

## Kawasaki Disease Hospitalization: Outcomes in Two Tertiary Care Hospitals in Bangladesh

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### Abstract

Kawasaki disease (KD) is an acute self-limiting inflammatory disease associated with vasculitis, affecting predominantly medium sized vessels and encountered these cases infrequently in clinical practice. The most concerning complication is coronary artery aneurysm (CAA) leading to myocardial infarction or sudden death. Fever is the essential feature. Kawasaki disease is invariably associated with an inflammatory process with elevated C-reactive protein (CRP), erythrocyte sedimentation rate (ESR) and white blood cell count. Early recognition and treatment with IVIG (Intravenous immunoglobulin), and aspirin showed highest protection against development of coronary artery disease. Incidence of KD is more in East Asia or in Asian ancestry living in other countries. The reason for high incidence in developing country is still unknown. Recently a significant number of cases attended in day to day practice which led conducting this study to assess the pattern of presentation, management and outcome after treatment and to aware the health care providers about the nature of the disease. This observational study conducted during September 2014 to March 2016. All the cases reported to the department of paediatric echocardiography for coronary artery analysis and suspected as KD were included in the study. History, clinical examination and investigation reports were analyzed from records. Age, gender, clinical feature, management, follow-up, echocardiography findings and outcome were analyzed. Data were collected from records of Echocardiography Department and Paediatric Cardiology Department of Lab Aid Cardiac Hospital and Combined Military Hospital, Dhaka. Among 27 cases, 16 were male (49.25%) and 11 were female (40.75%). Age distribution showed 8 (29.63%) were under one year of age, 13(48.14%) were in 1-5 years age group, 6 (22.23%) were in more than 5 years age group. All 27 cases were presented with fever, strawberry tongue, conjunctivitis, skin rash with peeling. Raised ESR, CRP and neutrophilic leukocytosis were found in all 27 cases. Cervical lymphadenopathy was found in 15 (55.52%) cases. Coronary artery changes were observed in 24 cases (88.89%). IVIG was given in 25 (92.60%) cases and Aspirin was given in 27 cases. Complete cure was achieved in 25 (92.59%) cases and one case died from thromboembolic event of radial artery and amputation of hand. The outcome of KD depends on the severity of coronary artery involvement. Patients with aneurysm larger than 08 mm are at highest risk of myocardial infarction. Less than 08 mm aneurismal dilatation regress with time. In this series outcome was excellent due to timely diagnosis and proper intervention.

### Introduction

Kawasaki disease is a syndrome composed of acute febrile illness of unknown cause which affects under five children.<sup>1,2</sup> This disease was first described by Tomisaku Kawasaki in 1967.<sup>1</sup>

Incidence is high in Asian and Pacific region which is 30 per 100,000<sup>2</sup>. There is seasonal predominance in winter and spring, and children less than one year of age are more prone to KD.<sup>3</sup> KD is associated with systemic vasculitis particularly affecting the coronary arteries,

causing coronary artery aneurysm in 15 to 25% of untreated patient. Two to three of untreated cases die from coronary vasculitis.<sup>3-5</sup>

In the United States, Kawasaki disease is considered as the leading cause of acquired heart disease in children<sup>5</sup>. Kawasaki disease develops quickly and runs an aggressive course over a period of weeks. Typically, the condition then resolves. Even though it resolves, there may be cardiac complications years later. Principal symptoms associated with Kawasaki disease include: spiking fevers that last 5 or more days (required to make a diagnosis of Kawasaki disease), inflamed conjunctiva (eyes) without pus, red chapped lips, red mucous membranes in the mouth, red tongue that has the appearance of a strawberry, rashes on the trunk of the body, red palms of hands and red soles of feet, oedema of hands and feet, peeling skin on hands, feet and genitals, swollen lymph node usually near the neck and occasionally joint pain and swelling often on both sides of body.<sup>1-6</sup> During the acute illness, blood vessels throughout the body become inflamed. This vasculitis can produce several acute cardiac problems, including tachycardia; inflammation of the cardiac muscle (myocarditis), which in some cases can lead to severe, life-threatening heart failure and mild mitral regurgitation.<sup>7</sup>

Some suspect there is an infectious cause of Kawasaki disease, but none has been proven. There are several immunologic irregularities linked with Kawasaki disease, and some believe it is an autoimmune condition. In the United States, Kawasaki disease affects 4,000 children each year. It is more prevalent in Japan with occurrence of 5,000 to 6,000 cases each year.<sup>6,7</sup> After completion of diagnosis, treatment should be started immediately, so that damage to coronary arteries and heart can be prevented. Intravenous immunoglobulin (IVIG) given in high doses is considered standard treatment for Kawasaki disease. High dose aspirin is typically a part of the treatment plan as well. With early treatment for Kawasaki disease, full recovery is

possible for most, but 2% of Kawasaki disease patients die from complications of coronary artery inflammation. Echocardiography of the patient should be performed at 6 months interval at least for years after complete cure to exclude remote possibility of involvement of coronary arteries. Electrocardiography (ECG) is also advised in some centers.<sup>6</sup> Cardiac enzymes are advised in case of thrombotic events in coronary arteries and myocardial infarction.<sup>3</sup>

As expert echocardiography for recognition of coronary artery involvement was available in Paediatric Echocardiography Department of Lab Aid Cardiac Hospital and Paediatric Cardiology Department of Combined Military Hospital, most of the suspected cases were referred in these two places for echocardiography. Furthermore, management needs involvement of pediatric cardiologist also. So, a large number of patients were attended from many centres mainly for diagnostic purpose by echocardiography and later also for management.

Considering these, this study was designed to assess the clinical presentation, management and outcomes of management in two tertiary care hospitals in Bangladesh.

## **Materials and Methods**

This observational study was conducted in Combined Military Hospital Dhaka and Lab Aid Cardiac Hospital from September 2014 to March 2016. Cases initially reported to Paediatric Echocardiography department for study of coronary arteries. Referring doctors were paediatricians and they referred the cases with the suspicion of Kawasaki disease. All these cases were admitted in paediatric cardiology department of these two hospitals for management. Detail history and clinical examinations were obtained. Laboratory investigations of the patients were analysed also and new investigations were advised if necessary to establish diagnosis. Echocardiography findings were recorded and analysed. The entire patients

who fulfilled criteria for Kawasaki disease had given appointment for repeat echo after one after one week, two weeks, six weeks, six months and one year to follow coronary artery status. Treatment plan was decided by the respective physicians who refer the cases initially and cases with coronary artery change were managed by paediatric cardiologist as well. Follow-up of the cases were done with laboratory reports of acute phase reactants, platelet count and echocardiography. As the cases were under care of same paediatric cardiologist in both hospitals, data of patient were collected from both places and later analysed for present study.

## Results

Eight (29.62%) cases were under one year, 13 (48.14%) cases were between one to 5 years and 6 (22.23%) cases were above five years. Sixteen (49.25%) cases were male and 11(40.75%) cases were female (table I).

**Table I:** Age and sex distribution of patients (n = 27)

Age	Number	Percentage (%)
Less than 1 Years	08	29.63
One to five Years	13	48.14
More than 5 Years	06	22.23
<b>Sex</b>		
Male	16	49.25
Female	11	40.75

All 27 (100%) cases had fever, straw berry tongue, conjunctival congestion and peeling of skin. Cervical lymphadenopathy was observed in 15 (55.56%) cases. Thrombocytosis was observed in 25 (85.18%) cases. Raised CRP, ESR and neutrophilic leukocytosis were observed in all cases (table II).

**Table II:** Clinical presentation and laboratory findings of the patients (n=27)

Clinical/ Lab Findings	Number	Percentage (%)
Fever	27	100.0
Rash	27	100.0
Peeling of skin	27	100.0
Conjunctival congestion	27	100.0
Cervical Lymphadenopathy	15	55.6
Strawberry tongue	27	100.0
Thrombocytosis	25	92.6
Raised CRP and ESR	27	100.0
Neutrophilic leukocytosis	27	100.0

Aneurismal dilation of LCA (5mm-8mm) was noticed in 10(37.03%) cases, Dilated LCA(3mm-5mm) in 5(18.52%) cases, dilated RCA (3mm - 5mm) in 5(18.52%) cases, dilatation of both RCA and LCA was observed in 4(14.81%) cases and no coronary changes in 3(11.12%) cases. Heart failure was observed in 2(7.41%) cases and pericardial effusion was observed in 1(3.70%) case (table III).

**Table III:** Distribution of coronary artery abnormalities and other changes in the heart (n=27)

Disease	Number	Percentage (%)
LCA aneurysmal change(Z score >2.5 to <5 and <8 mm)	10	37.03
Dilated LCA (Z score 2 to <2.5)	05	18.51
Dilated RCA (Z score 2 to <2.5)	05	18.51
Dilated LCA+ RCA Change	04	14.81
No Change (Z score <2)	03	11.11
Heart Failure	02	7.40
Pericardial effusion	01	3.70

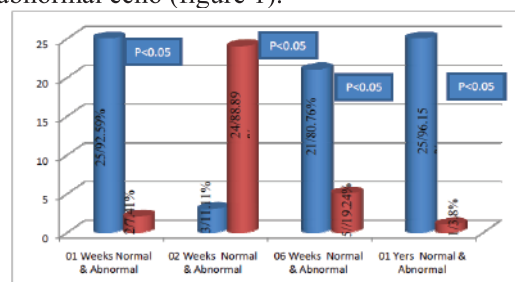
Twenty five (92.60%) cases received IVIG and all 27 cases received aspirin in high dose initially followed by low dose. Corticosteroid was not used in any cases (table IV).

**Table IV:** Treatment received by patient (n =27)

Disease	Number	Percentage
IVIG in single dose 2 gm/kg over 10 hours	25	92.59%
Aspirin in high doses (100mg/kg)	27	100%
Aspirin in Low doses (5mg/kg)	27	100%
Corticosteroid	NIL	00%

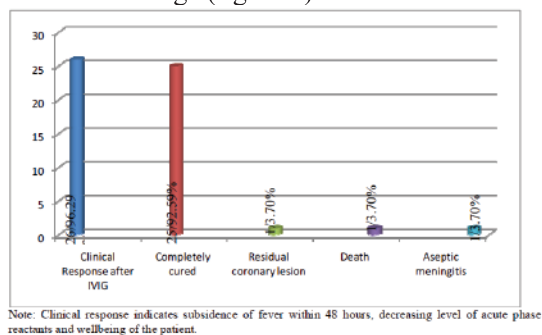
IVIG: Intravenous immunoglobulin.

At 1<sup>st</sup>week 25(92.59%) cases had normal echo findings. At 2<sup>nd</sup> weeks 24(88.89%) cases had abnormal echo. At 6 weeks 21(80.76%) cases had normal Echo and at one year 25 (96.15%) cases had normal echo and 1(3.80%) case had abnormal echo (figure 1).



**Figure 1:** Follow-up echocardiography of patients (n= 27)  
Note: One patient died in 2<sup>nd</sup> week

At 1 year follow up twenty five cases were found completely cured, only one case had slightly dilated left coronary artery ( $p<0.05$ ). Death due to thrombotic complication of radial artery was one in acute stage (figure 2).



**Figure 2:** Outcome distribution of patient after one year follow up (n=27)

## Discussion

Kawasaki disease is the commonest cause of acquired heart diseases in children. It is the 2<sup>nd</sup> commonest vasculitis illness of childhood after Henoch-Schönlein Purpura.<sup>4-8</sup> Approximately 85% children with KD are under 5 years of age with peak incidence between 18 to 24 months.<sup>1,8</sup> In this study, most of the patients (48.14%) were in one to five years age group. Kawasaki disease is rare in less than three months or more than five years of age but coronary artery aneurysm is very common in this group.<sup>8</sup> Though there is ethnic bias towards Asian children but no study was conducted in Bangladesh to see the incidence.<sup>7,8</sup> Male preponderance noticed in all studies which corresponded with this study.<sup>5,6</sup> There was seasonal preponderance also and it was found most of the cases reported between September to March in this study.<sup>5</sup> Kawasaki disease case numbers were highest in January through March and approximately 40% higher than in the months of lowest case numbers from August through October in northern hemisphere.<sup>6</sup> The aetiology of KD is unknown but history of preceding respiratory tract infection and gastroenteritis was observed in 13 cases in this study. Many published reports implicate a number of bacterial and viral pathogens including retro virus, Epstein bar virus, corona virus, staphylococcus, streptococcus as infectious

triggers of KD.<sup>7-10</sup> Some studies support super antigen triggered process but others have not confirmed. Some studies suggest genetic contribution. These genes are ITPKC, ABCC4, FCGR2A, CD4D and a gene region near FAMI67A-BLK. Some genes are also associated with non-response to Immunoglobulin and coronary artery change including CASP3 and FCGR3B.<sup>11-16</sup>

Diagnostic criteria for KD are fever for 5 days or more along with any four of the following features.<sup>3,4</sup>

- a. Bilateral conjunctival congestion;
- b. Oral changes;
- c. Peripheral extremity changes;
- d. Rash; or
- e. Cervical lymphadenopathy .

If coronary artery is dilated or aneurysmal dilatation is present then only three clinical features are required for diagnosis. In this series fever, rash, oral changes, and conjunctival congestion was present in 100% cases. Coronary changes were noticed in 89.89% cases. Some of the cases are incomplete cases who have insufficient clinical features but they appear subsequently and coronary changes are very frequent in these cases.<sup>3</sup> No incomplete cases in this series. Some KD cases may have aseptic meningitis, arthritis, pneumonitis, dysuria or otitis media. One aseptic meningitis case was found in this series. In measles predominant area, diagnosis of KD is sometime missed because of some similar features.<sup>6</sup> As KD is invariably associated with inflammation, elevation of ESR, CRP, and raised WBC count is always there.<sup>4</sup> In the absence of inflammation KD diagnosis is unlikely. Thrombocytosis appears towards the end of 2<sup>nd</sup> week, therefore may not be helpful.<sup>5</sup> In this series, thrombocytosis was to be found in 92.59% cases. Echocardiography was done at diagnosis, at 2 weeks, at 6 weeks to look for coronary artery changes. Significant aneurysm more than 8 mm was not observed in any cases. Other cardiac complications like heart failure, arrhythmia, pericardial effusion, myocardial

ischemia may occur in KD cases.<sup>7</sup> Most of the cases had dilated coronary arteries and treated with IVIG before developing aneurysm in this series. Intravenous immunoglobulin and Aspirin is the main drug used for treatment of KD.<sup>6</sup> High dose aspirin was used in all cases. High dose aspirin of 100 mg/kg was given to patient till they became afebrile followed by low dose aspirin 5mg/kg till coronary arteries returned to normal. Early recognition and treatment with IVIG and aspirin can prevent coronary artery aneurysm which was shown by many studies.<sup>1,2,5,6</sup> This study also supports this observation and given IVIG to 25 cases but two cases came after 2 weeks of onset of illness when IVIG had no role in preventing coronary artery changes. Exact mechanism of action of IVIG is unknown, but it has generalized anti-inflammatory property. Two gm/kg IVIG may be given as single dose. Randomized control trial comparing divided low dose IVIG (400 mg/kg/days for 4 days) versus a single infusion of high dose (2gm/kg over 10 hour) showed single dose infusion has a greater therapeutic effect in the prevention of CAA.<sup>17,18</sup> Single dose protocol was used in this series. Some studies showed corticosteroids were used in IVIG resistant cases to prevent coronary artery changes in 20% cases. But some other studies suggested that corticosteroids were associated with increased risk of CAA.<sup>19</sup> No corticosteroid was used in any of cases. Clinical trials evaluating the use of corticosteroid plus IVIG have confusing results. But corticosteroids have some roles in (a) IVIG resistant cases, (b) patient with most severe disease, and (c) patient with coronary and peripheral aneurysm with confusing inflammation.<sup>20-23</sup> Prognosis of the disease depends on coronary artery involvement. As per American Heart Association, a new classification of coronary artery abnormalities is based on z- scores as follows:<sup>24,25</sup>

- No involvement: always <2
- Dilation only: 2 to <2.5, a decrease in Z score during follow-up  $\geq 1$
- Small aneurysm:  $\geq 2.5$  to <5

- Medium aneurysm:  $\geq 5$  to <10, and absolute dimension <8 mm
- Large or giant aneurysm:  $\geq 10$ , or absolute dimension  $\geq 8$  mm.

IVIG should be administered as soon as possible within 10 days of fever onset.

Latest AHA guidelines highlight other situations in which IVIG may also be appropriate for patients who are beyond the 10-day window, and it is recommended for children who present after the 10<sup>th</sup> day with “ongoing systemic inflammation as manifested by elevation of ESR or CRP (CRP >3.0 mg/dL) together with either persistent fever without other explanation or coronary artery aneurysms (luminal dimension Z score >2.5).”

Patient with aneurysm more than 8 mm has greater risk of MI. Less than 8 mm aneurysm usually regresses in course of time. In this series aneurysm more than 8 mm was not observed in any cases. So, outcome in these cases were excellent. One case who died, having radial artery thrombosis, and died from amputation related complications. One case had slightly dilated coronary artery upto one year follow-up.

## Conclusion

Kawasaki disease (KD) is a self-limiting disease and usually resolves within 12 days, if there is no coronary or cardiac involvement. High dose aspirin should be stopped when patient become afebrile. Low dose aspirin should be continued until coronary become normal. CAA more than 8mm needs lifelong aspirin therapy. Echocardiography should be repeated at 2 weeks and 6 weeks for all cases and 6 monthly for those having CAA or dilated coronary arteries. In this series, outcomes were excellent, as standard guidelines were followed and only one patient died in acute phase, and was due to thromboembolic manifestation in radial artery and its surgical management, and not related to KD directly. KD should be included in differential diagnosis for any child suffering from unexplained fever with positive supportive findings.

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