ARTICLE

Management and Outcome of Persistent or Recurrent Fever After Initial Intravenous Gamma Globulin Therapy in Acute Kawasaki Disease

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Objective: To determine differences in clinical characteristics, laboratory findings, and cardiac complications between patients with acute Kawasaki disease who received additional treatment for persistent or recurrent fever vs those who did not.

Design: Nonconcurrent case series; medical record review.

Setting: Tertiary care pediatric hospital.

Patients: One hundred eighty-five consecutive patients diagnosed as having acute Kawasaki disease at The Hospital for Sick Children, Toronto, Ontario, from 1995 to 1997.

Main Outcome Measure: Prevalence of cardiac complications.

Results: Twenty-one patients (11%) received additional treatment with intravenous gamma globulin (IVGG) with or without intravenous methylprednisolone for persistent fever lasting for more than 48 hours or recurrent fever after initial treatment with IVGG. Patients who received additional treatment did not differ significantly from other patients regarding age, sex, race, or diagnostic criteria. Compared with the patients who did not receive additional therapy, the patients who received additional treatment had shorter median interval from fever onset to initial dose of IVGG (5 vs 6 days; $P=.006$) and longer total days of fever (9 vs 6 days; $P<.001$). Initial laboratory investigations did not differ significantly. On initial echocardiography, patients who received additional therapy were significantly more likely to have pericardial effusion (33% vs 15%; $P=.04$), ventricular dysfunction (14% vs 2%; $P=.002$), and coronary artery ectasia (76% vs 43%; $P=.004$) but not aneurysms (10% vs 5%; $P=.47$). At 12 months after diagnosis, there were no significant differences between the 2 groups regarding the prevalence of coronary artery ectasia or aneurysms.

Conclusion: Patients receiving additional treatment for persistent or recurrent fever have similar demographic and clinical characteristics, greater initial cardiac involvement, and similar overall outcomes.

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KAWASAKI DISEASE is the leading cause of acquired heart disease in children in the developed world, with coronary artery aneurysms occurring in 20% to 25% of untreated cases.[1,2] Treatment with intravenous gamma globulin (IVGG) within 10 days of onset of fever has been shown in clinical trials to reduce the risk of coronary artery aneurysms to 4% to 8%.[2,3] However, 10% to 30% of children treated with IVGG are refractory to treatment and are febrile for at least 3 days after treatment initiation.[3,4]

Additional treatment with IVGG appears to be safe,[4] but a number of children continue to have persistent or relapsing fever despite the additional courses of IVGG.[4,5] In contrast, although IV corticosteroids have been found to be efficacious in resolving fever,[1,6] Kato et al[1] reported that the use of steroids was associated with an increased prevalence of coronary artery aneurysms as high as 65%. Other studies have found no increased risk.[5-7] Thus, the appropriate management of children with persistent or relapsing fever despite standard therapy remains controversial.

The purpose of this study was to determine differences in clinical characteristics, laboratory findings, and cardiac complications between patients with acute Kawasaki disease who received additional treatment with IVGG and/or IV corticosteroids for persistent or recurrent fever and patients who did not.

PATIENTS AND METHODS

STUDY POPULATION

The subjects were consecutive patients diagnosed as having acute Kawasaki disease at The Hospital for Sick Children, Toronto, Ontario, between January 1, 1995, and December 31, 1997. The decision to administer additional doses of IVGG and/or IV corticosteroids was individualized and at the discretion of the treating physician, although it has been our policy to use a second dose of IVGG initially for patients with persistent (>48 hours) or recurrent fever after initial treatment with IVGG.

MEASUREMENTS

Medical record review was performed to abstract patient demographics, clinical findings, course of fever, treatment received, and cardiac complications. As per an institutional protocol, all patients diagnosed as having acute Kawasaki disease were evaluated with laboratory investigations and echocardiography at the time of hospital admission and at 1 month, 2 months, and 1 year after diagnosis. Most clinical information was maintained concurrently in a computer database. Echocardiographic findings at diagnosis, maximal findings at 1 to 2 months after diagnosis, and findings at 1 year after diagnosis are reported. Angiography was reserved for patients with giant coronary artery aneurysms and multiple nongiant coronary artery aneurysms.

DATA ANALYSIS

Data are described as frequencies, medians with ranges, and means with SDs as appropriate. Differences in characteristics and outcomes of patients who did and did not receive additional treatment were sought with χ^2 tests, Fisher exact tests, *t* tests, and Kruskal-Wallis analysis of variance as appropriate. Where there are missing data, the number of nonmissing values is given.

RESULTS

A total of 185 children were diagnosed as having acute Kawasaki disease at The Hospital for Sick Children from January 1, 1995, to December 31, 1997. The **Figure** illustrates the treatment received and response to treatment. Six children were not treated with IVGG because of late presentation with resolution of fever at time of diagnosis or parental refusal. None of these children subsequently developed coronary artery aneurysms, although 2 had transient coronary artery ectasia on follow-up echocardiograms. The remaining 179 children received 1 dose of IVGG (2 g/kg), with 155 children showing defervescence within 48 hours and remaining afebrile. One child whose fever resolved with the single course of IVGG was treated with an additional course of IVGG (1 g/kg) and IV methylprednisolone (30 mg/kg daily for 3 days followed by a tapering course of oral prednisone) for myocarditis with reduced ventricular function. This child was not included in the additional treatment group for data analysis, since the patient received additional treatment for myocarditis rather than for persistent or recurrent fever. In contrast, 24 children (13%) had fever that persisted for more than 48 hours after the single dose of IVGG or had a recurrence of fever. Three of these children did not receive additional treatment and experienced defervescence within 72 hours of the initial course of IVGG.

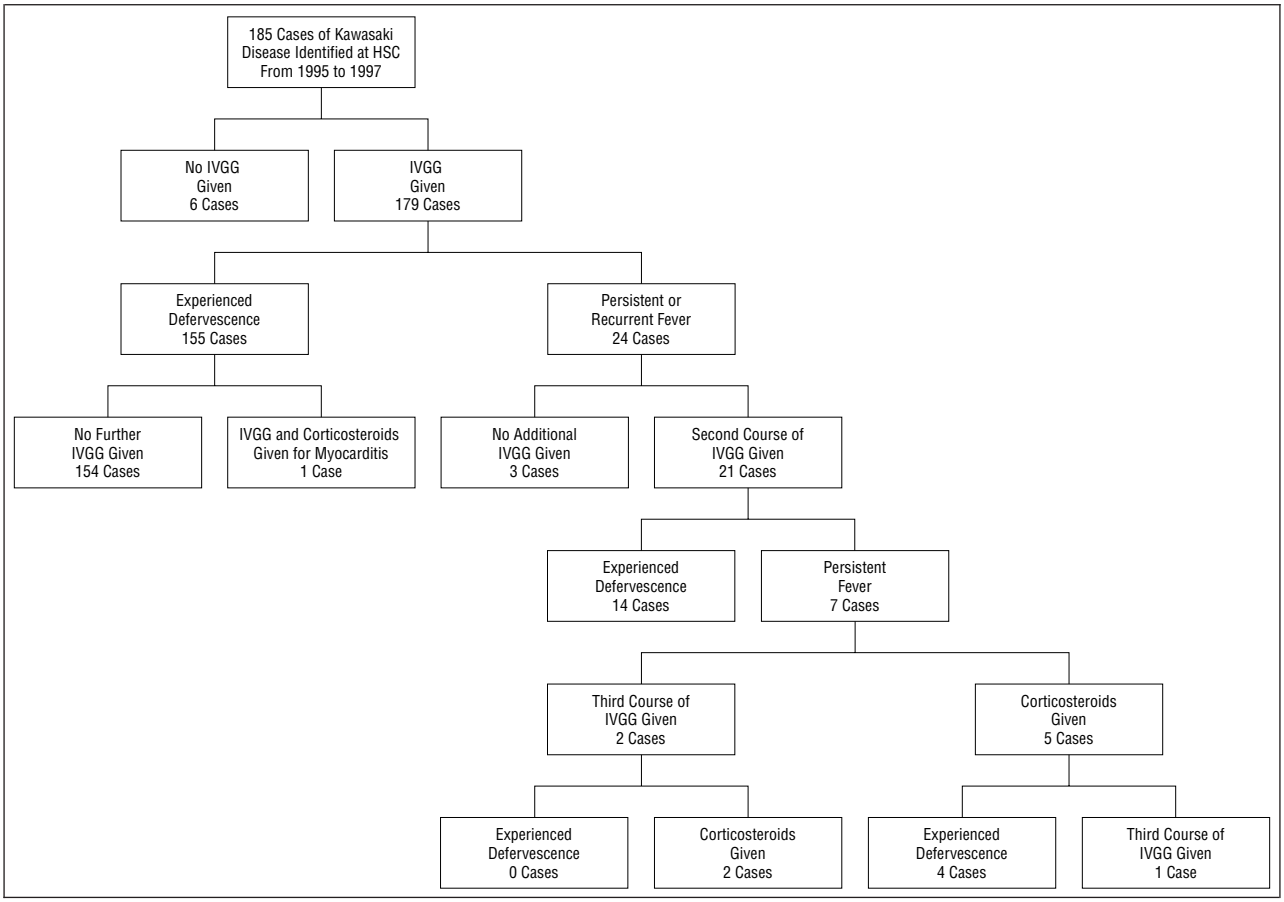
The remaining 21 children (11%) received additional treatment for persistent or recurrent fever. All 21 children were first treated with a second course of IVGG (1 or 2 g/kg). Fever resolved within 24 hours of the second course of IVGG in 14 children (67%) but persisted in 7 children. Two of the children with persistent fever were then treated with a third dose of IVGG (1 or 2 g/kg). Neither responded to the third course and were treated with IV methylprednisolone (30 mg/kg daily for 1 or 3 days). The remaining 5 children who did not respond to the first 2 courses of IVGG were treated with IV methylprednisolone (30 mg/kg daily for 1 or 3 days) rather than a third course of IVGG. Two of 3 children who received a 3-day course of IV methylprednisolone were then prescribed a tapering course of oral prednisone. One child who received a 1-day course of IV methylprednisolone had a recurrence of fever 3 days after the IV methylprednisolone and was treated with a third dose of IVGG (2 g/kg), with resolution of fever.

The demographic data for the 21 patients who received additional treatment for persistent or recurrent fever and the 164 patients who did not are presented in **Table 1**. There were no significant differences between the 2 groups regarding median age, sex, or race.

Table 2 compares the clinical characteristics of the 2 groups. There were no significant differences in the number of diagnostic criteria, Kawasaki disease type, or frequency of specific clinical characteristics. The median number of days from fever onset to the initial dose of IVGG was significantly less in the additional treatment group compared with the no additional treatment group (5 vs 6 days; $P=.006$). The median total number of days of fever (9 vs 6 days; $P<.001$) and median number of days in hospital (8 vs 3 days; $P<.001$) were significantly greater in the additional treatment group.

Table 3 shows the laboratory test results at the time of hospital admission and at 1 month, 2 months, and 1 year after diagnosis. There were no significant differences in the initial laboratory findings between the 2 groups, with the exception of higher median alanine aminotransferase levels in the additional treatment group (85.5 U/L) vs the no additional treatment group (28 U/L; $P=.02$).

Table 4 shows the echocardiographic findings at the time of hospital admission and at 1 to 2 months and 1 year after diagnosis. On initial echocardiography, children who received additional treatment were significantly more likely to have pericardial effusion (33% vs 15%; $P=.04$); ventricular dysfunction, defined as an ejection fraction of less than 55% (14% vs 2%; $P=.002$); and coronary artery ectasia (76% vs 43%; $P=.004$) but not coronary artery aneurysms (10% vs 5%; $P=.47$). How-



Flowchart showing treatment received and response to treatment. HSC indicates The Hospital for Sick Children; IVGG, intravenous gamma globulin.

Table 1. Demographic Data

Variable	No Additional Treatment (n = 164)	Additional Treatment (n = 21)	*P*
Median age, y (range)	3.0 (0.2-13)	3.6 (0.5-15.2)	.31
Sex, No. (%)			
Male	110/164 (67)	15/21 (71)	.69
Female	54/164 (33)	6/21 (29)	
Race, No. (%)			
White	89/154 (58)	9/19 (47)	.49
Asian	34/154 (22)	8/19 (42)	
Other	31/154 (20)	2/19 (11)	

ever, at 1 year after diagnosis, there was no significant difference between the 2 groups regarding coronary artery ectasia or aneurysms.

All patients diagnosed as having Kawasaki disease underwent echocardiography at diagnosis. None of the patients with initial cardiac findings or who received additional treatment were lost to follow-up. Of the patients who did not have coronary artery aneurysms at diagnosis, 3 developed aneurysms at 2 months after diagnosis. Of these 3 patients, 1 had persistent aneurysms at 1 year, 1 had no aneurysms at 1 year, and 1 was subsequently lost to follow-up. None of the patients with no coronary artery aneurysms at 2 months after diagnosis were subsequently found to have aneurysms at 1 year after diagnosis. Angiography was used in a select number of patients and was in agreement with echocardiographic findings.

COMMENT

A considerable proportion of children with acute Kawasaki disease do not respond to standard therapy with IVGG. Previous studies have reported that 10% to 30% of children have fever persisting for 72 hours or more after the initial IVGG therapy is completed.[3,4] In our study, we found that 24 (13%) of 185 children diagnosed as having acute Kawasaki disease had fever that persisted more than 48 hours after the initial IVGG treatment or had a recurrence of fever. Of these, 21 children received additional treatment, all with a second course of IVGG, 3 with a third course of IVGG, and 7 with IV methylprednisolone.

We found no significant difference between the children who received additional treatment and those who did not in age, sex, race, or clinical characteristics. There was also no significant difference in laboratory results on admission and at 1 month, 2 months, and 1 year after diagnosis. We also found that, although patients receiving additional treatment were more likely to have coronary artery ectasia on initial echocardiography, they were not more likely to have coronary artery aneurysms. There were no significant differences in the

prevalence of coronary artery ectasia or aneurysms at 1 year after diagnosis.

One interesting finding was that children who received additional treatment had a significantly lower median number of days from fever onset to the initial course of IVGG. The significance of this is unclear. Yanagawa et al[8] had found that there were greater cardiac sequelae and giant aneurysms in children who received IVGG on day 3 or less of their illness, although this was not as dramatic as those who received IVGG on day 10 or more. The authors had hypothesized that this was due to a bias caused by including severe cases with full clinical symptoms as early as day 3 after onset. Similarly, the earlier initial treatment in the additional treatment group in our study may be due to bias caused by more severe cases in the additional treatment group and/or inclusion of more cases with late presentations in the no additional treatment group. Yanagawa et al[8] also found that the prevalence of cardiac sequelae and giant coronary artery aneurysms was at the lowest in children treated with IVGG between day 6 and day 8 of illness. Hence, another possible explanation may be that there is a narrow window within which IVGG is most effective, with decreased effectiveness not only with delayed treatment but also with too early treatment.

However, there are a number of limitations of our study that need to be considered. First, this was a nonconcurrent study, in which patients were not randomized to treatment regimens. There were no established protocols for additional treatment for persistent or recurrent fever. Second, the subjects were a heterogeneous group. Since the treatment decisions were largely at the discretion of the treating physician, patients in the additional treatment group received various combinations of additional courses of IVGG and/or IV methylprednisolone at different doses. Also, patients who did not receive additional treatment included patients with persistent fever lasting longer than 48 hours, patients who had not received any IVGG, and patients who were treated with IVGG more than 10 days after fever onset. Finally, the additional treatment group was composed of a small number of patients, which likely compounded the difficulties caused by the lack of randomization and heterogeneity of the patients.

The appropriate management of children with persistent or recurrent fever despite an appropriate initial dose of IVGG treatment is uncertain. Intravenous gamma globulin significantly reduces the risk of cardiac complication compared with aspirin only as initial treatment.[2,9] Additional treatment with further courses of IVGG has been found to be safe, with no evidence of congestive heart failure, increased prevalence or exacerbation of myocardial dysfunction, or hypotension.[4] However, the same study found that 30% of children receiving a second course of IVGG continued to have persistent or recrudescent fever, and 50% of these patients did not respond to a third course of IVGG.[4] Similarly, Wright et al[5] found that 2% of all children treated for acute Kawasaki disease had "IVGG-resistant" disease, which did not respond to additional doses of IVGG. In our study, one third of patients who received a second dose of IVGG continued to have persistent fever, and neither of the 2 patients who received a third dose of IVGG responded. Hence, although treatment with additional doses of IVGG may be safe, it does not appear to be highly effective against persistent fever.

Table 2. Clinical Characteristics

Characteristic	No Additional Treatment (n = 164)	Additional Treatment (n = 21)	P
No. of diagnostic criteria, No. (%)			
3	2 (1)	0 (0)	.62
4	16 (10)	1 (5)	
5	60 (37)	6 (29)	
6	86 (52)	14 (67)	
Kawasaki disease type, No. (%)			
Typical	146 (89)	20 (95)	.48
Atypical	7 (4)	1 (5)	
Incomplete	11 (7)	0 (0)	
Clinical criteria, No. (%)			
Conjunctivitis	154 (94)	20 (95)	.81
Cervical lymphadenopathy	121 (74)	15 (71)	.82
Oral mucosal changes	160 (98)	21 (100)	.47
Rash	149 (91)	21 (100)	.15
Extremity changes	138 (84)	20 (95)	.18
Median No. of days from fever onset to initial dose of IVGG (range)*	6 (2-29)	5 (4-9)	.006
Median total No. of days of fever (range)	6 (2-29)	9 (5-11)	<.001
Median No. of days in hospital (range)	3 (0-23)	8 (2-28)	<.001

*Excludes 6 patients not treated with intravenous gamma globulin (IVGG).

In contrast, corticosteroids appear to be more effective in the resolution of fever compared with IVGG.[5,6] However, the use of corticosteroids in acute Kawasaki disease had been considered unsafe, since Kato et al[1] reported that 65% of patients who had received oral prednisolone alone (2-3 mg/kg daily for at least 2 weeks, then 1-1.5 mg/kg daily for 2 weeks) for treatment of acute Kawasaki disease developed coronary artery aneurysms at 1 to 2 months after fever onset. The authors had hypothesized that steroids may act to expedite the formation of coronary artery aneurysms and inhibit the intimal proliferation within the aneurysms, thus preventing aneurysm regression. Of note, none of the patients who received oral prednisolone and aspirin (30 mg/kg daily) in combination developed coronary artery aneurysms in that same study. More recently, studies have found that corticosteroids, when used with aspirin, are not associated with an increased rate of coronary artery aneurysms when used as initial treatment of acute Kawasaki disease[6,7] and for the treatment of persistent or recurrent fever after initial treatment with IVGG.[5] Thus, the use of corticosteroids needs to be reevaluated as an option for patients who do not respond to an initial dose of IVGG and perhaps for initial treatment for acute Kawasaki disease.

In conclusion, the optimal treatment of the 10% to 30% of children with persistent or recurrent fever despite initial treatment with IVGG remains controversial. There appear to be no characteristics that distinguish these nonresponders. Patients who received additional treatment had a greater number of abnormali-

Table 3. Laboratory Results*

Laboratory Components	No Additional Treatment (n = 164) No.	No Additional Treatment (n = 164) Median (Range)	Additional Treatment (n = 21) No.	Additional Treatment (n = 21) Median (Range)	P
At hospital admission					
Albumin, g/L	84	35.5 (21-59)	15	7 (26-43)	.81
ALT, U/L	103	28 (6-781)	18	85.5 (8-296)	.01
AST, U/L	102	38 (9-545)	17	48 (23-181)	.16
ESR, mm/h	96	82.5 (1-134)	16	63 (4-135)	.46
Hemoglobin, g/L	111	107 (81-141)	19	108 (86-138)	.25
Leukocytes, $\times 10^9$/L	116	13.4 (2.8-37.8)	20	13.4 (3.5-29.3)	>.99
Platelets, $\times 10^9$/L	111	363 (47-1176)	20	324 (110-631)	.14
At 1 mo					
Albumin, g/L	54	40 (31-46)	8	37 (28-42)	.16
ALT, U/L	9	31 (24-147)	0	. . .	. . .
AST, U/L	57	38 (23-71)	8	36.5 (16-177)	.59
ESR, mm/h	55	31 (1-99)	8	47.5 (16-126)	.08
Hemoglobin, g/L	57	113 (89-137)	8	100.5 (85-119)	.03
Leukocytes, $\times 10^9$/L	57	7.7 (4-17.5)	8	8.4 (5.7-17.6)	.91
Platelets, $\times 10^9$/L	57	330 (126-832)	8	414 (231-1462)	.13
At 2 mo					
Albumin, g/L	89	41 (27-47)	9	41 (34-46)	.88
ALT, U/L	14	28.5 (20-37)	1	52	. . .
AST, U/L	88	39 (21-73)	10	31.5 (21-54)	.05
ESR, mm/h	90	6.5 (1-60)	10	21 (1-80)	.03
Hemoglobin, g/L	92	119 (93-139)	10	107 (93-134)	.14
Leukocytes, $\times 10^9$/L	92	8.4 (3.9-16.6)	10	9.2 (7.1-41.9)	.30
Platelets, $\times 10^9$/L	91	352 (200-602)	10	419 (230-675)	.09
At 1 y					
Albumin, g/L	31	42 (34-50)	3	41 (39-42)	.51
ALT, U/L	2	28.5 (19-38)	0	. . .	. . .
AST, U/L	30	36 (19-59)	5	32 (24-34)	.13
ESR, mm/h	33	8 (1-95)	5	12 (8-40)	.23
Hemoglobin, g/L	33	122 (76-147)	5	117 (107-120)	.10
Leukocytes, $\times 10^9$/L	33	8.1 (6.0-14.7)	5	8.5 (5.7-14.2)	>.99
Platelets, $\times 10^9$/L	33	306 (199-473)	5	295 (206-450)	.52

*ALT indicates alanine aminotransferase; AST, aspartate aminotransferase; ESR, erythrocyte sedimentation rate; and ellipses, data not applicable.

Table 4. Cardiac Findings

Findings	No. (%) of Patients: No Additional Treatment	No. (%) of Patients: Additional Treatment	P
At hospital admission	(n = 164)	(n = 21)	
Electrocardiographic changes	18 (11)	3 (14)	.66
Pericardial effusion	25 (15)	7 (33)	.04
Mitral regurgitation	25 (15)	6 (29)	.12
Aortic insufficiency	3 (2)	0 (0)	.54
Ventricular dysfunction	3 (2)	3 (14)	.002
Coronary artery ectasia	71 (43)	16 (76)	.004
Coronary aneurysm*	9 (5)	2 (10)	.47
At 1-2 mo	(n = 161)	(n = 21)	
Coronary artery ectasia	36 (22)	8 (38)	.11
Coronary aneurysm*	8 (5)	1 (5)	>.99
At 1 y	(n = 156)	(n = 21)	
Coronary artery ectasia	15 (10)	3 (14)	.45
Coronary aneurysm*	4 (3)	1 (5)	.47

*Includes 1 patient with giant coronary aneurysm in the no additional treatment group.

ties on the initial echocardiography, but there was no significant difference at 1 year after diagnosis compared with patients who had not received additional treatment. Although additional treatment with IVGG may be safe, patients may be IVGG resistant and not respond to additional courses of IVGG. The use of corticosteroids in combination with aspirin needs to be reevaluated in light of recent research in the treatment of acute Kawasaki disease as adjunctive, and possibly first-line, treatment. Further research into this area may reveal new therapeutics but will likely require multi-institutional clinical trials for sufficient enrollment. Finally, whether aggressive treatment of persistent or recurrent fever affects outcome remains unanswered.

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