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Research Article

Pattern of management and outcome of dengue fever in pediatric in-patients in a tertiary care hospital: a prospective observational study

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ABSTRACT

Background: Dengue is one of the most important mosquito borne viral diseases presenting with varied symptomatology. A broad-angled evaluation with integration of clinical and laboratory parameters would direct the physicians through the stages of the disease process and the line of management. The objectives were to identify the pattern of management of dengue fever in pediatric in-patients and to assess the outcome.
Methods: A prospective observational study was carried out in pediatric inpatients. Data were collected by intensive case record review. Patients of age group 1-18 years of both genders diagnosed of dengue fever were included. The prescribing pattern in children presenting at various stages of dengue fever was analyzed. The outcome was assessed in terms of course in hospital and duration of hospital stay**.**
Results: A total of 110 patients diagnosed with dengue fever with one or more warning signs were admitted during the study period. Thirty percent cases had liver enzymes more than 3 times the normal and 68% patients had platelet count <1,00,000/cumm. Two cases of dengue encephalitis were reported. Most common intravenous fluid given was ringer lactate followed by isolyte P and others. Most common antibiotic prescribed was ceftriaxone followed by ampicillin and others. The symptomatic treatment given consisted of paracetamol, anti-acidity drugs and anti-emetic drugs. Vitamin K was prescribed to 41% and zinc and folic acid supplements were prescribed to 30% children. There was no correlation found between vitamin K and outcome of the disease.
Conclusion: Antibiotics and vitamin K though not a part of standard World Health Organization guidelines was seen to be an important part of management. Supportive care with judicious fluid management during the critical and recovery period with continuous monitoring is required for all patients. Further comparative studies are needed to establish the role of antibiotics and other supportive measures like zinc and folic acid on the outcome of the disease.

Keywords: Dengue fever, Management, Outcome, Observational study, Pediatric

INTRODUCTION

Dengue is a self-limiting acute mosquito borne disease characterized by fever, headache, muscle and joint pains, rash, nausea and vomiting. It is caused by an arbovirus and spread by Aedes mosquitoes. Some infections result in hemorrhagic manifestations and in its severe form is known as dengue shock or severe dengue, which can threaten the patient's life primarily through increased vascular permeability and hypotensive shock. Time and again dengue has given rise to pandemics all over the world. Dengue has a wide spectrum of clinical presentations, often with unpredictable clinical evolution and outcome. A small proportion progress to severe disease characterized by plasma leakage with or without hemorrhage. World Health Organization (WHO) has conferred it as a notifiable disease and since 2005 dengue is considered as a public health emergency of international concern.[1] WHO statistics have also shown that dengue burden from children in South East Asian Region (SEAR) countries is increasing. The first evidence of occurrence of dengue fever in India was reported during 1956 from Vellore district in Tamil Nadu. Every year during the period of July-November there is an upsurge in the cases of dengue/dengue hemorrhagic fever (DHF).[2] Children are at higher risk of acquiring severe dengue. Epidemiological studies conducted in India during 2001 dengue epidemic have shown that DHF has been predominantly restricted to children.[3-5] Reports from other

studies have shown that deaths due to dengue are potentially avoidable, and morbidity can be reduced to a great extent with appropriate measures.[6] A broad-angled evaluation with integration of clinical and laboratory parameters would direct the disease process as well as the on-going treatment and outcome of the disease.

The primary objective of our study was to identify the pattern of management of dengue fever in pediatric in-patients in our hospital and to assess the outcome of disease management. The secondary objective was to analyze the effect of vitamin K on progression of disease and recovery.

METHODS

A prospective observational study was carried out in pediatric general ward and intensive care unit of a tertiary care center in South India. Approval from Scientific Committee and Ethics Committee was obtained. Ascent was obtained from children above 7 years. The data were collected from case files in pediatric general ward and pediatric intensive care unit. Patients aged between 1 to 18 years of both genders who were admitted to our hospital from June 1, 2012 to November 30, 2012 and diagnosed with dengue fever with one or more warning signs were included in the study. The patients were considered to have dengue fever if they presented with fever along with at least two of symptoms such as anorexia and nausea, rash, aches and pains, warning signs, leucopoenia, and positive tourniquet test.[1] Furthermore, admitted were patients whose diagnosis was laboratory confirmed (NS1 antigen, immunoglobulin M [IgM], and immunoglobulin G [IgG]) and had warning signs. The warning signs which would prompt the physician to admit and keep the patient under observation are abdominal pain or tenderness, persistent vomiting, clinical fluid accumulation (ascites, pleural effusion), mucosal bleed, lethargy, restlessness, liver enlargement >2 cm, increase in hematocrit with a rapid decrease in platelet count.[1] Case sheets were examined to identify the symptoms and signs at the time of presentation, and their course in hospital were followed up to observe the development of complications and outcome. The details of all the laboratory investigations done, and line of management was noted. The basic tests (biochemical, hematological and radiological) consisted of complete blood count, urine analysis, chest X-ray, and ultrasound abdomen. IgM and IgG antibodies against dengue and NS1 antigen were detected using a commercial enzyme-linked immunoassay kit. Additional tests such as IgM antibodies for leptospirosis, smear for malaria, blood culture, urine culture, coagulation profile, endoscopy, etc. were done on clinical suspicion if required.

Statistical analysis

The descriptive variables were expressed in terms of mean. Categorical variables were represented as frequency and proportions. Pearson's correlation coefficient was used to compare the patient data with the outcome. Independent t-test was used to correlate vitamin K and outcome of the disease. $p<0.05$ was taken as statistically significant. The patients who died during the study period were excluded from the analysis of secondary objective.

RESULTS

A total of 110 patients diagnosed with dengue fever were admitted during the study period. The basic descriptive parameters of patients at the time of admission are depicted in Table 1. The study population consisted of 47% females and 53% males, respectively.

All the patients presented with one or more warning signs as mentioned in Table 2. Seventy patients were diagnosed with dengue fever with warning signs and 40 patients presented with shock. Fifty patients were positive for NS1 antigen, 23 and 25 were positive for IgG and IgM, respectively. The laboratory report for the rest of the patients was not available (Table 3).

Management

All the patients received intravenous (IV) fluids, antibiotics, and other supportive measures. The most common IV fluid prescribed was ringer lactate followed

Table 1: Descriptive parameters.

	Mean
Age (years)	7.07
Platelets (lakh/cumm)	0.68
ALT (IU)	290.37
AST (IU)	329.32
Albumin (g/L)	3.37
PT (s)	24.03
aPTT (s)	60.61
INR	2.54

ALT: Alanine transaminase, AST: Aspartate transaminase, PT: Prothrombin time, aPTT: activated partial thromboplastin time, INR: International normalized ratio

Table 2: Warning signs.

Warning signs	Frequency (%)
Fluid leakage (rising haematocrit, ascites, pleural effusion)	21 (19.1)
Platelet count <1,00,000/cumm	75 (68.1)
Persistent vomiting	50 (45.4)
ALT/AST >3 times normal upper limit	33 (30)

ALT: Alanine transaminase, AST: Aspartate transaminase

by isolyte P and DNS with KCl. The most common antibiotic prescribed was ceftriaxone, ampicillin, amoxicillin, and amikacin was added when mixed infection was suspected. The other symptomatic treatment consisted of paracetamol, anti-acidity drug (injection rantac), anti-emetics (injection emeset), vitamin K and zinc and folic acid supplements. Few physicians also prescribed hepamerz per oral (Table 4). Forty patients who presented with severe dengue or dengue shock required dopamine infusion. Among these 12 patients required a second ionotrope i.e. dobutamine. Ten patients required mechanical ventilation support. All patients recovered with these measures while ten patients died during the study period secondary to multi-organ failure.

The duration of stay ranged from 1 to 18 days with a mean of 6 days. The mean duration of stay for patients who received and did not receive vitamin K was 6.79 and 5.75 days, respectively. The patients who died during the study period were excluded from the analysis of this secondary objective. Independent t-test showed that vitamin K did not have any significant influence on duration of stay in the hospital (p=0.07). It was also observed that there was no significant difference between male and female patients in terms of outcome of the disease (p=0.8).

Table 3: Diagnosis at the time of admission.

	Frequency (%)
Dengue fever with warning signs	70 (63.64)
Severe dengue/shock	40 (36.36)
NS-1	50 (48.1)
IgG	23 (22.1)
IgM	25 (24)

IgG: Immunoglobulin G, IgM: Immunoglobulin M

Table 4: Treatment prescribed and its frequency.

Treatment	Frequency (%)
Ringer lactate	46 (41.8)
Isolyte P	43 (39.1)
½ DNS with KCl	21 (19.1)
Ceftriaxone	58 (52.7)
Ampicillin	40 (36.3)
Ceftriaxone + amikacin	8 (7.2)
Amoxicillin	3 (2.7)
Ceftriaxone + tazobactum + amikacin	1 (0.9)
Paracetamol	102 (94.4)
Antiacidity drug (ranitidine)	96 (88.1)
Antiemetic drug (ondansetron)	51 (49)
Vitamin K	45 (42.5)
Zinc and folic acid	29 (29.6)
Hepamerz	9 (9.1)
Dopamine	40 (36.7)
Dobutamine	12 (11)
Platelet transfusion	28 (27.5)
Fresh frozen plasma	37 (34.3)

DISCUSSION

In our study, the most common age group that presented with the complications of dengue was between 4 and 12 years. Liver enzymes (serum glutamic oxaloacetic transaminase/serum glutamic-pyruvic transaminase) were raised to more than 3 times the normal upper limit in about 30% of the cases (dengue hepatitis). Other studies have shown approximately 40% cases of altered transaminases and among 80% of them were associated with prolonged hospitalization.[7,8] During the study period, we encountered two cases of encephalitis that were attributed to dengue virus. One case recovered by day10 and another died. Kanade and Shah in 2011 have reported one case of dengue encephalitis, which recovered without any sequelae in 2 weeks.[9] In our study, there were 6 cases with other concurrent infections, 4 of them were suspected to have malaria and were put on artesunate. We could not get the details of the type of malaria. There were two cases of concurrent lower respiratory tract infection.[10,11] The mortality in our study was found to be approximately 10%, which was a little higher than in previous studies, which showed mortality rate ranging 1-8%.[12,13]

Our study did not show significant correlation of vitamin K with recovery and duration of stay. Though Vitamin K in complicated dengue was still used widely, WHO does not recommend vitamin K at any stage of the disease. Prophylactic platelet transfusion was also not recommended. A study done by Bhaskar et al. showed that in adults, platelet transfusion and fresh frozen plasma did not affect the unfavorable outcome that followed most of the patients who died during their study and suggested that there could be other factors that influenced the outcome.[14] WHO states that there is no evidence that supports the practice of transfusing platelet concentrates and/or fresh-frozen plasma for severe bleeding in dengue and often exacerbates the fluid overload. The outline of steps in the management of dengue fever is given below. Further details about each step can be accessed from WHO guidelines.[1]

Outline of the WHO Guide for management of dengue fever.

Step I. Overall assessment
1. History, including information on symptoms, past medical, and family history
2. Physical examination, including full physical and mental assessment
3. Investigation, including routine laboratory and dengue-specific laboratory.

Step II. Diagnosis, assessment of disease phase and severity.

Step III. Management

1. Disease notification
2. Management decisions. Depending on the clinical manifestations and other circumstances, patients may:
   - Be sent home (Group A);
   - Be referred for in-hospital management (Group B);
   - Require emergency treatment and urgent referral (Group C).

In our study, we could not assess the role of antibiotics on the outcome of disease. Further comparative studies between patients treated with and without antibiotics are needed to establish their role in the management of dengue. A new compound which is the aglycone analogue of antibiotic teicoplanin (code name LCTA-949) has been found to inhibit DENV-induced cytopathic effect in a dose-dependent manner.[15] The future of this antibiotic in the treatment of complications of dengue would be worth watching. While the newer drugs are on a long journey of development and approval the management until a long time to come would mainly depend on IV fluid resuscitation, antipyretics and other drugs for its symptomatic treatment. Based on the three randomized controlled trials comparing the different types of fluid resuscitation regime in dengue shock in children, there is no clear advantage to the use of colloids over crystalloids in terms of the overall outcome. However, colloids may be the preferred choice if the blood pressure has to be restored urgently that is, in those with pulse pressure <10 mm Hg. Colloids have been shown to restore the cardiac index and reduce the level of hematocrit faster than crystalloids in patients with intractable shock.[16-18]

IV fluids mostly crystalloids and colloids when indicated, paracetamol 10mg/kg body weight/dose, which can be repeated at the interval of 6 hrs and blood transfusion when hematocrit is <40% of initial value in children and adult females are usually recommended. For a disease that is complex in its manifestations, management is relatively simple, inexpensive and very effective in saving lives so long as correct and timely interventions are instituted. The key is early recognition and understanding of the clinical problems during the different phases of the disease, leading to a rational approach to case management and a good clinical outcome.

CONCLUSION

Dengue is usually a short lasting and self-limiting disease. However, severe infections can be lethal, especially if it is a secondary infection. There is no specific treatment for dengue as of now. The only rationale of its management lies in the supportive care with judicious fluid management during the critical and recovery period with continuous monitoring and assessment.

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REFERENCES

1. Dengue: Guidelines for Diagnosis, Treatment, Prevention and Control. Geneva: World Health Organization; 2009.
2. Guidelines for Clinical Management of Dengue Fever, Dengue Hemorrhagic Fever and Dengue Shock Syndrome. Government of India; 2008.
3. Guzmán MG, Kouri G, Bravo J, Valdes L, Vazquez S, Halstead SB. Effect of age on outcome of secondary dengue 2 infections. Int J Infect Dis. 2002;6(2):118-24.
4. Kamath SR, Ranjit S. Clinical features, complications and atypical manifestations of children with severe forms of dengue hemorrhagic fever in South India. Indian J Pediatr. 2006;73(10):889-95.
5. Narayanan M, Aravind MA, Thilothammal N, Prema R, Sargunam CS, Ramamurty N. Dengue fever epidemic in Chennai: a study of clinical profile and outcome. Indian Pediatr. 2002;39(11):1027-33.
6. Centers for Disease Control and Prevention (CDC). Dengue hemorrhagic fever – US-Mexico border, 2005. MMWR Morb Mortal Wkly Rep. 2007;56(31):785-9.
7. Souza LJ, Alves JG, Nogueira RM, Gicovate Neto C, Bastos DA, Siqueira EW, et al. Aminotransferase changes and acute hepatitis in patients with dengue fever: analysis of 1,585 cases. Braz J Infect Dis. 2004;8(2):156-63.
8. Parkash O, Almas A, Jafri SM, Hamid S, Akhtar J, Alishah H. Severity of acute hepatitis and its outcome in patients with dengue fever in a tertiary care hospital Karachi, Pakistan (South Asia). BMC Gastroenterol. 2010;10:43.
9. Kanade T, Shah I. Dengue encephalopathy. J Vector Borne Dis. 2011;48(3):180-1.
10. Thangaratham PS, Jeevan MK, Rajendran R, Samuel PP, Tyagi BK. Dual infection by dengue virus and Plasmodium vivax in Alappuzha District, Kerala, India. Jpn J Infect Dis. 2006;59(3):211-2.
11. Bhalla A, Sharma N, Sharma A, Suri V. Concurrent infection with dengue and malaria. Indian J Med Sci. 2006;60(8):330-1.
12. Lee IK, Liu JW, Yang KD. Clinical characteristics and risk factors for concurrent bacteremia in adults with dengue hemorrhagic fever. Am J Trop Med Hyg. 2005;72(2):221-6.
13. Malavige GN, Velathanthiri VG, Wijewickrama ES, Fernando S, Jayaratne SD, Aaskov J, et al. Patterns of disease among adults hospitalized with dengue infections. QJM. 2006;99(5):299-305.
14. Bhaskar ME, Moorthy S, Kumar NS, Arthur P. Dengue haemorrhagic fever among adults – An observational study in Chennai, South India. Indian J Med Res. 2010;132:738-40.
15. De Burghgraeve T, Kaptein SJ, Ayala-Nunez NV, Mondotte JA, Pastorino B, Printsevskaya SS, et al. An

analogue of the antibiotic teicoplanin prevents flavivirus entry *in vitro*. PLoS One. 2012;7(5):e37244.
16. Dung NM, Day NP, Tam DT, Loan HT, Chau HT, Minh LN, et al. Fluid replacement in dengue shock syndrome: a randomized, double-blind comparison of four intravenous-fluid regimens. Clin Infect Dis. 1999;29(4):787-94.
17. Ngo NT, Cao XT, Kneen R, Wills B, Nguyen VM, Nguyen TQ, et al. Acute management of dengue shock syndrome: a randomized double-blind comparison of 4 intravenous fluid regimens in the first hour. Clin Infect Dis. 2001;32(2):204-13.
18. Wills BA, Nguyen MD, Ha TL, Dong TH, Tran TN, Le TT, et al. Comparison of three fluid solutions for resuscitation in dengue shock syndrome. N Engl J Med. 2005;353(9):877-89.

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