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Dengue Death Review: A Tool to Adjudge the Cause of Dengue Mortality and Use of the Tool for Prevention of Dengue Deaths

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Abstract**—**Dengue is a mosquito-borne viral disease endemic in many countries in the tropics and sub-tropics. The state of Punjab in India shows cyclical and seasonal variation in dengue cases. The Case Fatality Rate of Dengue has ranged from 0.6 to 1.0 in the past years. The department has initiated review of the cases that have died due to dengue in order to know the exact cause of the death in a case of dengue. The study has been undertaken to know the other associated co-morbidities and factors causing death in a case of dengue. The study used the predesigned proforma on which the records (medical and Lab) were recorded and reviewed by the expert committee of the doctors. This study has revealed that cases of dengue having co-morbidities have longer stay in hospital. Fluid overload and co-morbidities have been found as major factors leading to death, however, in a confirmed case of dengue hepatorenal shutdown was found to be major cause of mortality. The data obtained will help in sensitizing the treating physicians in order to decrease the mortality due to dengue in future.

Keywords**—**Dengue, death, morbidities, DHF, DSS.

I. Background

THE State of Punjab in India is endemic for Dengue and causes significant morbidity and mortality. The reasons of mortality due to dengue should be ascertained in order to know the exact cause and the patho-physiology of the mortality. This will help the planners to know the exact number of actual deaths due to dengue and will also help to formulate guidelines for treating physicians for prevention of mortality.

II. Introduction

Dengue is rapidly growing as an important public health problem in the region. A large number of the human population is at risk. According to the World Health Organization, 1.8 billion people, or more than 70% of the global at-risk population, live in the WHO Southeast Asia and the Western Pacific regions which account for nearly 75% of current global disease burden from dengue [1]. India is a developing country which is facing dual epidemics of communicable disease and non-communicable disease. Dengue in India shows classical cyclical and seasonal variation with large number of morbidity and mortality. The disease affects mainly children, but in recent years it is becoming more of an adult disease [2]. There are approximately 2.5 billion population at risk or 24.2% of the total world population. An estimated 1.3 billion people or 52% of the population residing in the SEA Region are at risk of DF/DHF or approximately 87% of SEAR population are at risk. Seven of the ten countries in the Region regularly report disease incidence, i.e. Bangladesh, India, Indonesia, Maldives, Myanmar, Sri Lanka and Thailand. [7]

WHO 1997, guidelines on management of Dengue Haemorragic Fever (DHF) which suite mainly to the pediatric age group and adults do not fulfill these criteria in case of sever dengue which leads to mortality [3], [4]. In 2009, a new WHO guideline emphasized prominent gastro-intestinal symptoms in defining probable dengue and warning signs as predictors of severe dengue, and re-defined severe dengue beyond DHF and DSS [1]. The case fatality ratio (CFR – deaths per 100 cases) has declined from 3.3% in 1996 to 0.4% in 2010 in India [6]. It is a well-known fact that during the epidemics any death due to other morbidity is reported as dengue death which in turn increases the false mortality rate.

Dengue has affected mainly adult population in the State of Punjab over the years. Similarly, mortality rate is higher in adult population.

Aedes aegypti is the most potential vector for transmission of dengue. In India, *Aedes aegypti* is the main vector in most urban areas; however, *Aedes albopictus* is also found as vector in few areas of southern India. [11]. *Aedes aegypti* has been found to be responsible for transmission of dengue in Punjab.

The study has been undertaken to ascertain the exact cause of death in a case of dengue and this study describe the cohorts of dengue deaths in Punjab, confirm by the evidence based mechanism by the expert technical committee during 2012-2014.

III. Pathophysiology

The hallmark of DHF is the increased vascular permeability resulting in plasma leakage, contracted intravascular volume, and shock in severe cases. The leakage is unique in that there is selective leakage of plasma in the pleural and peritoneal cavities and the period of leakage is short (24–48 hours). Rapid recovery of shock without sequelae and the absence of inflammation in the pleura and peritoneum indicate functional

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changes in vascular integrity rather than structural damage of the endothelium as the underlying mechanism [9].

IV. Study Area

This study was carried out in the State of Punjab in India and is situated in Northern India. The state is bordered by the Indian states of Jammu and Kashmir in North, Himachal Pradesh in East, Haryana in South and Southeast, Rajasthan in Southwest, and the Pakistani province of Punjab in West. The state capital is located in Chandigarh, a Union Territory and also the capital of the neighboring state of Haryana. The cases of dengue have been reported from all the 22 districts of the State during this period and deaths have also been reported throughout the State. All the death cases of dengue reported during the study period from any part of the State were included in the study.

V. Lab Confirmation

Only the cases were considered as dengue positive cases in the study which were confirmed by the ELISA test as per recommendation of Govt. of India. For confirmation of dengue infection, Government of India (GoI) recommends use of ELISA-based antigen detection test (NS1) for diagnosing the cases from the first day onwards and antibody detection test IgM capture ELISA (MAC-ELISA) for diagnosing the cases after the fifth day of onset of disease [5]

VI. Study Duration

Dengue shows cyclical pattern of alternate year. In view of this, the data for three years 2012-2014 was taken into account for fair representation. 2012 and 2014 were lean years while 2013 witnessed very high number of dengue cases as compared to previous years. The study is still continuing for 2015 which has shown an acute upsurge in number of dengue cases in the State.

VII. Study Design

This study was multicenter retrospective study. Any reported dengue death was reviewed at two levels: first in the district by Districts Dengue Death Review Committee (DDDRC) followed by review at state by the state level committee known State Dengue Death Review Committee (SDDRC). The district committee did the primary screening of the reported dengue death, while the state committee with members of different specializations, public health experts, and member of Indian Medical Association (IMA) and representative of the treating hospital did the final review of each dengue death. All the medical records, lab records and findings of the district committee were undertaken for review by the State team.

VIII. Data Collection

Data was collected on the pre-designed proforma by the district team. The data was collected as per the hospital records (medical, laboratory and radiological). The hospital records were examined in detail to know the course of the disease along with the intervention provided to the patient from time to time. After review at the district level, the same records along with the hospital records were sent to the State level for review in detail by the State committee to know whether the deaths were dengue related or not, if related, then the exact pathophysiology of dengue deaths. At times, where the hospital records were insufficient or duration of stay in hospital was of shorter duration, verbal autopsy of the family members was done to establish the course of illness.

IX. Methodology

A retrospective study was undertaken to examine the dengue deaths reported in last three years (2012-2014) in the state of Punjab, India with a view to determine whether the reported death was actually due to dengue only or due to some co-morbidities or was incidental. A pretested proforma was designed as per the case definition of dengue to be filled by the committee of the experts based on the medical, laboratory findings and verbal autopsy of the family members. Total 138 reported dengue deaths were analyzed by the expert team the State Dengue Death Review Committee (SDDRC) to know whether the deaths were dengue related or not. If related, then the team tried to ascertain the exact pathophysiology of dengue death. The deaths were categorized in three sets:

1. Not a dengue case and death not due to dengue,
2. Dengue case but death not attributed to dengue, and
3. Dengue case with death attributed to dengue.

Laboratory confirmation of the dengue case was done as per the ELISA based tests (NS1 Antigen and IgM Mac ELISA). The cause of the death along with the co-morbidities was ascertained by the State team in case of the deaths which were found to be due to dengue.

The state team also invited the physicians of the treating hospitals (from where a death case was reported) for the opinion in order to make it unbiased for the treating hospital.

X. Results

Total 134 reported dengue deaths were analyzed by the expert team at two level and after the final discussion by State Dengue Death Review committee (SDDRC) the dengue deaths are confirmed.

Table I shows total number of deaths reported in year 2012, 2013, and 2014. On the basis of evidence and expert advices, 29.8% of total reported dengue deaths were confirmed as deaths due to dengue by the SDDRC.

TABLE I
Total Number of Dengue Deaths Year Wise

Year	Total reported dengue deaths	Death due to dengue (%)	Deaths not due to dengue (%)
2012	15	8 (53.3%)	7(46.6%)
2013	97	24(24.7%)	73(75.2%)
2014	22	8(36.6%)	14 (63.6%)
Total	**134**	**40(29.8%)**	**94 (70.1%)**

Table II shows the age and gender distribution of confirmed dengue deaths during study period. There is no difference between the dengue mortality among males and females. However, the table shows that the mortality is higher in adult population. This corresponds to the dengue cases reported in the State during this period. This finding has been contrary to the findings in other researches wherein the age of the patient and host genetics are risk factors of DHF. Although DHF can and does occur in adults, most cases are in children less than 15 years of age, and circumstantial evidence suggests that some population groups may be more susceptible to vascular leak syndrome than others [12].

TABLE II
AGE AND GENDER DISTRIBUTION OF CONFIRM DENGUE DEATHS

Year	2012	2013	2014
Gender	N=8	N=24	N=8
Male	4 (50%)	17 (71%)	7 (87%)
Female	4(50%)	7 (29%)	1(13%)
Mean age (in years)	**41.6+ 24.8**	**30.0±17.0**	**23.1±17.7**

p value <0.05

TABLE III
COMPARISON OF DENGUE AND NON-DENGUE DEATHS IN TERMS OF DAYS OF DISEASES AND ADMISSION

Year	Variable	Dengue deaths	Non dengue deaths
2013	Days of disease	5.9±2.9	9.4±8.9
	Days of admission	3.5±2.1	4.7±6.3
2014	Days of disease	8.3±3.7	18.6±12.7
	Days of admission	4.2±2.7	8.0±8.7

p value <0.05

Table III shows the comparisons of dengue deaths with non-dengue deaths in comparison to days of disease and admission. The table illustrates that more the duration between the onset of symptoms and the death, the death due to dengue was unlikely. The duration of admission was more if the patient as having illnesses other than dengue or had some co-morbidity.

TABLE IV
CLASSIFICATION OF REPORTED DENGUE DEATHS BY SDDRC

Year n=134	Dengue case and death due to Dengue	Dengue case but death not attributed to dengue	Non dengue death
2012 (n=15)	8 (53.4%)	7 (46.6%)	0
2013 (n= 97)	24 (24.7%)	18(18.5%)	55(56.8%)
2014 (n=22)	8 (36.4%)	8(36.4%)	6(27.2%)

TABLE V
DESCRIPTION OF DEATHS NOT ATTRIBUTED TO DENGUE

Year	Co-morbidity	Fluid over load	Septicaemia and other Pyogenic Illnesses	Others
2012 (n=7)	4(57.1%)	-	2(28.5%)	1(14.2%)
2013 (n=18)	8(44.4%)	3(16.6%)	6(33.3%)	1(05.5%)
2014 (n=8)	4(50%)	2(25%)	2 (25%)	-

Table IV shows classification of dengue death in 3 categories viz dengue case and death due to dengue, dengue case but death not due to dengue and not a dengue death. According to the SDDRC, a large number of deaths are due to dengue, whereas, many dengue cases died due to other co-morbidities. However, it was seen many deaths were over reported by media and institutions as dengue deaths.

Table V describes the distribution of deaths which were not attributed to the dengue. In all almost one–fourth of the deaths occurred due to septicaemia or other pyogenic infections whereas dengue laboratory test was just a finding in these cases. In last two year, one –fourth of the cases died due to fluid overload which indicate the over enthusiastic fluid administration at hospital leading to the cardiac overload and hence death. Some degree of fluid overload is inevitable in patients with severe plasma leakage. The skill is in giving them just enough intravenous fluid to maintain adequate perfusion to keep them alive, while waiting it out until the plasma leakage process spontaneously reverses, and at the same time avoiding excessive fluid overload. [6]

The volume of fluid replacement should be just sufficient to maintain effective circulation during the period of plasma leakage. Excessive fluid replacement and continuation for a longer period after cessation of leakage will cause respiratory distress from massive pleural effusion, ascites, and pulmonary congestion/ oedema. This can be dangerous [8]. The volume of initial and subsequent fluid resuscitation depends on the degree of shock and can vary from 10-20 mL/kg ideal body weight. The volume and rate of fluid replacement should be carefully titrated to the clinical response to maintain an effective circulation while avoiding an over replacement. Fluid therapy has to be judiciously controlled to avoid fluid overload which could result in massive pleural effusion, pulmonary oedema or ascites [10]. Majority of the cases had chronic diseases like Cardiac illnesses, Diabetes etc which were worsened due to haemodyamic disturbances in dengue.

TABLE VI
DESCRIPTION OF DEATHS DUE TO DENGUE

Year	Haemorrhage including cerebral bleed	Shock	Hepatorenal Involvement	Effusions (Pleural & Peritoneal)	Others (Scrub)
2012 (n=8)	2(25%)	2(25%)	4(50%)	0	0
2013 (n=24)	2(8.33%)	7(29.2)	11(45.8%)	2(8.33%)	2(8.33%)
2014 (n=8)	1(12.5%)	2(25%)	4(50%)	0	1(12.5%)

Table VI shows that in all these years 37.5% to 50% deaths were attributed to haemorrhages and shock. Although there were no DHF cases but shock due to capillary leakages was established as a cause of death in these cases. It was seen that majority of the deaths were caused when there was involvement of liver and kidneys leading either to fulminant hepatic failure or heptaorenal shutdown. Dengue patients with chronic renal failure (CRF) have a significantly higher risk of severe dengue and mortality [5]. The hallmark of DHF is the increased vascular permeability resulting in plasma leakage, contracted intravascular volume, and shock in severe cases. The leakage is unique in that there is selective leakage of plasma in the pleural and peritoneal cavities and the period of

leakage is short (24–48 hours). Rapid recovery of shock without sequelae and the absence of inflammation in the pleura and peritoneum indicate functional changes in vascular integrity rather than structural damage of the endothelium as the underlying mechanism. [9]. Despite the name, the critical feature that distinguishes DHF from dengue fever is not hemorrhaging, but rather plasma leakage resulting from increased vascular permeability [13].

Unusual manifestations of patients with severe organ involvement such as liver, kidneys, brain or heart associated with dengue infection have been increasingly reported in DHF and also in dengue patients who do not have evidence of plasma leakage. These unusual manifestations may be associated with co-infections, comorbidities or complications of prolonged shock. Exhaustive investigations should be done in these cases. [9]

Unusual manifestations, including acute liver failure and encephalopathy, may be present, even in the absence of severe plasma leakage or shock. Cardiomyopathy and encephalitis are also reported in a few dengue cases. However, most deaths from dengue occur in patients with profound shock, particularly if the situation is complicated by fluid overload. [1]

Patients with prolonged or uncorrected shock may give rise to a more complicated course with metabolic acidosis and electrolyte imbalance, multi organ failure and severe bleeding from various organs. Hepatic and renal failure are commonly observed in prolonged shock. Encephalopathy may occur in association with multiorgan failure, metabolic and electrolyte disturbances. Intracranial haemorrhage is rare and may be a late event. Patients with prolonged or uncorrected shock have a poor prognosis and high mortality. [9]

XI. Discussion

It has been observed that there is no significant sex distribution of the deaths due to dengue while the deaths are more in adult population. It has been seen during the review of the dengue deaths that during outbreak of dengue or during dengue season, there is over reporting of dengue deaths especially by private hospitals wherein cases do not fit into case definition of dengue. It has also been observed that fluid overload has been seen as an avoidable reason of death in certain cases. It has also been observed that haemodynamic disturbance following dengue leading to multiple organ failure especially liver and kidneys is a significant cause of death in these cases. Any injury or illness of these organs aggravates the illness. It was also observed that there were very less cases of frank haemorrhagic fever reported. It was also found that 3 (three) death cases had co-infection of Scrub typhus and these patients had acute renal failure which is more common in cases of scrub. It was also seen during the review of the reports that private hospitals were administering platelets to most of dengue cases although the evidence of haemorrhages were very less.

XII. Conclusion

All the hospitals attending to the dengue cases should have dengue corners where the initial examination and vitals including tourniquet test should be done, which will help in triaging of the dengue cases. The nursing staff should have close watch on input and output of the dengue cases since they are prone to capillary leakage and any amount of over fluid administration leading to effusions and other complications could be prevented at the earliest. The treating physicians should observe the lab findings and a dengue case having haemodynamic disturbance along with hepatorenal involvement should be labeled as high risk case as maximum mortality has been reported with this complication. Capacity building of medical and paramedical staff regarding intravenous fluid and platelet administration is desired. The dengue treatment guidelines should incorporate these findings which can help in early recognition of the serious cases in order to prevent mortality.

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