

# Kawasaki disease in East Mazandaran, Islamic Republic of Iran, 1997–2002

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داء كاواساكي في مازندران الشرقية بجمهورية إيران الإسلامية في الفترة 1997–2002

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**الخلاصة:** أجرينا دراسة استيعادية لجميع حالات داء كاواساكي التي أدخلت مراكز الإحالة الرئيسية في سادي مازندران الشرقية خلال الفترة من 1 تشرين الثاني/نوفمبر 1997 إلى 30 تشرين الأول/أكتوبر 2002. وقد ثبتت إصابة 25 حالة من إجمالي 29 حالة كانت محتملة الإصابة، مما يظهر أن معدل الوقوع السنوي الوسطي كان 7.3 حالة لكل مئة ألف طفل دون الخامسة من العمر. وكان العمر الوسطي لجميع الحالات 38 شهراً (3.5 - 80 شهراً) وكانت الأكثرية من الذكور. وبلغ متوسط الزمن المنقضي بين بداية المرض وبين تشخيصه  $8.2 \pm 3.1$  يوماً. وكان 5 من المرضى من إجمالي 25 مريضاً يعانون من شذوذات قلبية وعائية قبل المعالجة. وتم علاج جميع المرضى بالغلوبيولين المناعي بالحقن في الوريد، وقد استجاب 22 مريضاً (88%) لجرعة واحدة من العلاج بالغلوبيولين المناعي والجرعات عالية من حمض الأسيتيل ساليسيليك، وقد احتاج مريضان إلى جرعة ثانية من الغلوبيولين المناعي، واحتاج مريض واحد إلى جرعة ثالثة منه. وتحقق الشفاء التام لجميع المرضى باستثناء مريض واحد يخضع للمتابعة والمعالجة.

**ABSTRACT** We conducted a retrospective review of all cases of Kawasaki disease admitted to the major referral centres in Sari, East Mazandaran from 1 November 1997 to 30 October 2002. Of 29 probable cases, 25 were confirmed, giving an average annual incidence rate of 7.3 per 100 000 in children 0–5 years. The mean age of all cases was 38 months (range: 3.5–80 months). There was a male predominance. The mean time between the onset of illness and diagnosis was  $8.2 \pm 3.1$  days. Five of the 25 patients had cardiovascular abnormalities before treatment. All patients were treated with intravenous immunoglobulin and 22 (88%) responded to a single dose of treatment and high doses of acetylsalicylic acid; 2 patients needed a second dose of IVIG, and 1 patient required a third. Complete recovery was noted in all patients except for 1, who is under follow-up and treatment.

## Maladie de Kawasaki dans la partie orientale de la province de Mazandaran (République islamique d'Iran), 1997-2002

**RÉSUMÉ** Nous avons réalisé une étude rétrospective de tous les cas de maladie de Kawasaki admis dans les principaux centres d'orientation-recours de Sari (partie orientale de la province de Mazandaran) du 1<sup>er</sup> novembre 1997 au 30 octobre 2002. Vingt-cinq (25) des 29 cas probables ont été confirmés, ce qui donne un taux d'incidence annuel de 7,3 pour 100 000 chez les enfants de 0-5 ans. L'âge moyen de tous les cas était de 38 mois (extrêmes 3,5-80 mois). Il y avait une prédominance masculine. Le temps moyen entre le début de la maladie et le diagnostic était de  $8,2 \pm 3,1$  jours. Cinq des 25 patients présentaient des anomalies cardiovasculaires avant le traitement. Tous les patients ont été traités par immunoglobuline intraveineuse et 22 (88 %) ont répondu à une seule dose de traitement et à de fortes doses d'acide acétylsalicylique ; 2 patients ont eu besoin d'une seconde dose d'immunoglobuline intraveineuse et un patient a eu besoin d'une troisième dose. Une guérison complète a été constatée chez tous les patients sauf un, qui fait l'objet d'un suivi et d'un traitement.

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## Introduction

Kawasaki disease is an acute vasculitis of infants and children which has been reported worldwide. High fever, bilateral non-purulent conjunctivitis, cervical lymphadenopathy, skin rash, and oral mucosal and extremity changes characterize the disease. The diagnosis of Kawasaki disease is clinical and based on the presence of fever and at least 4 of the above-mentioned clinical findings, after exclusion of other childhood conditions that may give rise to similar signs and symptoms [1,2]. Kawasaki disease affects the coronary arteries in 20%–25% of untreated patients [3,4]. Administration of intravenous immunoglobulin (IVIG) within the first 10 days of illness decreases the prevalence of coronary artery abnormalities (CAA) to 2%–5% [5–7]. Several infectious agents, environmental and bacterial toxins as well as unusual response to a variety of different superantigens have been suggested to cause Kawasaki disease, however the actual cause is unknown [8,9].

Epidemiological studies indicate that host factors, including age, sex and race, influence the occurrence of the disease [9]. Kawasaki disease occurs worldwide [10–18] with the highest incidence reported in Japan [10,19]. This disease is now the most common cause of acquired heart disease in North American and Japanese children [11,19,20].

Kawasaki disease was first recognized in Iranian children in the early 1980s [21]. However, except for a few case reports [22–24], little information is available on the epidemiology of the disease in our country [21]. This kind of information is particularly lacking in the northern part of the country. Thus we aimed to provide more detailed data on the epidemiological picture, clinical presentation, laboratory

findings, management and outcomes of Kawasaki disease in Iranian children in East Mazandaran (northern Islamic Republic of Iran) during the 5-year period between 1997 and 2002.

## Methods

East Mazandaran is located in the north of the Islamic Republic of Iran. It has an estimated population of 1.5 million and a temperate climate. Six hospitals in East Mazandaran admit and care for paediatric patients (1 university teaching hospital and 5 others with limited paediatric beds). We undertook a retrospective review of the medical records of all cases with Kawasaki disease referred, treated or discharged from these hospitals in the 5-year period from November 1997 to October 2002. We confirmed diagnosis of Kawasaki disease based on criteria outlined by the American Heart Association [1,2]. The diagnosis of CAA by echocardiography (2D ECHO) was based on the criteria established by the Japanese Ministry of Health [25]. Information concerning demographic, clinical and laboratory data, and management and outcome of each case was obtained from patients records. Parametric data were expressed as mean and standard deviation (SD) and range, incidence of the disease was calculated by dividing the number of positive cases by the population of the region obtained from the census office of Sari (53 000 for 0–5 years for each year; 73 000 for 5–9 years for each year).

## Results

Of 29 probable cases in the 5-year period, 25 were confirmed as Kawasaki disease. Yearly distribution of cases was: 2, 9, 5, 5, 4 for the years 1997–2002 respectively.

The average annual incidence rate of the disease was 7.3 per 100 000 in the 0–5 year age group. Figure 1 shows the age distribution of Kawasaki disease. As observed in this study, 60% of cases were younger than 3 years, with a mean age of 38 (SD 22.3) months (range 3.5–80 months). There was a male predominance of 56% (1.27/1).

As shown in Figure 2 the majority of Kawasaki disease cases occurred in autumn (10 of 25, 40%), and 32%, 16% and 12% occurred in the spring, summer and winter respectively. The mean time interval between the occurrence of the first sign and diagnosis of the disease was 8.2 (3.1) days (range 3–17 days).

Fever for longer than 5 days was the most common finding in all patients, followed by red lips and oral changes (92%), bilateral conjunctival congestion (92%), changes in peripheral extremities (84%) and polymorphous skin rash (84%). Cervical lymph node enlargement was the least frequently reported cardinal sign (72%), and 84% of patients had some other significant signs and symptoms, such as irritability, diarrhoea, vomiting and joint pain (Table 1). Most of the patients had been

seen by an outside physician and had received antibiotics prior to their admission. Mild anaemia [mean haemoglobin level of 9.5 (SD 0.92) g/dL (range: 7.5–11.5 g/dL)], and leukocytosis [mean white blood cell count of 15 700 (SD 6721)/mm<sup>3</sup> (range: 8200–37 100/mm<sup>3</sup>)] were observed in most patients (Table 2). Sequential platelet counts showed thrombocytosis [mean pretreatment platelet of 350 000 (SD 152 000)/mm<sup>3</sup> (range: 110 000–598 000)/mm<sup>3</sup>]. However, 1–2 weeks post-treatment mean platelet counts were 655 000 (SD 130 000)/mm<sup>3</sup> (range: 379 000–914 000/mm<sup>3</sup>). Most patients had evidence of an acute phase response with a rise in their erythrocyte sedimentation rate (ESR) and/or C-reactive protein concentrations, the mean ESR being 86 (SD 39.5) mm/h (range: 17–152 mm/h).

All patients received 1 course of IVIG (23 patients, single infusion: 2 g/kg body weight, 2 patients 1 g/kg), and high dose acetylsalicylic acid (60–100 mg/kg per day). Seventy-two (72) hours after completion of IVIG infusion, 22 (88%) of the 25 patients responded and became afebrile. The 3 (12%) patients with persistent fever were re-treated with a second infusion of

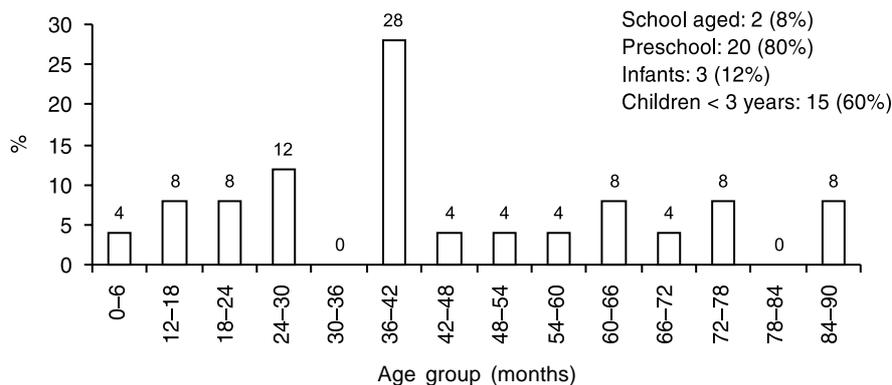


Figure 1 Age distribution of the 25 patients with Kawasaki disease in East Mazadaran by month

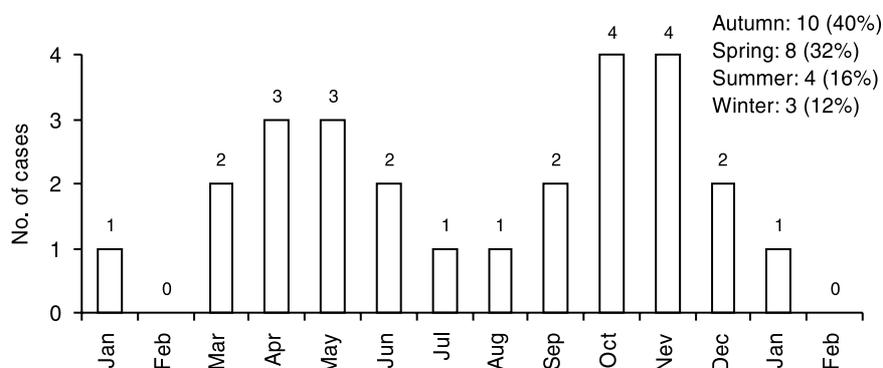


Figure 2 Monthly and seasonal distribution of Kawasaki disease in children in East Mazandaran

IVIg, 2 of whom responded to treatment. Because of progressive CAA and continued fever in 1 patient (resistant case), a third dose of IVIG (1 g/kg) was given and the patient subsequently improved.

ECG and ECHO detected cardiovascular abnormalities (CVA)-CAA in 5 out of 25 patients (20%) in the first 48 hours of diagnosis and/or treatment: one 3.5-month-old patient with evidence of ischaemic heart

disease on ECG and mild pericardial effusion on ECHO, and 4 patients with CAA on ECHO. During the 3–12 months of follow up, CVA and CAA of 4 of these patients improved. One patient continued to have mild CAA. Patients' characteristics and haematological findings of patients with or without cardiac complications are shown in Table 3. CVA-CAA were significantly more common among those who had a longer time to diagnosis and treatment [11.67 (SD 4.6) days before treatment versus 7.19 (SD 2.6) days before treatment,  $P = 0.024$ ] and older patients [60.75 (SD 20.22) months versus 32.8 (SD 21.45) months,  $P = 0.03$ ].

Table 1 Patients fulfilling the diagnostic criteria of Kawasaki disease

Criteria	No of patient (n = 25)	%
Fever > 5 days	25	100
Oral mucosal changes	23	92
Conjunctivitis	23	92
Rash	21	84
Peripheral extremity changes	21	84
Cervical lymphadenopathy	18	72
Others <sup>a</sup>	21	84

<sup>a</sup>Others: associated signs and symptoms such as nausea, vomiting, abdominal pain, irritability, drowsiness, headache, arthralgia, arthritis, dysuria, frequency, diarrhoea, hepatomegaly, tachycardia, sweating and aseptic meningitis.

## Discussion

The patients described in this study had characteristics and results of laboratory investigations similar to those reported in series from other countries. The disease was seen more often in boys than girls (1.27/1) as reported in other studies [3,10–19]. The estimated annual incidence rate of Kawasaki disease in this study was 7.3/100 000 children under 5 years of age, which is lower than that reported from Japan (90–

**Table 2 Haematological laboratory findings in the patients with Kawasaki disease**

Variable	Mean	SD	Range
Haemoglobin (g/dL)	9.5	0.92	7.5–11.5
White blood cell counts (/mm <sup>3</sup> )	15 700	6 721	8 200–37 100
Neutrophil counts (/mm <sup>3</sup> )	11 564	2 605	4 900–29 680
Platelet count (/mm <sup>3</sup> ):			
Before treatment	350 000	152 000	110 000–598 000
2–3 weeks after treatment	655 000	130 000	379 000–916 000
Erythrocyte sedimentation rate (mm/h)	86	39.5	17–152

SD = standard deviation.

112/100 000 children) [10,19,21] and China (18.2–30.6/100 000 children) [16], similar to some populations in the United States of America (USA) (4.3–47.1/100 000 children) [2,11–13,26] and more than that reported from England and Australia (3.4–3.7/100 000 children) [14,15] and Jamaica (2.7/100 000 children) [17]. The

finding that 84% of cases were children under 5 years is consistent with 80% of age-specific clustering of illness in Japan and the USA [1–13,19]. However, our incidence rate is higher than previously reported (60%) from southern Islamic Republic of Iran [21]. The mean age of presentation (38 months) was higher than that in Japan

**Table 3 Characteristics of patients with Kawasaki disease according to presence or absence of cardiac complications**

Variable	Cardiac complication (n = 5)		No cardiac complication (n = 20)		P-value
	Mean	SD	Mean	SD	
Sex ratio: male/female	4/1		1/1		
Age (months)	60.75	20.22	32.84	21.45	0.03
Duration of fever before treatment (days)	11.67	4.60	7.19	2.60	0.02
Haemoglobin (g/dL)	9.32	1.08	9.53	0.80	NS
White blood cell count (/mm <sup>3</sup> )	16180	3105	20922	19066	NS
Neutrophil count (%)	75.2	6.76	74.55	9.46	NS
Platelets before treatment (/mm <sup>3</sup> )	255.20	181.73	359.22	140.96	NS
Peak platelet count (/mm <sup>3</sup> )	674.60	84.55	659.83	84.55	NS
Erythrocyte sedimentation rate (mm/h)	75.80	46.51	85.55	35.84	NS

SD = standard deviation.

NS = not significant.

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(9–10 months) [19], China (median 2.3 years) [16] and the USA (2.3 years) [12,13,26] but was similar to that in Thai children (37 months) [18] and lower than reported from southern Islamic Republic of Iran (53 months) [21].

The number of children with the disease peaked in the autumn and spring in our study, whereas the number of patients increased in winter in Japan [19], in winter and spring in the USA [12,13,26] and southern Islamic Republic of Iran of Iran [21], and in spring and summer in China [16]. These findings suggest that susceptibility to Kawasaki disease may be related to climate and season.

The clinical manifestations of Kawasaki disease in the children in our study were similar to those reported previously [1,2,9,21]. Of the 5 cardinal clinical features, lymphadenopathy was the least frequently seen. This concurs with 70% of reports from Japan [19], USA [11,12] and China [16]. Conjunctivitis, exanthem, oropharyngeal and changes in peripheral extremities were seen in more than 80% of the patients and were consistent with the findings of other studies [1,2,9,16–18] as well as one report from southern Islamic Republic of Iran of Iran [21].

Cardiovascular complications are the most common cause of both short- and long-term morbidity and mortality in patients with Kawasaki disease, as noted by previous reports [3,7,9,11]. In our study, the frequency of CVA-CAA in the patients, before or shortly after the start of treatment was 20% (5 out of 25 patients). This contrasts with 2 multi-centre studies of Kawasaki disease which reported 6 of 158 (3.8%) patients and 17 of 523 (3.2%) patients with CVA-CAA [5,7]. However, our frequencies are within the range reported in other reports—55 of 377 patients (14.6%) [27] and 6 of 28 patients (21%) [28].

Male gender, older age and delayed diagnosis were identified as the risk factors for development of CVA-CAA in patients with Kawasaki disease which concurs with some studies [9,28–30] but not with others [27,30,31]. Haematological laboratory findings of patients with and without cardiac involvement were not to significantly different from each other.

A large dosage of IVIG in conjunction with high dose of acetylsalicylic acid (60–100 mg/kg per day) initiated within 10 days of the onset of the fever decreases the occurrence of CVA-CAA [1,2,5,6,27]. After a single infusion of IVIG (2g/kg) plus acetylsalicylic acid (60–100 mg/kg/day), 88% of our patients (22 of 25) responded to the treatment within 48–72 hours; they became and remained afebrile and progression of cardiac disease was stopped and improvements noted. These results are similar to other reports that indicated more than 85% of patients with Kawasaki disease responded to 1 course of IVIG [1,5,6,7,27]. Retreatment with IVIG or administration of pulse steroids or cytotoxic drugs in children with persistent fever or worsening CAA is advocated by some clinicians [27,31–36]. In our study, 3 patients who failed to respond to the initial IVIG and acetylsalicylic acid treatment were treated with a second dose of IVIG, 2 of them responded well, but the third patient did not; his fever persisted and CAA worsened. He finally responded after a third dose of IVIG and became afebrile and CAA progression stopped.

In conclusion, our study provides the first representative information on the epidemiological characteristics of Kawasaki disease among children in East Mazandaran, Islamic Republic of Iran. The annual incidence of the disease in our sample is similar to that reported by most studies undertaken in industrialized countries and

most of the patients responded to the recommended treatment regimen. Because of the danger of the cardiac involvement, the diagnosis of Kawasaki disease should be

considered in any child with persistent fever, signs of mucocutaneous inflammation and laboratory data associated with systemic inflammation.

### References

1. Dajani AS et al. Diagnosis and therapy of Kawasaki disease in children. *Circulation*, 1993, 87:1776–80.
2. American Heart Association Committee on Rheumatic Fever, Endocarditis and Kawasaki Disease. Diagnostic guidelines for Kawasaki disease. *American journal of diseases of children*, 1990, 144:1218–9.
3. Rowley AH, Shulman ST. Kawasaki syndrome. *Pediatric clinics of North America*, 1999, 46:313–29.
4. Kato H et al. Fate of coronary aneurysm in Kawasaki disease: Serial coronary angiography and long-term follow-up study. *American journal of cardiology*, 1982, 49:1758–66.
5. Newburger JW et al. The treatment of Kawasaki syndrome with intravenous gamma-globulin. *New England journal of medicine*, 1986, 315:341–7.
6. Furusho K et al. High-dose intravenous gammaglobulin for Kawasaki disease. *Lancet*, 1984, 2(8411):1055–8.
7. Newburger JW et al. A single intravenous infusion of gamma globulin as compared with four infusions in the treatment of acute Kawasaki syndrome. *New England journal of medicine*, 1991, 324:1633–9.
8. Meissner HC, Leung DYM. Superantigens, conventional antigens and the etiology of Kawasaki syndrome. *Pediatric infectious disease journal*, 2000, 19(2):91–4.
9. Petty RE, Cassidy JT. Kawasaki disease In: Petty RE, Cassidy JT, eds. *Textbook of pediatric rheumatology*, 3rd ed. Philadelphia, WB Saunders, 2001:580–94.
10. Yanagawa H et al. Incidence survey of Kawasaki disease in 1997 and 1998 in Japan. *Pediatrics*, 2001, 107(3):E33.
11. Taubert KA, Rowley AH, Shulman ST. Seven year national survey of Kawasaki disease and acute rheumatic fever. *Pediatric infectious disease journal*, 1994, 13(8):704–8.
12. Holman RC et al. Kawasaki syndrome among American Indian and Alaska Native children, 1980 through 1995. *Pediatric infectious disease journal*, 1999, 18(5):451–5.
13. Bronstein DE, Besser RE, Burns TC. Passive surveillance for Kawasaki disease in San Diego County. *Pediatric infectious disease journal*, 1997, 16(11):1015–8.
14. Dhillon R et al. Management of Kawasaki disease in the British Isles. *Archives of disease in childhood*, 1993, 69:631–6.
15. Royle JA et al. Kawasaki disease in Australia 1993–1995. *Archives of disease in childhood*, 1998, 78:33–9.
16. Du ZD et al. Epidemiologic picture of Kawasaki disease in Beijing from 1995 through 1999. *Pediatric infectious disease journal*, 2002, 22(2):103–7.
17. Pierre R, Sue-Ho R, Watson D. Kawasaki syndrome in Jamaica. *Pediatric infectious disease journal*, 2000, 19(6):539–43.
18. Thisyakorn C, Thisyakorn U. Kawasaki disease in Thai children. *Pediatric infectious disease journal*, 2000, 19(6):539–43.

- tious disease journal*, 1995, 14(4):324–5.
19. Yanagawa H et al. Epidemiologic pictures of Kawasaki disease in Japan from the nationwide incidence survey in 1991 and 1992. *Pediatrics*, 1995, 95:475–9.
  20. Taubert KA, Rowley AH, Shulman ST. Nationwide survey of Kawasaki disease and acute rheumatic fever. *Journal of pediatrics*, 1991, 119:279–82.
  21. Sadeghi E, Amin R, Agamee GH. Kawasaki syndrome: the Iranian experience. *Eastern Mediterranean health journal*, 2000, 7(1/2):16–25.
  22. Sarram A. *Kawasaki disease. New concepts and 15 case reports*. Paper presented at the Annual Congress of the Iranian Society of Pediatrics and the 23rd Memorial Congress of Professor Mohammad Gharib, 4–8 May 2002, Thran, Iran [in Persian].
  23. Kordivarian R. Kawasaki disease. Report of 13 cases from Alzahra Hospital, Isfahan. *Isfahan medical sciences journal*, 1337 (1998), 16(3):77–6 [in Persian].
  24. Soleimani GhR, Siadati A. *Etiologic evaluation of Kawasaki disease in patients referred to a pediatric medical center (Markaz Tebbi)*. Paper presented at the 14th International Congress of Pediatrics, 12–17 October, 2002, Tehran, Iran.
  25. *Research committee on Kawasaki disease. Report of subcommittee on standardization of diagnostic criteria and reporting of coronary artery lesion in Kawasaki disorder*. Tokyo, Ministry of Health and Welfare, 1984.
  26. Belay ED et al. The incidence of Kawasaki syndrome in West Coast health maintenance organizations. *Pediatric infectious disease journal*, 2000, 19(9):826–32.
  27. Burns JC et al. Intravenous gammaglobulin treatment and retreatment in Kawasaki disease. *Pediatric infectious disease journal*, 1998, 17(12): 1144–8.
  28. Stockheim JA, Innocentini N, Shulman ST. Kawasaki disease in older children and adolescents. *Journal of pediatrics*, 2000, 137(2):250–2.
  29. McCrindie BW et al. Summary and abstract of the sixth international Kawasaki disease symposium. *Pediatric research*, 2000, 47:544–70.
  30. Koren G et al. Kawazaki diseases: review of risk factors for coronary aneurisms. *Journal of pediatrics*, 1986, 108:388–92.
  31. Fukunishi M et al. Prediction of non-responsiveness to intravenous high-dose gammaglobulin therapy in patients with Kawasaki disease at onset. *Journal of pediatrics*, 2000, 137:172–6.
  32. Hashino K et al. Re-treatment for immune globulin-resistant Kawasaki disease: a comparative study of additional immune globulin and steroid pulse therapy. *Pediatrics internationalto: official journal of the Japan Pediatric Society*, 2001, 43(3):211–7.
  33. Onouchi Z, Kawasaki T. Overview of pharmacological treatment of Kawasaki disease. *Drugs*, 1999, 58(5):813–22.
  34. Raman V et al. Response of refractory Kawasaki disease to pulse steroid and cyclosporin A therapy. *Pediatric infectious disease journal*, 2001, 20(6):635–7.
  35. Dale RC et al. Treatment of severe complicated Kawasaki disease with oral prednisolone and aspirin. *Journal of pediatrics*, 2000, 137:723–6.
  36. Wallace CA et al. Initial intravenous gammaglobulin treatment failure in Kawasaki disease. *Pediatrics*, 2000, 105(6):E78.