Clinical and Laboratory Profile of Fatal Dengue Cases at a Tertiary Care Private Hospital in Mumbai, India

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Abstract. Dengue-related mortality has significantly reduced with early and appropriate fluid resuscitation. However, we continue to see dengue-related fatalities in patients despite early intervention and advanced critical care support. This was a retrospective study conducted at a tertiary care private hospital in Mumbai, India. All patients dying of dengue in the calendar year 2017 were studied. Details related to age, gender, condition at presentation, laboratory parameters, treatment administered, and time to death were abstracted from case records. A total of 575 patients with a diagnosis of dengue were admitted to the hospital in 2017, of which 15 died (mortality rate 2.6%). Four patients died in the emergency medical unit; 11 patients who died after admission to the inpatient unit had multi-organ dysfunction at the time of presentation, with shock, severe liver dysfunction, and severe metabolic acidosis. Only 4/11 patients had hemoconcentration, and 10/11 patients had high white cell counts. In five patients where serum ferritin was performed, it was more than 40,000 ng/mL. Death occurred at a median time of 2 days after hospitalization despite good supportive care. Although there is scope for improvement of supportive care in these patients, it appears that other interventions are urgently needed to improve outcomes in severe dengue. This calls for more research into the immunopathology of dengue, evaluation of anti-inflammatory drugs, intravenous immunoglobulins, antivirals, and improved vaccines.

INTRODUCTION

Dengue fever is a major public health problem in many parts of the world, with an estimated 3.9 billion people in 128 countries at risk and 96 million clinically apparent infections.¹ India contributes to 34% of the global burden, with an estimated 33 million infections.¹ Although the course is uncomplicated and associated with quick recovery in most patients, in a small subset, the course is complicated with capillary leak, shock, and bleeding. Early recognition of complicated illness by rigorous clinical and laboratory monitoring and institution of appropriate fluid resuscitation based on the WHO guidelines has resulted in marked reduction of disease mortality.^{2,3} However, dengue-related fatalities continue to occur even in well-equipped critical care units such as in our hospital. We therefore decided to analyze the risk factors and disease profile of all patients dying with dengue at our hospital in the year 2017.

METHODS

This is a retrospective study conducted at a private tertiary-level multispecialty 750-bedded hospital in Mumbai, India. The hospital is accredited by National Board for Accreditation for Hospitals, the Joint Commission International, National Board for Laboratory Medicine, and the College of American Pathologists. It has a well-staffed/equipped 120-bedded adult and pediatric critical care unit. All patients dying of dengue in the year 2017 were analyzed. The diagnosis of dengue was established if a patient had a compatible clinical syndrome with either a positive dengue non-structural protein 1 (NS1) antigen or dengue IgM or high-titer dengue IgG by ELISA. Details related to age, gender, condition at presentation,

laboratory parameters, treatment administered, and time to death were abstracted from case records and analyzed.

RESULTS

In the year 2017, 575 patients with a diagnosis of dengue were admitted to the hospital. Fifteen patients (eight adults and seven children) died, with a mortality rate of 2.6%. Four children died soon after presenting to the emergency department (Table 1). We now describe the characteristics of the remaining 11 fatalities (eight adults and three children, nine males and two females) (Table 2). The median age was 28 years (range 4–67 years). All patients were previously healthy with no significant comorbidities and had short duration of illness before presentation. All patients were critically sick at admission, with shock and multi-organ dysfunction. Only 4/11 patients had Hb of more than 14 (median Hb of 11.8 with range 5.1–17.9). The trend in the Hb is depicted in Table 3. Seven of the 11 patients had an elevated white cell count beyond 12,000/ μ L (median 15,000/ μ L, range 5,910–36,040/ μ L). The neutrophil percentage ranged from 30% to 92%. All except one patient had platelet counts less than 30,000/ μ L (range 8,000–159,000). Serum C-reactive protein (CRP) was less than 4 mg/dL in nine patients, whereas in two others, it was 200 mg/L. Serum procalcitonin (PCT) values were available in eight patients; in five they were less than 2 ng/mL. There was no correlation between the white blood cell (WBC) counts and CRP and PCT values; most patients with very high WBC counts did not have significantly elevated CRP and PCT values. All patients had liver dysfunction with elevated bilirubin, very high liver enzymes with mean aspartate amino transferase of 4,000 units/L (range 150–7,000), mean alanine aminotransferase of 2,370 (range 67–6,370), and markedly deranged coagulation parameters with elevated prothrombin and activated partial thromboplastin time. Seven of eleven patients had renal dysfunction (three of four patients with normal creatinine were children). All patients had severe acidosis at presentation (mean pH of 7), with

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TABLE 1
Profile of patients dying in the emergency medical unit (N = 4)

	Case 1	Case 2	Case 3	Case 4
Age, gender	9 months, female	9 years, male	4 years, female	7 years, male
History of illness	Fever for 3–4 days and respiratory distress Hematemesis and epistaxis Transferred from another hospital	Fever for 3 days Hematemesis Malena Transferred from another hospital	Fever for 4 days	Admitted to hospital since 3 days
Previous investigations	Hb 8.9, TLC 7,300, and platelets 80,000 Dengue NS1 antigen positive	Platelets 17,000 Dengue NS1 antigen positive	Hb 11.8 and TLC 4,500 Platelets 120,000 Dengue NS1 antigen positive	NS1 antigen positive
Heart rate, pulses	120/minute, pulses not felt	142/minute, feeble	150/minute, feeble pulses	130/minute, pulses not palpable
Blood pressure	Not recordable	100/40	Not recordable	Not recordable
RR	Intubated and on bag and tube ventilation	32/minute	60/minute on 8 L oxygen	30/minute and on 10 L/minute oxygen by mask
Sensorium	Drowsy	Normal	Drowsy	Drowsy
Physical examination	Abdominal distension Bleeding from nostrils	Temperature 102.3 F	Bilateral reduced air entry, massive abdominal distension	Distended abdomen
Treatment given	Fluids and inotropes through the intraosseous line Mechanical ventilation	Fluids, inotropes, intubation, and mechanical ventilation	IV fluids, intubation and ventilation, inotropes, central line, arterial line, and pleural drainage	IV fluids, central line, inotropes, intubation and mechanical ventilation, dextrose, and NaHCO ₃
Investigation results	Not done	Not done	pH 7.047, ABE-19, and HCO ₃ 10 Hb 13.5	pH 6.7, base excess-27.5, and HCO ₃ 6.5 Hb 6.1
Duration of stay before death	6 hours	4 hours	3 hours	4 hours 10 minutes

ABE = absolute base excess; Hb = hemoglobin; IV = intravenous; TLC = total leukocyte count.

markedly elevated blood lactates (mean lactate 12.5 mmol/L range 4–21). Serum ferritin was tested in 5/11 patients, and, in all, it was more than 40,000 ng/mL. All patients were administered supportive care including fluids, blood products, inotropes, and mechanical ventilation, and in 7/11 patients renal replacement therapy. In all the five patients with very high serum ferritin, high-dose corticosteroids were administered, and four patients were also given intravenous immunoglobulin. Despite all this care, the course was relentless in all patients, with progressive shock, acidosis, liver, and renal dysfunction. Death occurred within 48 hours of hospitalization in 10/11 patients and in one patient after 96 hours.

DISCUSSION

The causes of death in study patients and possible corrective interventions are discussed further. It is generally believed that most deaths in dengue occur because of fluid leak, intravascular dehydration, and consequent shock. However, all the study patients received fluids and other supportive care before transfer. It is possible that in the four patients who had hemoconcentration at the time of admission to our hospital (Table 2), early shock was missed because of good mentation of the patients and casual clinical examination or inadequate fluid therapy. Conversely, many patients (4 + 7, Tables 1 and 2) did not have hemoconcentration on arrival, suggesting that they were well hydrated. Here, it is possible that early fluid therapy before the onset of capillary leakage or overzealous fluid administration may have been a contributory factor for death, particularly in the four patients who died soon after arrival (Table 1). Concealed internal bleeding could have been a contributory factor for fatal outcome in some patients. This is

supported by the fact that of the 11 patients (Table 2) all of whom were in or progressed to shock, six patients had no hemoconcentration/evidence of capillary leak to account for shock. Early and adequate packed cell transfusions could have possibly improved the outcomes in some of these patients (only four received packed cells). Myocardial dysfunction, a well-recognized complication of severe dengue, may also be a factor for refractory shock in some patients (although formal echocardiography and cardiac enzyme estimation was not performed in study patients). Although use of intra-arterial balloon pump or extracorporeal membrane oxygenation would have helped, these interventions are not possible in patients with severe dengue because of coagulopathy and thrombocytopenia and risk of bleeding. There was evidence of liver and kidney dysfunction in 10/11 and 7/11 of study patients which was multifactorial in origin. Whether any hepatoprotective strategies like N-acetylcysteine/ascorbic acid or glutathione or aggressive renal replacement therapies (only 4/7 received renal replacement therapy) would improve prognosis further is unknown.

It is also not clear whether dengue with such severe multi-organ dysfunction is due to an unusually virulent strain of the virus or aberrant host response. Do the very high ferritin levels in the study patients signify a hemophagocytic lymphohistiocytosis (HLH) syndrome complicating the primary infection or are they just a marker of severe disease/cytokine storm? There are several recent reports describing dengue complicated with HLH.⁴ However, because there is a significant overlap between clinical and laboratory features of severe dengue and hemophagocytic syndrome, over diagnosis of HLH in severe dengue is a distinct possibility. The nonresponse to high-dose steroids and even intravenous immunoglobulin in the study

TABLE 2
Salient details of the 11 patients who died because of dengue

SN	Demographics	Vital signs at admission	Initial investigations at the study site	Evidence of capillary leak	Treatment administered	Blood products administered	Duration of stay before death
1	28 years, female Dengue NS1, IgG, and IgM positive	PR 124/minute Intubated on bag and tube ventilation GCS 3/15 BP 110/90	Hb 7.2, TLC 21,770, and platelets 22,000 pH 6.9 and lactate 22 Creat 1.2 Bil 3.1, AST 6615, and ALT 28,630 PT/INR > 2 minutes Hb 12.3, TLC 8,000, and platelets 19,000 INR > 2 minutes	No effusion on CXR No ascites on USG	Mechanical ventilation Fluids and inotropes Steroids and antibiotics No renal replacement therapy	None	8 hours
2	28 years, male Dengue NS1 positive, and IgM and IgG negative	PR 131/minute Pulses poor BP not recordable RR 45/minute Saturation 90% on oxygen 15 L/minute BS 169 GCS 15/15	Bil 3.17, AST > 7,000, and ALT 4173 Creat 1.56 NH ₃ 265 Ferritin > 40,000 CRP 1.5	None on CXR and on clinical examination of abdomen	Mechanical ventilation Fluids (crystalloids and colloids) and inotropes Sodium bicarbonate Vitamin K Antibiotics and dexamethasone	6 units of FFP 6 units of RDP 6 units of cryo	24 hours
3	60 years, male Dengue NS1 positive and IgM positive	PR 104 RR 16 Saturation 98% BP 140/80 GCS 15/15 Temp 97.2 BS 41	Hb 15.9, TLC 15,860, and platelets 12,000 INR > 2 minutes Bil 9.08, AST 1,863, and ALT 867 Creat 4.03 Lactate 14.3 Ferritin > 40,000 LDH 3,534 PCT 3.2	USG abdomen showed moderate ascites	N-acetylcysteine Intravenous immunoglobulin SLED Fluids (crystalloids) Inotropes Mechanical ventilation Sodium bicarbonate Antibiotics and dexamethasone N-acetylcysteine CRRT	6 units of cryo 8 units of FFP 4 units of RDP	18 hours
4	38 years, female Dengue IgG positive, IgM positive, and NS1 negative	PR 163 BP 50 systolic RR 48 Saturation 97. GCS 15/15 BS 132	Hb 9.1, TLC 23,219, and platelets 23,000 Bil 3.67, AST 7,000, ALT 2,701, and CRP 5.3 PCT 2.7 Creat 2.26 Ferritin > 40,000	No effusion/ascites	Intravenous immunoglobulin Fluids (crystalloids and albumin) Inotropes Dexamethasone Antibiotics Mechanical ventilation Intravenous immunoglobulin 80 gm SLED and CRRT	12 units of cryo 8 units of FFP 6 units of RDP 2 units of packed red cells	48 hours
5	27 years, male Dengue IgM, IgG, and NS1 positive	PR 120 BP 100/60 RR 30 GCS 15/15 Saturation 97%	Hb 17.7, TLC 19,580, and platelets 15,000 CRP 0.895 PCT 1.38 Creat 0.83 INR 1.78 Bil 4.3 AST 3,816 and ALT 1,108 LDH 7,434 Ferritin > 40,000 CPK 10,853	Ascites on clinical examination USG gall bladder edema	Fluids and inotropes Mechanical ventilation Intravenous immunoglobulin 120 gm Dexamethasone and antibiotics SLED	10 units of RDP 6 units of cryo 4 units of FFP 1 unit of packed cells	96 hours
6	54 years, male Dengue IgG high-titer positive NS1 and IgM negative	PR 96/minute BP not recordable Intubated, saturation 100% Temp 99F	Hb 12.6 and TLC 8,580 Platelets 25,000 INR 1.79 Creat 3.27 Bil 1.91 AST 5,563 and ALT 2,224 PCT 17 CRP 22 PH 7.3 and lactate 6.2 CPK 9,554 Ferritin > 40,000	Bilateral pleural effusion and ascites on the computerized tomographic scan	Mechanical ventilation Fluids (crystalloids) and inotropes Antibiotics Dexamethasone SLED	1 unit of SDP 4 units of FFP 6 units of cryo	48 hours

(continued)

TABLE 2
Continued

SN	Demographics	Vital signs at admission	Initial investigations at the study site	Evidence of capillary leak	Treatment administered	Blood products administered	Duration of stay before death
7	26 years, male Dengue IgM and IgG positive	Intubated PR 130/minute BP 70 systolic Saturation 97% Feeble pulses Bleeding through ET tube BS 124	Hb 8.5, TLC 36,000, and platelets 32,000 CRP 1.6 PCT 0.69 Creat 2.03 Bil 3.93 INR 2.33 LDH 21.934 CPK 1,162 AST 7,000 ALT 7,431 pH 6.95 and lactate 21	No clinical or radiologic evidence of ascites or pleural effusion	Mechanical ventilation Fluids (crystalloids and albumin) Sodium bicarbonate Inotropes N-acetylcysteine Tranexamic acid SLED IV methylprednisolone Antibiotics	6 units of RDP 5 units of FFP 10 units of cryo	48 hours
8	67 years, male Dengue NS1 positive IgM and IgG negative	PR 120 BP 130/80 RR 48 Saturation 97% Cold peripheries	Hb 11.8, TLC 30,470, and platelets 159,000 INR 3 Bil 3.49 AST 151 ALT 67.5 Creat 2.56 PCT 0.19 CRP 1.336 pH 7.104 and lactate 14.2	No ascites on USG No effusion on CXR	Mechanical ventilation Fluids (crystalloids) Inotropes NaHCO ₃ Antibiotics Steroids SLED for 8 hours Vitamin K	4 units of FFP	18 hours
9	13 years, male NS1 antigen positive, and IgG and IgM negative	PR 125 RR 35 Saturation 98% GCS 15/15 BP 120/80 BS 94	Hb 14.9, TLC 5,910, and platelets 12,000 Bil 3.61 AST 7,000 and ALT 3,003 PT/INR 1.85 CRP 1.186 Creat 0.6 pH 7.32 and lactate 7	Clinical ascites And ascitic tap performed and 1 L of fluid drained	Fluids (crystalloids and albumin) Sodium bicarbonate Inotropes Mechanical ventilation N-acetylcysteine and vitamin K Antibiotics Hydrocortisone Factor VII a	2 units of SDP 2 units of packed cells 4 units of FFP	32 hours
10	4 years, male Dengue NS1 antigen positive, and IgG and IgM negative	PR 98 BP 94/44 RR 16 Saturation 85–87% Cold peripheries GCS 15/15	Hb 16.1, TLC 13,410, and platelets 8,000 CRP 0.281 Creat 0.6 Bil 0.6 AST/ALT not available pH 7.17 Lactate 5.5	Right pleural effusion Ascites	Fluids (crystalloids and albumin) Inotropes Mechanical ventilation Antibiotics Hydrocortisone Vitamin K Sodium bicarbonate Ascitic and pleural fluid drainage Fluids (crystalloids)	13 units of RDP 2 units of packed cells	36 hours
11	6 years, male Dengue NS1 positive, IgG positive, and IgM positive	PR 142, pulses not palpable BP not recordable Drowsy RR 30/minute Saturation 94% on oxygen by mask	Hb 5.1, TLC 6,672, and platelets 22,000 PT > 2 minutes Bil 0.69 AST 1124 and ALT 202 Creat 0.31 pH 6.67 Lactate 12.5	None	Sodium bicarbonate Mechanical ventilation	None	6 hours

ALT = alanine aminotransferase in IU/L; AST = aspartate amino transferase in IU/L; Bil = bilirubin in mg/dL; BP = blood pressure in mm of Hg; BS = blood sugar in mg/dL; Creat = creatinine in mg/dL; CPK = creatine phosphokinase in units/L; CRP = C-reactive protein in mg/dL; CRRT = continuous renal replacement therapy; cryo = cryoprecipitate; CXR = chest X-ray; FFP = fresh frozen plasma; GCS = Glasgow coma scale; Hb = hemoglobin in gm/dL; LDH = lactate dehydrogenase in units/L; NH₃ = ammonia in mg/dL; PCT = procalcitonin in ng/mL; PR = pulse rate/minute; PT/INR = prothrombin/international normalized ratio; RDPs = random donor platelets; SDPs = single donor platelets; SLED = sustained low efficiency dialysis; TLC = total leukocyte count per mm³; USG = ultrasonography.

Ferritin values are in ng/mL; lactate values are in mg/dL; platelets are presented in per mL.

TABLE 3
Changes in Hb in the study patients

Patient	Serial Hb in g/dL at various time points during hospital stay				
1	13.2	7.2	—	—	—
2	12.3	9.4	8.4	—	—
3	15.9	—	—	—	—
4	9.1	5.9	7.5	7.7	—
5	17.7	6.4	7.9	7.9	7.7
6	12.2	10.5	11.8	11.9	—
7	5.9	8.2	—	—	—
8	11.8	—	—	—	—
9	14.9	15.2	9.3	8.4	—
10	16.1	9.2	7.5	10.2	9.1
11	5.1	—	—	—	—

Hb = hemoglobin.

patients supports this possibility. There are several recent publications reporting elevated serum ferritin as a marker of poor prognosis in dengue.^{5–7} The high WBC counts seen in all the fatalities is also notable. High WBC counts have been earlier reported to be a marker of poor prognosis.⁸ Interestingly, the other acute inflammatory markers including CRP and PCT were not significantly elevated in most patients.

There are important lessons to be learned from this small study. The key to improving outcomes in severe dengue is accurate clinical assessment and proper timing, type, amount, and duration of intravenous fluids. Rational use of blood products and very good critical care support are crucial. However, we need something beyond this as well. At a basic science level, there is a need to study the genetics of the virus in patients with similar presentations as well as the immunology of the affected hosts. At a clinical care level, there is a need to scientifically evaluate through appropriately designed randomized controlled trials the role of high-dose corticosteroids, intravenous immunoglobulin, and other anti-inflammatory agents. Finally, at a research level, there is a need to develop effective antiviral drugs and better vaccines for dengue.⁹ Failing this, tragic losses of previously healthy individuals will continue.

Received June 4, 2019. Accepted for publication June 11, 2020.

Published online July 6, 2020.

Acknowledgment: The American Society of Tropical Medicine and Hygiene (ASTMH) assisted with publication expenses.

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REFERENCES

1. Bhatt S et al., 2013. The global distribution and burden of dengue. *Nature* 496: 504–507.
2. WHO Department of Control of Neglected Tropical Diseases (WHO/NTD), Special Programme for Research and Training in Tropical Diseases (WHO/TDR), 2012. *Handbook for Clinical Management of Dengue*. Geneva, Switzerland: World Health Organization.
3. Kalayanaraj S, 1999. Standardized clinical management: evidence of reduction of dengue hemorrhagic fever case-fatality rate in Thailand. *Dengue Bull* 23: 10–17.
4. Chung SM et al., 2017. Dengue-associated hemophagocytic lymphohistiocytosis in an adult: a case report and literature review. *Medicine (Baltimore)* 96: e6159.
5. Soundravally R, Agieshkumar B, Daisy M, Sherin J, Cleetus CC, 2015. Ferritin levels predict severe dengue. *Infection* 43: 13–19.
6. Van de Weg CA et al., 2014. Hyperferritinaemia in dengue virus infected patients is associated with immune activation and coagulation disturbances. *PLoS Negl Trop Dis* 8: e3214.
7. Ab-Rahman HA, Rahim H, AbuBakar S, Wong PF, 2016. Macrophage activation syndrome-associated markers in severe dengue. *Int J Med Sci* 13: 179–186.
8. Lee IK, Liu JW, Chen YH, Chen YC, Tsai CY, Huang SY, Lin CY, Huang CH, 2016. Development of a simple clinical risk score for early prediction of severe dengue in adult patients. *PLoS One* 11: e0154772.
9. Gan VC, 2014. Dengue: moving from current standard of care to state-of-the-art treatment. *Curr Treat Options Infect Dis* 6: 208–226.