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Clinical profile and outcome of dengue in children admitted in pediatric intensive care unit in Dhaka shishu (Children) Hospital, Dhaka, Bangladesh

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Abstract
Background: As dengue being a tropical infection presenting with varying degrees of severity of illness in Bangladeshi children, it is important to study the clinical profile, outcome, and predictors for mortality of moderate and severe dengue cases.
Objective: To find out the clinical profile and outcome of dengue in children admitted in PICU.
Study Design: Retrospective study.
Place and Duration of Study: Pediatric intensive care unit of Dhaka Shishu (Children) Hospital, Dhaka, Bangladesh from April 2018 to March 2019.
Methods: All patients admitted in PICU with the diagnosis of dengue fever during the study period were included in this study. Clinical characteristics, laboratory parameters, complications, outcome and predictors for mortality were studied.
Results: Fifty-eight seropositive dengue cases were admitted. Most common presenting symptoms were fever 58 (100%), vomiting 33 (56.8%) and abdominal pain 19 (32.7%). Among severe dengue (33), expanded dengue syndrome was present in 10 (30%) cases, expanded dengue syndrome with shock in 10 (30%), significant hemorrhage with shock in 2 (6%), hemorrhage without shock in 1(3%) and combination of expanded dengue syndrome with hemorrhage and shock in 10 (30%) cases. Pleural effusion was present in 38 (65.5%) and ascites in 18(31%) children. Among severe dengue, 12(36.3%) received invasive mechanical ventilation, 8(24%) received inotropes, 19(57.5%) received steroids and 7 (21%) had abdominal compartment syndrome requiring drainage of ascites.
Conclusion: Significantly more number of children who died received ventilator support and inotropes. Commonest cause of death is catecholamine resistant shock. There is no major adverse effect of steroids when used in severe dengue.

Keywords: dengue, dengue shock, clinical characteristics

1. Introduction

Dengue fever (DF) and dengue hemorrhagic fever (DHF) are caused by four antigenically distinct but related dengue virus (official name: *Dengue virus* [DENV]) serotypes transmitted primarily by *Aedes aegypti*. Dengue has rapidly spread in all regions of WHO in recent years [1]. The first reported epidemics of dengue fever occurred in 1779-1780 in Asia, Africa, and North America; in South East Asia a global pandemic of dengue after World war-II; the epidemic remained localized in this area till 1970 involving Thailand, Myanmar and other neighboring countries; in 1980 and 1990, the epidemic DHF spread west India, Pakistan, Sri Lanka, Maldives. In Bangladesh, the first outbreak of dengue fever was documented in 1964 in Dhaka; the first epidemic of DHF occurred in mid-2000, when 5,551 dengue infections were reported from Dhaka, Chittagong and Khulna cities, occurring mainly among adults; the case fatality rate was reported 1.7% with 93 deaths reported by Rahman M *et al*. [2] The 2019 dengue outbreak in Bangladesh is a nationwide occurrence of dengue fever in Bangladesh that began primarily in April 2019 and is still ongoing [1]. After the incubation period of 4-10 days, the infected Aedes aegypti mosquito is capable of transmitting the virus for the rest of its life The infection causes a flu-like illness and occasionally develops into a potentially lethal complication called severe dengue.[1]The global incidence of dengue has grown dramatically in recent decades [1]. About 3.9 billion people, in 128 countries, are at risk of infection with dengue viruses [3]. Even though most often dengue fever presents with self-limiting mild illness, severe dengue infection increases morbidity and few of them succumb to serious complications and death. Dengue is found in tropical and sub-tropical climates worldwide, mostly in urban and semi-urban areas [4]. Severe dengue is a leading cause of severe illness and death among children in some Asian and Latin American countries [4]. The exact clinical and laboratory profile is crucial for diagnosis as well as the successful management of the patients. Aim of the study was to observe the clinical features, outcome, complications and predictors of mortality moderate and severe dengue cases admitted in Pediatric Intensive Care Unit in Dhaka Shishu (Children) Hospital, Dhaka, Bangladesh.

2. Materials and Methods

All patients admitted with dengue fever in the age group of 1 month to 18 years during April 2018 to March 2019in PICU were considered for the study. Dengue serology (IgM and IgG antibody) and NS1 antigen were done in all patients. Patients with negative dengue serology were

excluded. Detailed clinical examination, serial monitoring of vital signs were done for all patients. Serial monitoring of hemogram, liver function tests, renal function tests, coagulation profile, serum electrolytes, chest X-ray, ultrasound of abdomen were performed. These cases were categorized based on NVBDCP classification [1]. Fluid management and respiratory support was provided following PICU standard protocol. Steroids were used in the following situations: massive pleural effusion with shock, need for more than three normal saline boluses, need for respiratory support and hem phagocytic lymphohistiocytosis (HLH). Massive pleural effusion was drained if following conditions were associated: respiratory acidosis, peak pressure more than 30cm H_2O on ventilator and hypoxia with FiO_2>0.6 by pigtail catheter placed by radiologist under ultrasound guidance. Ascites was also drained if there were clinical features of abdominal compartment syndrome. Widal test were done for few patients in whom co-infection was suspected. Ferritin, fibrinogen and triglycerides were also done in patients with clinical suspicion of hem phagocytic lymphohistiocytosis. Outcome measured was either recovery or death.

Statistical Analysis

Simple descriptive statistic of frequencies with percentages as applicable were arrived. To compare features among groups, with Fischer exact test, p <0.05 was considered for statistical significance. Epitools software was used. All data analyses was done with windows SPSS version 21.

3. Results

Of the total 70 patients admitted in PICU of Dhaka Shishu (Children) Hospital, Dhaka, Bangladesh from April 2018 to March 2019 with diagnosis of suspected dengue, 58 (82.8 %) were seropositive for dengue and satisfied the inclusion criteria. Fever, vomiting, abdominal pain and reduced urine output were the common presenting complaints. (Table 1) Most cases of severe dengue were in the age group of 5-10 years. Male: Female ratio was 1.4: 1 in general and among severe dengue cases male to female ratio was 1.3:1.

Table 1: Presenting complaints of children with enrolled dengue fever cases (N=58)

Symptoms	No of patients	Percentage
Fever	58	100
Vomiting	33	56.8
Abdomen pain	19	32.7
Reduced urine output	19	32.7
Inadequate intake	13	22.4
Cough	9	15.5
Body ache	8	13.7
Lethargy	8	13.7
Loose stools	7	12.0
Edema	7	12.0
Bleeding manifestation	6	10.0
Fast breathing	6	10.0
Head ache	6	10.0
Abdomen distension	5	8.0
Altered sensorium	5	8.0
Rash	3	5.0

Table 2: Age wise distribution of study population and classification of dengue severity (N=58)

Categories	0-1 year (n=14)	1-5 years (n=12)	5-10 years (n=22)	10-15 years (n=8)	15-18 years (n=2)	Total
Moderate dengue with high risk	8 (57.1%)	0	0	0	0	8
Moderate dengue with warning signs and symptoms	0	5(41.6%)	8(36.3%)	3(37.5%)	1(50%)	17
Severe dengue	6(42.8%)	7(58.3%)	14(63.6%)	5(62.5%)	1 (50%)	33

Patients were classified based on severity. Twenty-five patients were classified as moderate dengue and 33 patients as severe dengue. Among severe dengue patients, expanded dengue syndrome with or without shock was present in 20 (60.6%) which contributed to majority of severe dengue cases. Expanded dengue syndrome with both hemorrhage and shock was present in 10 (30.3%). Severe hemorrhage alone with or without shock was seen in only 3 (9.1%) (Table 2).

Table 3: Laboratory parameters and complications of enrolled dengue cases (N=58)

Parameters	No. of patients (%)
Leukopenia	17 (29.3)
Thrombocytopenia (<100,000/dL)	57(98.3)
Abnormal renal function test	6(10.3%)
Abnormal liver function test	36(62.1%)
Coagulopathy (PT INR >1.5)	11(19.1%)
Shock	22(37.9%)
Hemorrhage	8(13.8%)
Pleural effusion	38(65.5%)
Ascites	18(31.0%)
Probable HLH	6(10.3%)
Encephalitis	1(1.7%)

Pleural effusion was present in 38 (65.5%) and ascites in 18(31%) children. Shock was in 22 (37.9%), Hemorrhage (13.8%) out of 8 cases. One child died due to encephalitis, one child a case of thalassemia major with associated pseudomonas sepsis who also had catecholamine resistant shock, two deaths were due to catecholamine resistant shock due to severe capillary leakage and probable HLH (Table 3).

Table 4: Complications and outcome among enrolled dengue cases (N=58)

Complications		Death n (%)	Discharge n (%)	Total n (%)	P value*
	Total	**4**	**29**	**33**	
Capillary leak	Yes	2 (50.0)	21 (72.4)	23 (69.7)	0.57
	No	2 (50.0)	8 (27.5)	10 (30.3)	
Hemorrhage	Yes	3 (75.0)	5 (17.2)	8 (24.4)	0.04
	No	1 (25.0)	24 (82.7)	25 (75.6)	
Fluid refractory shock	Yes	3 (75.0)	5 (17.2)	8 (24.4)	0.04
	No	1 (25.0)	24 (82.7)	25 (75.6)	
Liver failure	Yes	4 (100.0)	9 (31.0)	13 (39.4)	0.02
	No	0	20 (68.9)	20 (60.6)	
Renal failure	Yes	3 (75.0)	3 (10.3)	6 (18.2)	0.01
	No	1 (25.0)	26 (89.6)	27 (81.8)	

**Fischer's exact test*

Severe capillary leak was present in 23 (69.6%) out of 33 children with severe dengue. Two (50%) out of 4 patients who died and 21 (72.4%) out of 29 who recovered had severe capillary leak. Hemorrhage was present in 8 (24.2%) out of 33 children with severe dengue. Three (75%) out of 4 patients who died and 5 (17.2 %) out of 29 who recovered had severe hemorrhage. Fluid refractory shock was present in 8 (24.2%) out of 33 children with severe dengue. Three (75%) out of 4 patients who died and 5 (17.2 %) out of 29 who recovered had fluid refractory shock. Significantly more number of children had fluid refractory shock and hemorrhage (p=0.04) Liver failure was present in 13 (39.3%) out of 33 children with severe dengue. All patients (4 out of 4) who died and 9 (31.0%) out of 29 who recovered had liver failure. Significantly more number of children had renal and liver failure among who died compared to those who survived (p=0.01 and p=0.02 respectively) (Table 4).

Table 5: Treatment modalities and outcomes among enrolled dengue cases (N=58)

Treatment modalities		Death n (%)	Discharge n (%)	Total	P value*
	Total	**4**	**29**	**33**	
Mechanical ventilation	Yes	4(100)	8(27.6)	12	0.01
	No	0	21(72.4)	21	
Inotropes	Yes	3(75)	5(17.2)	8	0.04
	No	1(25)	24(82.7)	25	
Hemodialysis	Yes	1(25)	0	1	0.12
	No	3(75)	29(100)	32	
Steroids	Yes	4(100)	15(51.7)	19	0.12
	No	0	14(48.3)	14	

*Fischer's exact test

Among severe dengue, one or the other form of respiratory support was needed for 30 (90.9%) patients. Among those who needed respiratory support, 13(43.3 %) were managed with high flow nasal cannula oxygen therapy, 5 (16.7 %) with non-invasive ventilation and 12(40%) using invasive ventilation. Five out of 12(41.7%) invasively ventilated patients needed pleural drain placement. Four among them required right sided pleural drain while one required bilateral drain. Significantly more number of dengue affected children who died needed mechanical ventilation when compared to those who survived (p=0.01) (Table 5). Seven patients who developed abdominal compartment syndrome needed ascitic drainage and four required both pleural and ascitic drainage. One child underwent hemodialysis for acute kidney injury and refractory acidosis who died. Steroids were used in 19 (57.5%) out of 33 children with severe dengue. All the four (100%) who died and 15 (51.7 %) children out of 29 who survived were given steroids, the difference was found to be statistically insignificant (Table 5). One child developed ventilator associated event who was ventilated for 7 days and one child had self-limited hypertension. Blood product transfusion was given in 24 out of 58 patients (41.3%). In 8 cases (33.3%) transfusions were not indicated. Reasons for unnecessary transfusions were high risk infants and persistent shock in spite of fluid boluses and urge to packed RBC transfusion before arrival of hematocrit report. Dengue associated HLH was suspected in 6 (10.3%) children, 4 (66.7%) were males and 2(33.3%) were females; two (33.3%) children died. Only 4 out of 8, HLH 2004 criteria were fulfilled in all children suspected hemophagocytic lymphohistiocytosis. Soluble CD 25 could not be done due to non-feasibility and children were hemodynamically unstable to undergo bone marrow aspiration cytology. They were treated with dexamethasone and intravenous Immunoglobulin. There were 4 deaths. Case fatality rate was 12.1% among severe dengue. All the four children who died were in the age group of 5-10 years.

4. Discussion

There is a wide variation among the clinical presentation of dengue infection, outcome and its predictors especially in severe dengue, the present study was designed to address these issues. All the 58 seropositive patients admitted in Pediatric Intensive care unit of Dhaka Shishu (Children) Hospital, Dhaka, Bangladesh during the study period were analyzed. Thirty-three patients had severe dengue. Male: female ratio was 1.4:1 in general and among severe dengue ratio was1.3:1. This is comparable to that of earlier reports by Vikram B *et al*,[5]Haridharshan GJ *et al*, [6] PothapregadaS *et al*, [7] Aggarwal A *et al*, [8] Kale AV *et al*, [9] and Rasul CH *et al*. [10] in the range of 1.1:1 to 1.7:1. Commonest age group in our study was 5-10 years. Vikram B *et al*, [5] and Haridharshan GJ *et al*. [6] showed a similar finding with common age group being 5-10 years. Pothapregada S *et al*. [7] and Gomber S *et al*. [11] showed 6-12 years as most commonly affected age group. Aggarwal A *et al*. [8] showed 7-9 years, Kale AV *et al*. [9] showed 11-15 years and Rasul CH *et al*. [10] showed 10-14 years as most commonly affected age group. Study by Kamath SR *et al* is different as infant being the commonest age group [12]. Reason for dengue being common in more than 5 years may be due to more involvement of children in outdoor activities during this age and most of the infants are kept covered preventing

them from mosquito bite. Fever was the most common clinical feature and was present in all patients which is comparable to the earlier observations [3, 4] whereas Pothapregada S *et al*. [7] reported fever in 94.6%, Aggarwal A *et al*. [8] reported fever in 93% of patients and Daniel R *et al*. [13] reported fever in 96.8% of patients. Vomiting was the second most common clinical feature and was present in 56.8% of patients followed by abdominal pain and reduced urine output in 32.7% which is like other reports [3, 4, 10]. Bhave *et al* reported pain abdomen as second common clinical feature followed by vomiting.[14]Pothapregada S *et al* reported conjunctival congestion followed by myalgia as second common presenting symptoms [7] Kale AV *et al* reported rash as the second common clinical feature followed by vomiting in severe dengue.[9]Chhotala YH *et al* reported headache followed by myalgiaas second common clinical presentation [15] Daniel R *et al*. reported headache followed by abdominal pain as second common clinical presentation [13]. Vomiting or abdominal pain were common findings in studies involving severe dengue patients. Severe dengue requiring pleural drain placement is very rare [7]. In our study, 15% of severe dengue patients needed pleural drain placement. Increased incidence in our study may be due to patients' profile with severe capillary leakage and being a referral center, we receive patients with fluid overload. In our study, 7 out of 33 (21.2%) severe dengue patients underwent ascitic drain placement. They had features of abdominal compartment syndrome. Abdominal compartment syndrome is known to occur in severe dengue and incidence is not known. Gala HC *et al* reported a fourteen-year boy with dengue and abdominal compartment syndrome who improved with paracentesis [16]. Study by Kamath SR *et al* reported abdominal compartment syndrome in 3 out 73 patients (4.1%) with Grade III and Grade IV Dengue hemorrhagic fever [12]. Higher incidence in our study may be due to severe capillary leakage among severe dengue patients as well as increased awareness about this condition compared to previous years. There is statistically significant association between fluid refractory shock, hemorrhage, renal failure, liver failure and death in our study which is same as study by Chulananda DAG *et al*.[17] We have used steroids in severe dengue patients with massive capillary leak. Corticosteroids are not recommended in national dengue guidelines.[2] Disruption of heparan sulfate (HS) fraction of endothelial glycocalyx via direct viral or NS1 mediated pathways is emerging as a possible mechanism of dengue vasculopathy and possible role of corticosteroids in preserving glycocalyx layer is being studied [18]. Study by Chulananda DAG *et al*. revealed no association between use of steroid as a therapeutic modality and death which is like our study [17]. In our study, there were no major complications of steroids. In the review by Rajapakse S *et al*, they observed that there were no major complications associated with the use of steroids in dengue in any studies [18]. Fifteen children who received steroids and survived in our study showed apparent benefit with improvement in respiratory distress as well as resolution of shock. In our study there is no statistical significance between severe capillary leakage and death probably due to the use of steroids. Dengue associated hemophagocytic lympho-histiocytosis is well known to occur [13, 14, 19]. More awareness about hem phagocytic lymphohistiocytosis is leading to increase in number of children diagnosed with dengue associated hemophagocytic lymphohistiocytosis which is associated with high mortality if left undiagnosed and untreated. In our study need for inotropes and mechanical ventilation are associated with higher mortality which is like the observation by Vikram B *et al*. [5] and Chulananda DAG *et al*. [17] Haridharsan *et al* did showed high mortality in ventilated children but not so in those who received inotropes.[6] Considering use of inotropes in severe dengue needs caution as intravascular volume is depleted due to severe capillary leakage. Inotropes may be helpful if there is a component of myocardial failure. Twelve percentage of severe dengue died which is higher compared to study by Vikram B *et al*. [5] and Kamath SR *et al*. [12] Higher mortality in our study is due to higher incidence of severe dengue with severe capillary leakage and refractory shock probably due to increased incidence of dengue due to more virulent strains. One of the limitations of this retrospective study is, in view of small sample size we could not do multivariate analysis to prove independent factors predicting mortality and the other one is dengue serology was not repeated in patients with initial negative result hence late seroconverts could have been missed.

5. Conclusion

Case fatality rate was 12.1% among severe dengue. Severe capillary leak with refractory shock unresponsive to any therapy is the common cause of death in dengue. Incidence of dengue associated HLH and awareness is probably increasing. Awareness and early diagnosis of this life-threatening condition is very important. Severe dengue and mortality is common in the age group of 5-10 years. Children who were mechanically ventilated and those who received inotropes had high mortality. Anuric renal failure and encephalitis are lethal complications associated with severe dengue. Well-designed controlled trials are needed to determine the role of steroids in dengue shock as there are no major adverse effects of steroids when used in dengue and had apparent benefit when used in severe dengue with severe capillary leakage and shock.

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