ASA because of elevated liver enzymes.

Corticosteroid treatment. All patients received IV corticosteroids, between 6 and 49 days after onset of KD (median 12 days). Twenty-five patients (96%) were treated with one or more pulses of IVMP (10-30 mg/kg/dose) (Table 1). Fourteen patients (54%) received 3 consecutive daily pulses of IVMP, 8 patients received a single pulse of IVMP, one patient received 2 pulses of IVMP, and 2 patients received 6 pulses of IVMP. Eight patients (31%) who received IVMP subsequently received daily oral corticosteroids for variable time periods (mean 3 mo; median 2.4 mo). One patient was treated with daily IVMP (2 mg/kg/day) for 3 days followed by oral corticosteroids rather than pulse IVMP therapy.

Effect of corticosteroids on fever. Twenty-two patients (85%) had rapid and sustained resolution of fever within 48 hours of receiving corticosteroids. Other acute phase symptoms and signs of KD such as rash, lymphadenopathy, and conjunctivitis also resolved promptly during corticosteroid treatment. Four patients (15%) had initial resolution of fever followed by recurrence within 48 hours. Of these 4, fever resolved after initiation of daily oral corticosteroids in one patient. In the remaining 3 patients, fever resolved after treatment with one additional dose of IVIG. These 3 patients had each received one dose of IVIG prior to IVMP treatment. Corticosteroid treatment had consisted of 3 pulses of IVMP in 2 patients, and 6 pulses in one patient. At last followup, 2 of these patients had CA aneurysms (one giant), and one patient who had received 6 pulses of IVMP had normal CA.

Coronary artery status prior to corticosteroids. Twenty-four patients (92%) had an echocardiogram performed prior to corticosteroid treatment. Echocardiograms were done 5 to 35 days after disease onset, and between 0 and 22 days (mean 5, median 3 days) prior to corticosteroids. Of these 24 patients, 10 (42%) had a CA lesion detected prior to corticosteroid treatment. CA aneurysms, including one giant aneurysm, were detected in 4 patients (17%). CA dilatations without CA aneurysms were detected in 6 patients (25%).

Coronary artery outcome. All patients had echocardiograms performed after receiving corticosteroid treatment. The first post-steroid echocardiograms were performed between 1 and 82 days following treatment with IVMP (mean 7, median 18 days). Of the 10 patients with CA abnormalities detected prior to corticosteroid treatment, abnormalities resolved in 6

patients. Persistent CA abnormalities occurred in the other 4 patients. One had multiple CA aneurysms, 2 had CA dilatations, and one had a persistent giant aneurysm.

Seven patients (27%) had CA abnormalities detected for the first time after corticosteroid treatment. Two of these patients had not had an echocardiogram prior to receiving corticosteroids. Of these 2 patients, one had received a 3 day pulse of IVMP starting on day 10 of illness, and the other starting on day 12. Their first followup echocardiograms were both on day 13 of illness, and both showed CA dilatations. Subsequent echocardiograms showed progression to CA aneurysms that persisted at last followup (1-3 years) in both of these patients. Moreover, fever persisted for 5 days after IVMP treatment. The remaining 5 patients had normal baseline echocardiograms performed between day 6 and 10 of illness, but subsequently were documented to have CA abnormalities after corticosteroid treatment. Two of these patients developed CA aneurysms and 3 developed CA dilatations. The timing of corticosteroid treatment, duration of fever following corticosteroids, as well as the timing and results of the pre-steroid echocardiograms, and the first and last followup echocardiograms in these 5 patients are summarized in Table 2. As indicated in this table, in the 2 patients in this group who developed CA aneurysms, fever persisted after treatment with IVMP, lasting for 3-10 days.

Overall, 8 of the 26 patients (31%) treated with corticosteroids developed CA aneurysms, including 3 with giant aneurysms. Four patients had CA aneurysm detected prior to IVMP. Pre-steroid echocardiograms detected the CA aneurysm on day 6 to 27 (mean day 13) of illness, 2 to 22 days (mean 10 days) prior to IVMP. Four patients had CA aneurysm first detected after IVMP, which had been given on day 10 to 24 of illness (mean day 15). In these patients, post-steroid echocardiograms were performed on days 13 to 49 (mean day 23) of illness, 1 to 25 days (mean 9 days) after IVMP. CA aneurysms, including 3 giant aneurysms, persisted in 5 patients (19%), but aneurysms had resolved in the remaining patients at the time of last followup (median 14 months; range 3 months to 5 years from diagnosis). Nine patients (35%) developed CA dilatations without evidence of CA aneurysms. In 3 patients these persisted at the last followup (median 3 months; range 2.5-10 months). Of patients with greater than or equal to one-year followup (n = 17), 46% had resolution of CA abnormalities.

In univariate analysis, younger age (less than 12 mos) was significantly related to the risk of developing a CA aneurysm ($p = 0.022$), consistent with other studies. No relationship was found between CA abnormalities and gender, duration of fever, or treatment with IVIG within 10 days of illness onset.

Adverse effects of corticosteroids. The sole reported adverse reaction to pulse therapy with IVMP was an urticarial rash in one patient.

DISCUSSION

One of the major challenges in the current management of KD is the treatment of patients who fail to respond to initial therapy with IVIG[27]. Treatment of this subgroup of patients with refractory KD has included additional IVIG, corticosteroids, and much less commonly, various immunosuppressive agents including cyclophosphamide and cyclosporin A[27-29], as well as plasma exchange[30] and the monoclonal antibody against tumor necrosis factor-alpha, infliximab[31]. In the current study, KD refractory to IVIG was the most common indication for corticosteroid use in patients with KD, and this treatment was found to be effective in the treatment of fever in the majority of patients. This is consistent with the limited published literature of corticosteroid use in refractory KD, in which prompt defervescence with corticosteroid treatment has been reported in small numbers of patients in 3 case series[13,15,24]. In addition, more rapid resolution of fever was seen with corticosteroids in the one prospective study of refractory KD patients that compared pulse steroid therapy to additional IVIG[16].

Corticosteroid use in our study population had a good short-term safety profile, with no significant reported adverse effects related to the infusion. The detection of CA abnormalities for the first time after corticosteroid treatment in 7 patients raises the question of whether any of these changes were related to the steroid treatment. However, the design of this retrospective study, and the lack of echocardiograms just before the use of IVMP, make it impossible to determine if

Table 2. Timing and results of IVMP treatment and pre-and post-steroid echocardiograms in patients with normal echocardiograms prior to IVMP and CA abnormalities first detected after corticosteroids.

Patient	Pre-Steroid Echo (day of illness)	Pre-Steroid Echo (result)	IVMP (day of illness)	First Post-Steroid Echo (day of illness)	First Post-Steroid Echo (result)	Days of Fever After IVMP	Echo at Last F/U (result)	Echo at Last F/U (mos)*
1	10	Normal	13	18	GCAA	3	GCAA	30
2	8	Normal	24	49	CAA	10	Normal	14
3	10	Normal	10	28	CAD	1	Normal	17
4	6	Normal	12	28	CAD	0	Normal	5
5	6	Normal	6	9	Normal	1	CAD	2.5

IVMP: intravenous methylprednisolone; GCAA: giant coronary artery aneurysm; CAA: coronary artery aneurysm; CAD: coronary artery dilatation. * Months after onset of KD.

corticosteroids played a role in the development of CA abnormalities. In 2 of these patients who had CA abnormalities first detected after IVMP treatment, echocardiography had not been performed prior to corticosteroid treatment, and it is therefore possible that CA abnormalities pre-dated corticosteroid treatment. In the 5 patients with normal baseline echocardiograms, who had CA abnormalities documented for the first time after corticosteroids (Table 2), the significant time periods between the pre-steroid echocardiograms and the first followup echocardiograms after IVMP, also make it impossible to determine if corticosteroids affected CA outcome. The echocardiograms prior to corticosteroid treatment were performed very early in the disease course (mean: day 8 of illness), and the echocardiograms showing CA abnormalities after corticosteroid treatment were performed between day 18 and 49 of illness (mean: day 23). It is, therefore, quite possible that these findings represent the natural history of the disease, as maximal CA dimensions have been reported 2 to 4 weeks from the onset of KD. The finding that fever persisted for greater than 24 hours following IVMP in the 2 patients in this group who developed CA aneurysms (Table 2) suggests that continuing active disease may have played a role in aneurysm formation. In the small prospective study of patients with refractory KD reported by Hashino, *et al*, CA abnormalities were also detected for the first time after corticosteroid pulse therapy. In that study, there was no statistically significant difference in the incidence of CA abnormalities found in the group treated with 20 mg/kg IVMP (77.8%) versus the group who received a third dose of 1 g/kg IVIG (62.5%)[16]. However, the study included only 17 patients, 9 of whom received corticosteroids, and did not have sufficient power to detect a beneficial or harmful effect of corticosteroids. In the 3 patients with transient CA dilatation during pulse therapy, the diameter of all CA had returned to baseline values 21 days after corticosteroid treatment[16].

Both the potentially beneficial and deleterious vascular effects of corticosteroids must be considered when contemplating their use in KD. Theoretically, corticosteroids should be effective in the treatment of KD, because the pathologic abnormality of the coronary arteries is a medium vessel vasculitis. The use of corticosteroids is widely accepted as part of standard treatment in most forms of vasculitis[32]. High doses of corticosteroids result in decreased inflammation by suppressing cytokine production, as well as by decreasing endothelial expression of cellular adhesion molecules[24,33,34]. Nevertheless, there are concerns that corticosteroids have the potential to impair remodeling of damaged vessel walls and may predispose to the development of aneurysms[16,18,35,36]. Smooth muscle proliferation and intimal thickening are believed to be the mechanisms of CA repair and aneurysm regression in KD[3,37]. *In vitro* studies have shown a reduction in the proliferative capacity of smooth muscle cells in the presence of corticosteroids[38,39], with the most pronounced effect seen in injured vessels. Cytokines that are involved in the reconstruction of the inflamed coronary vessel wall may also be inhibited by corticosteroids[35,40]. The procoagulant effect of corticosteroids is also of concern, particularly in the subacute phase of KD when the risk of thrombosis is highest[13]. Most patients in our series were treated with high dose pulse therapy with IVMP, which provides a potent antiinflammatory effect but has a very short half life[41]. It is possible that high dose pulse therapy, administered for a limited time during the acute disease together with administration of ASA, may turn off proinflammatory cytokines and the benefits may outweigh the potential negative effects on the vascular remodeling process.

A high prevalence of CA abnormalities was detected on echocardiograms performed on our study patients prior to corticosteroid treatment (42%). This likely reflects the fact that this was a select group of patients, all of whom had failed to respond to IVIG[12,13,16,42]. Previous studies that have also shown a high frequency of CA abnormalities among patients who have failed initial IVIG treatment include Hashino, *et al*[16] 48.6%; Fukunishi, *et al*[43] 38.5%; Han, *et al*[11] 76%; and Wallace, *et al*[13] 27% (CA aneurysms only). Prolonged duration of fever, which is the most consistent predictor of poor coronary outcome[44,45], likely contributed to the high frequency of CA abnormalities in our patients (median fever duration 12 days, range 6-49). It is reassuring that the frequency of CA abnormalities persisting at or beyond one year followup had decreased by close to 50%, which is consistent with previous studies[3,11], and suggests that corticosteroids did not significantly delay the healing process. This needs to be confirmed in future studies.

Limitations of this study include its retrospective nature, the lack of a control population, and the fact that patients were assessed in different institutions and received varying treatment regimens, including variable timing and numbers of IVIG infusions, and different doses and numbers of pulse IVMP. In addition, echocardiograms were not all assessed by a single cardiologist, Z scores could not be calculated because of missing data due to the retrospective nature of much of this review, and not all children had an echocardiogram within one day of starting steroids or within one day of becoming afebrile. The timing of echocardiograms is critical in determining the possible effects of corticosteroids on CA outcome, and the variable timing of echocardiograms in this study made it impossible to determine if corticosteroids played a role in the development of CA abnormalities. Nevertheless, the presence of a collaborative network of Canadian researchers (CPRA members) made possible a review of the national experience of corticosteroid treatment in KD, and as a result, the number of IVIG-refractory, corticosteroid-treated patients in this study is larger than in any previous report.

We conclude that persistent or recurrent fever is the most common indication for corticosteroid use in KD in Canada. Corticosteroids appeared effective for fever resolution in refractory KD and had a good short-term safety profile.

However, our study, like the growing body of literature on corticosteroid use in KD, could not determine if there was a beneficial or harmful effect of corticosteroids on CA outcome in this subgroup of KD. It is reassuring that many of the patients treated with corticosteroids had resolution of CA abnormalities on echocardiography at last followup. Had echocardiograms been routinely performed just before steroid use, and correlated with the length of continuing disease after corticosteroids, then the data would be more appropriate to answer the question of effects of corticosteroids on CA outcome. In the absence of specific therapy for KD directed against the causative agent(s), a multicenter randomized controlled trial of corticosteroids in patients with IVIG refractory KD is needed to evaluate their effect on coronary artery outcome.

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REFERENCES

1. Kawasaki T, Kosaki F, Okawa S, Shigematsu I, Yanagawa H. A new infantile acute febrile mucocutaneous lymph node syndrome (MLNS) prevailing in Japan. Pediatrics 1974;54:271-6.
2. Melish ME. Kawasaki syndrome. Pediatr Rev 1996;17:153-62.
3. Kato H, Sugimura T, Akagi T, et al. Long-term consequences of Kawasaki disease. A 10- to 21-year follow-up study of 594 patients. Circulation 1996;94:1379-85.
4. Burns JC, Glode MP. Kawasaki syndrome. Lancet 2004;364:533-44.
5. Taubert KA, Rowley AH, Shulman ST. Nationwide survey of Kawasaki disease and acute rheumatic fever. J Pediatr 1991;119:279-82.
6. Furusho K, Kamiya T, Nakano H, et al. High-dose intravenous gammaglobulin for Kawasaki disease. Lancet 1984;2:1055-8.
7. Newburger JW, Takahashi M, Burns JC, et al. The treatment of Kawasaki syndrome with intravenous gamma globulin. N Engl J Med 1986;315:341-7.
8. Newburger JW, Takahashi M, Beiser AS, et al. A single intravenous infusion of gamma globulin as compared with four infusions in the treatment of acute Kawasaki syndrome. N Engl J Med 1991;324:1633-9.
9. Durongpisitkul K, Gururaj VJ, Park JM, Martin CF. The prevention of coronary artery aneurysm in Kawasaki disease: a meta-analysis on the efficacy of aspirin and immunoglobulin treatment. Pediatrics 1995;96:1057-61.
10. Terai M, Shulman ST. Prevalence of coronary artery abnormalities in Kawasaki disease is highly dependent on gamma globulin dose but independent of salicylate dose. J Pediatr 1997;131:888-93.
11. Han RK, Sinclair B, Newman A, et al. Recognition and management of Kawasaki disease. CMAJ 2000;162:807-12.
12. Burns JC, Capparelli EV, Brown JA, Newburger JW, Glode MP. Intravenous gamma-globulin treatment and retreatment in Kawasaki disease. US/Canadian Kawasaki Syndrome Study Group. Pediatr Infect Dis J 1998;17:1144-8.
13. Wallace CA, French JW, Kahn SJ, Sherry DD. Initial intravenous gammaglobulin treatment failure in Kawasaki disease [abstract]. Pediatrics 2000;105:E78.
14. Sundel RP, Burns JC, Baker A, Beiser AS, Newburger JW. Gamma globulin re-treatment in Kawasaki disease. J Pediatr 1993;123:657-9.
15. Wright DA, Newburger JW, Baker A, Sundel RP. Treatment of immune globulin-resistant Kawasaki disease with pulsed doses of corticosteroids. J Pediatr 1996;128:146-9.
16. Hashino K, Ishii M, Iemura M, Akagi T, Kato H. Re-treatment for immune globulin-resistant Kawasaki disease: a comparative study of additional immune globulin and steroid pulse therapy. Pediatr Int 2001;43:211-7.
17. Kato H, Koike S, Yokoyama T. Kawasaki disease: effect of treatment on coronary artery involvement. Pediatrics 1979;63:175-9.
18. Yanagawa H, Kawasaki T, Shigematsu I. Nationwide survey on Kawasaki disease in Japan. Pediatrics 1987;80:58-62.
19. Kusakawa S, Tatara K. Efficacies and risks of aspirin in the treatment of the Kawasaki disease. Prog Clin Biol Res 1987;250:401-13.
20. Kijima Y, Kamiya T, Suzuki A, Hirose O, Manabe H. A trial procedure to prevent aneurysm formation of the coronary arteries by steroid pulse therapy in Kawasaki disease. Jpn Circ J 1982;46:1239-42.
21. Nonaka Z, Maekawa K, Okabe T, et al. Randomized controlled study of intravenous prednisolone and gamma globulin treatment in 100 cases with Kawasaki disease. Proceedings of the Fifth International Symposium on Kawasaki Disease 1995:328-31.
22. Shinohara M, Sone K, Tomomasa T, Morikawa A. Corticosteroids in the treatment of the acute phase of Kawasaki disease. J Pediatr 1999;135:465-9.
23. Sundel RP, Baker AL, Fulton DR, Newburger JW. Corticosteroids in the initial treatment of Kawasaki disease: report of a randomized trial. J Pediatr 2003;142:611-6.
24. Okada Y, Shinohara M, Kobayashi T, Inoue Y, Tomomasa T, Morikawa A. Effect of corticosteroids in addition to intravenous gamma globulin therapy on serum cytokine levels in the acute phase of Kawasaki disease in children. J Pediatr 2003;143:363-7.
25. Dale RC, Saleem MA, Daw S, Dillon MJ. Treatment of severe complicated Kawasaki disease with oral prednisolone and aspirin. J Pediatr 2000;137:723-6.
26. Dajani AS, Taubert KA, Takahashi M, et al. Guidelines for long-term management of patients with Kawasaki disease. Report from the Committee on Rheumatic Fever, Endocarditis, and Kawasaki Disease, Council on Cardiovascular Disease in the Young, American Heart Association. Circulation 1994;89:916-22.
27. Freeman AF, Shulman ST. Refractory Kawasaki disease. Pediatr Infect Dis J 2004;23:463-4.
28. Raman V, Kim J, Sharkey A, Chatila T. Response of refractory Kawasaki disease to pulse steroid and cyclosporin A therapy. Pediatr Infect Dis J 2001;20:635-7.
29. Kuijpers TW, Biezeveld M, Achterhuis A, et al. Longstanding obliterative panarteritis in Kawasaki disease: lack of cyclosporin A effect. Pediatrics 2003;112:986-92.
30. Imagawa T, Mori M, Miyamae T, et al. Plasma exchange for refractory Kawasaki disease. Eur J Pediatr 2004;163:263-4.
31. Lawrence S, Burns J, Bastian Jea. Infliximab therapy for refreactory Kawasaki disease [abstract]. Pediatr Res 2003;53:1929A.
32. Petty R, Cassidy J. Polyarteris nodosa and related vasculitides. In: Cassidy JT, Petty RE, editors. Textbook of Pediatric Rheumatology. Philadelphia: WB Saunders; 2001:595-603.
33. Youssef PP, Haynes DR, Triantafillou S, et al. Effects of pulse methylprednisolone on inflammatory mediators in peripheral blood, synovial fluid, and synovial membrane in rheumatoid arthritis. Arthritis Rheum 1997;40:1400-8.
34. Cronstein BN, Kimmel SC, Levin RI, Martiniuk F, Weissmann G. A mechanism for the antiinflammatory effects of corticosteroids: the glucocorticoid receptor regulates leukocyte adhesion to endothelial cells and expression of endothelial-leukocyte adhesion molecule 1 and intercellular adhesion molecule 1. Proc Natl Acad

Sci U S A 1992;89:9991-5.
35. Suzuki N, Seguchi M, Kouno C, Inukai K, Kito H, Kobayashi H. Rupture of coronary aneurysm in Kawasaki disease. Pediatr Int 1999;41:318-20.
36. Takahashi M, Mason W, Lewis AB. Regression of coronary aneurysms in patients with Kawasaki syndrome. Circulation 1987;75:387-94.
37. Sasaguri Y, Kato H. Regression of aneurysms in Kawasaki disease: a pathological study. J Pediatr 1982;100:225-31.
38. Longenecker JP, Kilty LA, Johnson LK. Glucocorticoid influence on growth of vascular wall cells in culture. J Cell Physiol 1982;113:197-202.
39. Voisard R, Seitzer U, Baur R, et al. Corticosteroid agents inhibit proliferation of smooth muscle cells from human atherosclerotic arteries in vitro. Int J Cardiol 1994;43:257-67.
40. Matsubara T, Furukawa S, Yabuta K. Serum levels of tumor necrosis factor, interleukin 2 receptor, and interferon-gamma in Kawasaki disease involved coronary-artery lesions. Clin Immunol Immunopathol 1990;56:29-36.
41. Baylis EM, Williams IA, English J, Marks V, Chakraborty J. High dose intravenous methylprednisolone "pulse" therapy in patients with rheumatoid disease. Plasma methylprednisolone levels and adrenal function. Eur J Clin Pharmacol 1982;21:385-8.
42. Ichida F, Fatica NS, Engle MA, et al. Coronary artery involvement in Kawasaki syndrome in Manhattan, New York: risk factors and role of aspirin. Pediatrics 1987;80:828-35.
43. Fukunishi M, Kikkawa M, Hamana K, et al. Prediction of non-responsiveness to intravenous high-dose gamma-globulin therapy in patients with Kawasaki disease at onset. J Pediatr 2000;137:172-6.
44. Koren G, Lavi S, Rose V, Rowe R. Kawasaki disease: review of risk factors for coronary aneurysms. J Pediatr 1986;108:388-92.
45. Levy M, Koren G. Atypical Kawasaki disease: analysis of clinical presentation and diagnostic clues. Pediatr Infect Dis J 1990; 9:122-6.