

# The 2011 Dengue Haemorrhagic Fever Outbreak in Lahore - An Account of Clinical Parameters and Pattern of Haemorrhagic Complications

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## ABSTRACT

**Objective:** To describe the frequency and outcome of dengue haemorrhagic fever (DHF) cases and determine the association of clinical and laboratory parameters with haemorrhagic complications.

**Study Design:** A descriptive study.

**Place and Duration of Study:** Combined Military Hospital, Lahore, from August to November 2011.

**Methodology:** Clinical profile and outcome of 640 adult patients hospitalized with a strong clinical suspicion of dengue fever (DF) was evaluated. Based on serological confirmation, these patients were divided into confirmed DF and probable DF cases. They were also categorized according to severity into dengue fever (DF), dengue haemorrhagic fever (DHF) and dengue shock syndrome (DSS) cases according to WHO guidelines. After detailed clinical evaluation, blood samples were taken for a complete blood count, urea, creatinine, sodium, potassium, bilirubin, alanine aminotransferase (ALT), prothrombin time (PT) and activated partial thromboplastin time (APTT). Patients were managed according to standard protocols with intravenous fluids and symptomatic treatment. SPSS 18 was used for statistical analysis of clinical data. Comparison of features among the groups was made using chi-square or t-test with significance at  $p < 0.05$ .

**Results:** There was 359 probable DF and 281 confirmed DF cases. The development of DHF, neurological manifestations and overall mortality was more frequent in confirmed DF group. Comparison between DHF/DSS and DF cases revealed a significant difference in vomiting ( $p = 0.04$ ), purpuric rash ( $p < 0.001$ ), systolic blood pressure ( $p = 0.002$ ), serum ALT ( $p < 0.001$ ), hospital stay ( $p < 0.001$ ), neurological involvement ( $p < 0.001$ ) and coagulopathy ( $p < 0.001$ ) between the two groups. Among 159 DHF patients, 108 (67.9%) had bleeding from gums and oral cavity, 73 (45.9%) had haemetemesis and 82 (51.5%) malaena, 41 (25.8%) had epistaxis, 12 (7.5%) developed intracranial bleeding, 18 (11%) had hematuria, 12 (7.5%) had fresh bleeding per rectum and 37 (23%) developed haemoptysis. Overall mortality was 3%, but mortality in DHF/DSS cases was 6% and 41.6% for DSS cases. Logistic regression analysis showed that abdominal pain, purpuric rash, ascites, thrombocytopenia, coagulopathy and raised ALT had a statistically significant predictability for developing DHF.

**Conclusion:** A variety of manifestations including that abdominal pain, purpuric rash, ascites, thrombocytopenia, coagulopathy and raised ALT had a statistically significant predictability for developing DHF. A knowledge and understanding of these complications would be useful for the management of patients if such outbreaks of DHF are encountered again.

**Key Words:** Dengue fever (DF). Dengue haemorrhagic fever (DHF). Dengue shock syndrome (DSS). Haemorrhagic complications.

## INTRODUCTION

Dengue fever is the most prevalent mosquito-borne viral illness. More than 50 million cases occur annually throughout the world.<sup>1</sup> The clinical manifestations range from an asymptomatic infection and a mild febrile illness to severe dengue haemorrhagic fever and life threatening shock syndrome.<sup>2</sup> There are four closely related, but serologically distinct dengue viruses, called DENV-1, DENV-2, DENV-3, and DENV-4, of the genus Flavivirus. Since there is only transient and weak cross-

protection among the four serotypes, persons living in an area of endemic dengue can be infected with three to four dengue serotypes during their lifetime. The patient's immune status and the corresponding dengue serotype have been shown to affect the severity of disease.<sup>3-5</sup>

Small outbreaks of dengue fever had been occurring off and on after rainy season in Pakistan since early nineties,<sup>6</sup> but it has been appearing regularly in the densely populated urban areas of Sind mainly Hyderabad and Karachi and in upper and central Punjab since 2005, during and after the rainy season. The author reported a clinical management experience of an outbreak of dengue fever in 2005 and 2006 at Karachi.<sup>7</sup> Out of 107 dengue fever (DF) cases, only 2 patients showed features of dengue haemorrhagic fever (DHF) and there was no mortality in the studied patients due to DF or DHF. But after heavy rains in 2011, there was a huge outbreak of DF and DHF in and around Lahore and

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certain other areas of central Punjab. A large number of DHF cases were recorded during this outbreak with a significant mortality.

The aim of this study was to describe the clinical data of indoor DF patients to observe the frequency and outcome of DHF cases, their relationship with other clinical parameters and the pattern of haemorrhagic complications.

## METHODOLOGY

This is a descriptive study conducted during an outbreak of DF at Lahore in 2011. The study was based on clinical profile and outcome of 640 hospitalized adult patients. All these patients were hospitalized in acute medical wards at Combined Military Hospital, Lahore, from August to November 2011 with a strong clinical suspicion of DF. The criteria of hospitalization for clinically suspected DF patients were uncontrolled vomiting, moderate to severe abdominal pain, moderate to severe dehydration and shock, platelet count less than  $50 \times 10^9/l$ , haemorrhagic manifestations and altered consciousness. This was the inclusion criteria for the patients in this study. All the other cases, hospitalized due to high grade fever, who did not show typical clinical and laboratory features of DF, were excluded. Patients with clinical presentation suggestive of DF and supported by positive reactivity of dengue specific IgM antibody were labeled as confirmed DF. Patients with suggestive clinical features and bicytopenia, negative reactivity for dengue specific IgM antibody were labeled as probable DF. Probable DF included those cases also in which serological confirmation was not considered necessary due to an obvious clinical diagnosis in the setting of an epidemic. Patients were also categorized according to severity into dengue fever (DF), dengue haemorrhagic fever (DHF) and dengue shock syndrome (DSS) cases according to WHO guidelines.<sup>8</sup>

After detailed clinical evaluation, blood samples were taken for a complete blood count and serum levels of urea, creatinine, sodium, potassium, bilirubin and alanine aminotransferase (ALT). Prothrombin time (PT) and activated partial thromboplastin time (APTT) were also checked. Blood counts were serially monitored till the platelet counts started showing a rising trend and reached the safe limits.

Haematological profile was done on Sysmex KX-21 haematology analyzer. Serum bilirubin, ALT and creatinine were done on Vitalab Selectra E chemistry analyzer and electrolytes were measured with Easlyte Na/K electrolytes analyzer. Dengue specific IgM antibody reactivity were performed by standard enzyme linked immunosorbent assay (ELISA) technique.

Patients were managed according to standard protocols with intravenous fluids and symptomatic treatment. Transfusions with platelets concentrate and fresh frozen

plasma were considered necessary only when patients showed active bleeding with very low platelet counts and/or evidence of coagulopathy (deranged PT and APTT). Patients were discharged from the hospital when they were afebrile, symptomatically better and showed an upward trend in platelet count.

Statistical Package for Social Sciences (SPSS) version 18 was used for statistical analysis. Data was presented in mean  $\pm$  standard deviation and number (percentage). Independent sample t-test was used to see the statistical significance of difference of means between various continuous variables in two groups of patients. Chi-square test was used when two dichotomous categorical variables were compared. Logistic regression analysis was done to see the predictability of various clinical and laboratory parameters on the occurrence of DHF. Significance was kept at  $p < 0.05$ .

## RESULTS

The descriptive analysis of 640 patients is presented by dividing them into two groups of 359 probable DF and 281 confirmed DF cases. The age of the patients ranged from 13 to 84 years with an average of  $38.1 \pm 14.2$  years in probable DF and  $38.6 \pm 14.8$  years in confirmed DF group. Ninety percent of patients were men in both groups. Fever, headache and body aches were present in more than 90% of patients in both groups. Vomiting was noted in more than 80% and abdominal pain in more than 70% of patients in both groups. Dengue haemorrhagic fever (DHF) criterion was fulfilled by 67 (18.7%) of probable DF and 85 (30.25%) of confirmed DF cases. No statistically significant difference was seen in various clinical variables between probable DF and confirmed DF groups except the development of DHF, neurological manifestations and overall mortality which were more frequent in confirmed DF group (Table I).

The Table II shows descriptive analysis and comparison of various clinical variables between DHF/DSS and DF cases. There was no significant difference in the age of patients in both groups. DHF presented in all age groups, from 13 to 81 years of age. Vomiting was more common in patients of DHF as compared to DF cases ( $p = 0.04$ ). Purpuric rash was seen in 29.6% of DHF as compared to 11.9% of DF patients ( $p < 0.001$ ). Average systolic blood pressure was  $103.2 \pm 15.7$  mmHg in DHF patients and  $106.1 \pm 8.1$  mmHg in DF cases ( $p = 0.002$ ). There was no significant difference in initial haemoglobin level and hematocrit and lowest total leucocyte count in both groups. Platelet counts were  $22.6 \pm 14.8 \times 10^9/l$  in DHF and  $35.3 \pm 22.7 \times 10^9/l$  in DF patients ( $p < 0.001$ ). Serum ALT levels on presentation was  $132.8 \pm 193.3$  units/l in DHF and  $69.8 \pm 65.7$  units/l in DF cases ( $p < 0.001$ ). Hospital stay was  $5.1 \pm 3.0$  days in DHF, ranging from 3 to 30 days as compared to DF group in which it was  $3.4 \pm 1.0$ , with a range of 1 to 8 days ( $p < 0.001$ ). Significant neurological involvement

**Table I:** Descriptive analysis of probable and confirmed DF cases.

	Dengue fever probable (n = 359)	Dengue fever confirmed (n = 281)	p-value
Age (years)	38.1 ± 14.2	38.6 ± 14.8	0.6
Women	36 (10%)	27 (10%)	0.8
Men	323 (90%)	254 (90%)	
Duration of symptoms (days)	5.2 ± 1.5	5.0 ± 1.4	0.1
Fever	359 (100%)	281 (100%)	
Headache	339 (94%)	273 (97%)	0.6
Bodyaches	332 (92.5%)	267 (95%)	0.5
Nausea/vomiting	313 (87.2%)	249 (88.6%)	0.6
Abdominal pain	267 (74.4%)	223 (79.4%)	0.1
Dengue haemorrhagic fever	67 (18.7%)	85 (30.25%)	0.001
Neurological manifestations	13 (3.6%)	25 (8.9%)	0.007
Purpuric rash	56 (15.6%)	48 (17.1%)	0.4
Temperature (degree Fahrenheit)	101.2 ± 1.4	101.2 ± 1.4	0.8
Systolic blood pressure (mmHg)	105.3 ± 8.9	105.6 ± 12.5	0.6
Diastolic blood pressure (mmHg)	69.2 ± 7.7	69.9 ± 8.9	0.3
Haemoglobin (g/dl)	13.7 ± 1.5	13.7 ± 1.6	0.7
Hematocrit (mm)	41.6 ± 4.5	41.3 ± 4.8	0.4
Total leucocyte count (x 10 <sup>9</sup> /litre)	3.6 ± 1.2	3.8 ± 1.8	0.1
Platelet count (x 10 <sup>9</sup> /litre)	34 ± 23.5	29.7 ± 19	0.01
Coagulopathy	67 (18.7%)	85 (30.2%)	0.001
ALT (units/litre)	79.8 ± 87.1	93.7 ± 144.6	0.1
Hospitalization (days)	3.6 ± 1.2	4.0 ± 2.4	0.003
DSS	6 (1.7%)	18 (6.4%)	0.003
Mortality	3 (0.8%)	17 (6%)	< 0.001

*p* < 0.05 is considered significant.

was seen in 23 (14.5%) of DHF and 15 (3.1%) of DF patients (*p* < 0.001). Ascites was recorded in 43 (27%) and mild pleural effusion was noted in 20 (12.5%) cases of DHF. Coagulopathy (deranged PT and APTT) was present in 120 (75.5%) patients of DHF and 32 (6.7%) patients of DF (*p* < 0.001).

Among 159 DHF patients, 108 (67.9%) had bleeding from gums and oral cavity, 73 (45.9%) presented with haemetemesis and 82 (51.5%) with malaena, 41 (25.8%) had epistaxis, 12 (7.5%) patients developed intracranial bleeding, 18 (11%) had hematuria, 12 (7.5%) had fresh bleeding per rectum, 37 (23%) showed some degree of haemoptysis but frank alveolar haemorrhages were suspected on chest radiographs in 4 serious patients only. About 102 (64%) of DHF patients developed spontaneous bruising, 1 (0.6%) developed perirenal haematomas and 1 (0.6%) presented with large haematomas in the abdominal wall muscles at both flanks resembling intra-abdominal/renal masses but was differentiated on ultrasonographic examination. Eleven (52%) out of 21 female patients presented with excessive vaginal bleeding (Table III).

Overall mortality in 640 indoor patients was about 3% (20/640). Among DHF/DSS group 17 (6%) patients died. Twenty four patients (3.75%) developed dengue shock syndrome (DSS), 10 of whom could not survive, so case fatality rate for DSS cases was 41.6%. Three (0.8%) patients from DF group died who had significant

**Table II:** Descriptive analysis and comparison of DHF/DSS and DF cases.

	DHF/DSS (n = 159)	DF (n = 481)	p-value
Age (years)	39.5 ± 14.7	38.0 ± 14.4	0.2
Women (n = 63)	21 (13.2%)	42 (8.7%)	0.1
Men (n = 577)	138 (86.8%)	439 (91.3%)	
Duration of symptoms (days)	5.4 ± 1.5	5.0 ± 1.5	0.007
Fever	159 (100%)	481 (100%)	
Headache	152 (95.5%)	460 (95.6%)	0.1
Bodyaches	146 (92%)	453 (94%)	0.1
Vomiting	147 (92.5%)	415 (86.3%)	0.04
Abdominal pain	137 (86.2%)	353 (73.4%)	0.001
Neurological manifestations	23 (14.5%)	15 (3.1%)	< 0.001
Purpura	47 (29.6%)	57 (11.9%)	< 0.001
Temperature (degree Fahrenheit)	101.2 ± 1.5	101.2 ± 1.3	0.8
Systolic blood pressure (mm Hg)	103.2 ± 15.7	106.1 ± 8.1	0.002
Diastolic blood pressure (mm Hg)	68.6 ± 11.3	69.8 ± 6.9	0.1
Ascites	43 (27%)	8 (1.6%)	< 0.001
Pleural effusion	20 (12.5%)	5 (1%)	0.001
Haemoglobin (g/dl)	13.6 ± 1.8	13.8 ± 1.4	0.3
Hematocrit (mm)	41.6 ± 5.5	41.4 ± 4.4	0.5
Total leucocyte count (x 10 <sup>9</sup> /litre)	3.6 ± 1.9	3.7 ± 1.4	0.4
Platelet count (x 10 <sup>9</sup> /litre)	22.6 ± 14.8	35.3 ± 22.7	< 0.001
Coagulopathy	120 (75.5%)	32 (6.7%)	< 0.001
ALT (units/litre)	132.8 ± 193.3	69.8 ± 65.7	< 0.001
Confirmed dengue	89 (56%)	192 (39.9%)	< 0.001
Probable dengue	70 (44%)	289 (60.1%)	
DSS	24 (15.1%)	0	
Hospitalization (days)	5.1 ± 3.0	3.4 ± 1.0	< 0.001
Mortality	17 (6%)	3 (0.8%)	< 0.001

*p* < 0.05 is considered significant.

**Table III:** Haemorrhagic manifestations of DHF cases.

Bleeding manifestation	Percentage in DHF cases (n = 159)
Bleeding from gums/oral cavity	108 (67.9%)
Epistaxis	41 (25.8%)
Haemetemesis	73 (45.9%)
Malaena	82 (51.5%)
Fresh bleeding per rectum	12 (7.5%)
Haematuria	18 (11%)
Metrorrhagia	11 (7%)
Intracranial bleeding	12 (7.5%)
Petechiae / ecchymoses	102 (64%)
Peri-renal haematomas	1 (0.6%)
Haematomas in abdominal muscles	1 (0.6%)
Haemoptysis	37 (23%)

thrombocytopenia and neurological manifestations of dengue fever but did not show any overt bleeding manifestations. All the other (97%) patients eventually recovered. They were discharged from the hospital when they were haemodynamically stable, platelet counts showed progressive rise and there were no signs of coagulopathy.

Logistic regression analysis was carried out using age, gender, abdominal pain, systolic and diastolic blood pressures, purpuric rash, hematocrit, platelet count, serum ALT and coagulopathy as predictor variables and presence of DHF or DF as the dependent variable.

A test of the full model using all predictors against a constant only model, was statistically reliable. The model correctly predicted 93.5% of DF cases and 74.3% of DHF cases. Logistic regression model showed that amongst the considered predictor variables, only abdominal pain ( $p = 0.006$ ), purpuric rash ( $p = 0.03$ ), ascites ( $p = 0.01$ ), platelet count ( $p = 0.001$ ), coagulopathy ( $p < 0.001$ ) and serum ALT levels ( $p = 0.02$ ) had a statistically significant predictability for developing DHF.

## DISCUSSION

The 2011 outbreak of Dengue in the urban areas of northern and central Punjab especially Lahore had been the worst outbreak of DF in Pakistan so far, with a high number of DHF cases and a high mortality due to associated complications. Out of 640 hospitalized DF cases 159 (24.8%) had DHF, including 24 patients of DSS. There was no significant difference in clinical and laboratory parameters of suspected and confirmed DF cases. The Dengue IgM/IgG antibody tests were negative either because the test was not done due to obvious diagnosis in the setting of an epidemic or most of the tests were done within the first 8 – 10 days of illness. When clinical parameters were compared in DHF and DF group, high grade fever, headache, bodyaches were present in more than 90% of patients in both groups with no significant difference. Vomiting, abdominal pain, neurological manifestations and purpuric rash were more common in DHF patients. Systolic blood pressures recorded at admission were significantly low in DHF as compared to DF cases. Male majority in the studied patients does not necessarily represent the gender distribution of DF or DHF cases in the community, it represents the pattern of entitlement in the Military Hospitals, which by default, is responsible for more male cases in the hospitals than females.

Logistic regression analysis has suggested that the presence of abdominal pain, purpuric rash, ascites, very low platelet count, significantly raised ALT and evidence of coagulopathy in the form of prolonged prothrombin time and activated partial thromboplastin time have high predictability value for the development of DHF, as has already been reported in literature.<sup>9,10</sup> It is important for the clinicians to recognize the signs of impending deterioration like persistent vomiting, severe abdominal pain, a high or increasing hematocrit level that is concurrent with a rapid decrease in the platelet count, serosal effusions, mucosal bleeding, and lethargy or restlessness. These features usually appear at the time of defervescence and may indicate that clinically significant vascular leakage is developing in the patient.<sup>11</sup>

Most patients with gum bleeding, epistaxis, haemoptysis and petechiae / ecchymoses had mild bleeding episodes and did not require any transfusion of blood products.

Patients with significant bleeding had haematemesis and melaena or hematuria. Diagnostic upper gastrointestinal endoscopy was done in 4 patients only, which revealed multiple gastric erosions in 3 patients and a bleeding duodenal ulcer in one patient. Few patients had significant haemoptysis, 4 of which were suspected to have alveolar haemorrhages.

Overall mortality was 3.1% but this case fatality rate was calculated in seriously ill hospitalized cases of dengue fever only and does not reflect the overall mortality due to dengue fever in the community. Mortality was 6% in DHF/DSS cases. Case fatality rates vary widely in different studies from other parts of the world e.g., in Brazil, case fatality for DHF had been reported from 1.45% to 11.25%.<sup>12</sup> Currently, case fatality rate of upto 1% are acceptable in DHF but lack of early identification and management of DHF can lead to case fatality rate of more than 20% and that of DSS upto 44%.<sup>13,14</sup> Case fatality rate for DSS cases was 41.6% in this study. Outbreaks of severe DHF with high mortality rates had also been reported from India and Bangladesh.<sup>15</sup> A recent study from Chennai, India, reported 14% mortality in adult DHF patients.<sup>16</sup>

Major outbreaks of dengue fever had been regularly occurring since 2005 in various parts of the country. A few recent studies have reported the circulation of all four dengue virus serotypes in the previous years, during DF outbreaks in and around Lahore region.<sup>17-19</sup> The disease has definitely established its endemicity in Pakistan. We did not study serologically whether the infection was primary or secondary,<sup>20</sup> but it seemed that majority of the DHF cases were diagnosed without a history of primary dengue infection recently or in the previous years. There may be subclinical exposure in some cases but that too would be a limited one as the disease is new to the region and a huge outbreak like this did not occur in the past. Some other studies have also presented cases of DHF in individuals without antibodies from previous infections.<sup>21</sup> Besides, it is a matter of great concern that a large population has been exposed to dengue virus now, in a region where presence of all four serotypes has already been confirmed, so the future risk of severe DHF outbreaks is very high in a pre-sensitized population.

Global resurgence of DF/DHF is a major public health concern nowadays. Rapidly increasing population, uncontrolled urbanization, increased air and road travel, failure to control vector growth, lack of awareness and poor performance of public health sector are the factors responsible for this resurgence. The risk factors for infection with DV are the increased density of the mosquito vector, reinfestation with *A. aegypti* of a new geographical area, warm and humid climate, increased population density, water storage pattern in houses, storage of junk in open spaces, including tyres and coconut shells etc. that trap rain water and introduction

of new serotype of the virus, etc. There are no licensed vaccines or anti-viral therapies for prevention or treatment, although there are some in development.<sup>22,23</sup> So the only effective way to prevent epidemic DF/DHF is to control the mosquito vector and prevent its bite. Considering the resource limitation in the public health sector and poor sanitation in big cities, one may see bigger outbreaks of DHF in future if the efforts remain half-hearted, inadequate and ineffective.

This study has some limitations. As it includes hospitalized cases only, the proportion of female cases does not represent the gender distribution of DF in the community and the data does not include the paediatric cases. Despite that, it clearly shows the burden of DHF, identifies the clinical factors predicting the onset and severity of DHF cases and pattern of haemorrhagic complications in these patients.

### CONCLUSION

DHF is endemic in Pakistan. We encountered a lot of haemorrhagic and serious complications of the disease during this outbreak. An understanding of these complications and prompt management of complicated and potentially serious cases in intensive care and high dependency units by experienced staff can effectively reduce the mortality rate.

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