

THE IMPACT OF A PROGRAM FOR STRENGTHENING DENGUE HEMORRHAGIC FEVER CASE MANAGEMENT ON THE CLINICAL OUTCOME OF DENGUE HEMORRHAGIC FEVER PATIENTS

Saengdao Mayurasakorn¹ and Nipar Suttipun²

¹Pediatric Department, Buri Ram Hospital; ²Buri Ram Provincial Health Office, Buri Ram, Thailand

Abstract. This study compared the case fatality ratio (CFR) of dengue shock syndrome (DSS) patients admitted to Buri Ram Hospital, an area with CFR of 0.11, 0.43 and 0.23% in 2002, 2003 and 2004, respectively, to obtain a provincial model for dengue case management using the I. development of a special program for strengthening dengue hemorrhagic fever (DHF) case management (No deaths in DSS patients), II. a retrospective review of the medical records of dengue fever (DF), DHF and DSS patients referred to Buri Ram Hospital. We compared the data during the 3 periods of the implementation of this program. Data was statistically analyzed using χ^2 or Fisher's exact test for categorical variables, one-way ANOVA for continuous data with normal distribution and Kruskal-Wallis test for nonparametric variables. The numbers of DF, DHF and DSS cases in Buri Ram were 1,332, 1,700 and 1,630 person, respectively, during 2006-2008. The number of DSS patients increased after implementation of the program: 12.2, 51.2 and 47.22 for 2006, 2007 and 2008, respectively, but the complications of the disease decreased. The CFR during 2006, 2007 and 2008 were 0.15, 0 and 0.06% ($p > 0.05$). The program for strengthening DHF case management did improve clinical outcomes in dengue patients after the implementation. The CFR in 2008 was only 0.06%, lower than the goal of the Ministry of Public Health (<0.13%). This program is still running, sustaining low CFR in dengue patients. It may be used as a model for other provinces in Thailand that have high dengue deaths.

Key words: DHF, case management, clinical outcomes, program for strengthening

INTRODUCTION

Dengue hemorrhagic fever (DHF) has been a major health problem in Thailand for more than 5 decades. During the past decade, more adult cases (age > 15 years)

have been found and at present, adults and children are almost equally affected (Pancharoen, 2002). The Thai Ministry of Public Health launched the National Prevention and Control Program of Dengue in 1999 with the goal of reduction of the case fatality rate (CFR) to < 0.2%. After implementation of this program, the CFR reduced from 0.34% in 1998 to 0.16% in 2002 (Ministry of Public Health, 1999). In Buri Ram Province, the morbidity rate for

Correspondence: Dr Saengdao Mayurasakorn, Pediatrics Department of Pediatrics, Buri Ram Hospital, Buri Ram, Thailand.
Tel: 66 (0) 44 615002; Fax: 66 (0) 44 621385
E-mail: jum_mu07@hotmail.com

dengue infections in 2002, 2003 and 2004 were 82.97, 48.43 and 86.7 per 100,000/population, while the CFR were 0.11, 0.43 and 0.23%, respectively. Since dengue infection morbidity reduction and CFR were not attained in Buri Ram, the Buri Ram Provincial Health Office, together with Buri Ram Hospital, established a 3-year program of "No deaths in DSS patients" in 2006.

Dengue shock syndrome (DSS) patients are the group with the greatest risk for complications due to shock, such as acute hepatic failure, acute renal failure, acidosis, disseminated Intravascular coagulation (DIC) and electrolyte imbalance. (Guzman and Kouri, 2001; Ranjit *et al*, 2005; Wills *et al*, 2005). Early diagnosis and proper initial management are important to reduce morbidity and CFR in dengue infection (Kalayanarooj, 1998, 1999). The availability of consultation, having an effective referral system, and medical audits are important for effective management of DHF patients. The objectives of the "No deaths in DSS patients" program were a reduction of CFR of DSS patients admitted/referred to Buri Ram Hospital and to obtain a provincial model of dengue case management and clinical practice guidelines (CPG) for all levels of healthcare personnel.

MATERIALS AND METHODS

The study was cross-sectional in type, with inclusion criteria of all DSS patients aged <15 years old referred to Buri Ram Hospital during 1 January 2006-31 December 2008, where DSS was diagnosed following WHO criteria (WHO, 1997). The exclusion criterion was a patient who did not meet WHO criteria for DSS.

The "No deaths in DSS patients" program consisted of 4 components: 1. the

development and distribution of the Buri Ram dengue clinical practice guidelines, including a DHF monitoring chart, information regarding proper initial intravenous fluid management and the referral system for both children and adult patients with dengue infection [based on Queen Sirikit National Institute of Child Health (QSNICH's clinical practice guideline) (Nimmannitya, 1993, 1997; WHO, 1997)]; 2. training of all personnel involved and procuring adequate equipment and supplies necessary for dengue case management; 3. regular monitoring of performance and outcomes at all levels by an evaluation team which included pediatricians, pediatric nurses from Buri Ram Hospital and Buri Ram Provincial Health Office; and 4. Setting up a dengue referral system, providing 24-hour telephone consultation for dengue case management.

A retrospective review of the medical records was carried out for DF, DHF and DSS patients who were referred to Buri Ram Hospital, comparing the time before (1 January 2006 - 31 December 2006), during (1 January 2007 - 31 December 2007) and after (1 January 2008 - 31 December 2008) implementation of the "No deaths in DSS patients" program.

Clinical complications were recorded, including gastrointestinal bleeding (GIB), acute renal dysfunction and liver dysfunction. Laboratory results were recorded including AST, ALT, BUN and creatinine (Cr) on initial presentation and their highest value.

The following definitions were used for this study: liver failure was defined as clinical or laboratory (prothrombin time/laboratory prothrombin time for the day above the cut-off of 2, increased bilirubin) and evidence of liver failure complicated by encephalopathy in patients without a previous history of liver disease

Table 1
Data of dengue patients admitted/referred to Buri Ram Hospital.

	2006	2007	2008	<i>p</i> -value
Total DF, DHF, DSS cases	1,332	1,700	1,630	-
Referred DF, DHF, DSS cases	72 (5.4)	41 (2.41)	72 (4.4)	-
Referred DSS cases (<i>N</i>)	16	21	34	-
Percent of all referred patients	22.22	51.22	47.22	0.001
Percent of all dengue patients	1.2	1.23	2.08	
Male:female ratio	1.5 : 1	1.2 : 1	1.2 : 1	0.744
Age (years): mean (SD)	8.98 (3.77)	8.10 (2.97)	9.19 (3.93)	0.264
LOS (days): mean (SD)	3.55 (4.20)	3.49 (2.23)	3.04 (1.92)	0.569

Table 2
Laboratory data from referred DHF patients.

	2006, <i>N</i> =72	2007, <i>N</i> =41	2008, <i>N</i> =72	<i>p</i> -value
Mean maximum Hct (Exclude GIB cases)	43.56 (5.91)	46.34 (6.46)	45.22(4.47)	0.04
Rising Hct > 20% (%)	46 (63.9)	31 (77.5)	46 (63.9)	0.27
WBC ≥5,000 ≤10,000 (%)	14 (19.4)	5 (12.2)	12 (16.7)	0.910
WBC (SD)	4,265.82 (3,195.23)	4,135.46 (2,484.67)	4,147.46 (2,487.12)	0.958
Platelet <50,000 (%)	54 (75.0)	30 (73.2)	41 (56.9)	0.047
Platelet <100,000 (%)	66 (91.71)	40 (92.3)	67 (93.1)	0.953
Median AST U	362	224	256	0.40
AST >1,000 U (%)	9 (21.4%)	3 (8.8%)	10 (18.2%)	0.322
AST >5,000 U (%)	3 (7.1%)	1 (2.9%)	3 (5.5%)	0.720
Median ALT (U)	117	112	103.5	0.128
ALT >1,000 U (%)	2 (4.8%)	0 (0%)	3 (5.5%)	0.0396
ALT >5,000 U (%)	0	0	1 (1.8)	0.498
Mean albumin (SD)	2.87 (0.68)	2.34 (0.56)	2.52 (0.74)	0.003
Albumin <3.5 g% (%)	35 (83.3)	34 (82.92)	52 (92.1)	0.03

Hct, hemotocrit; GIB, gastrointestinal bleed

(Poovorawan *et al*, 2006). Renal failure was defined as a sudden increase in serum creatinine concentration of >177 µmol/l (2.00 mg/dl), a serum creatinine >2 times the previous value or a value greater than the upper limit of the normal value for the patient's age (Vachvanichsanong *et al*, 2006). Fluid overload was defined by clinical evidence of a distended abdomen with ascites or respiratory distress (tachypnea

and dyspnea) requiring more than one dose of diuretic for treatment. A significant GIB was defined by bleeding that required blood transfusion.

Statistical analysis

Clinical complications and laboratory results among dengue patients per year were compared using χ^2 or Fisher's exact test for categorical variables, one-way

Table 3
Complications of DHF patients.

	2006 N = 1,332	2007 N = 1,700	2008 N = 1,630	<i>p</i> -value
Liver failure	3	1	2	0.810
Renal failure	2	0	0	0.479
GIB	6	0	4	0.258
Fluid overload	6	1	5	0.952
Total cases with complications (one patient may have more one than complication)	25	19	18	0.067
Deaths	2	0	1	
CFR (referred)	2.98	0	0.86	
CFR (total admitted)	0.15	0	0.06	

GIB, gastrointestinal bleed; CFR, case fatality rate

ANOVA for continuous data with normal distribution and Kruskal-Wallis test for nonparametric variables.

RESULTS

The total patients with DF, DHF and DSS admitted to all hospital in Buri Ram Province in 2006, 2007 and 2008 were 1,332, 1,700 and 1630, respectively. The DSS patients admitted did not differ by year in mean age, sex distribution or Length of stay (LOS), The number of DSS cases after implementation of the program were: 12.2, 51.2 and 47.2% in 2006, 2007 and 2008, respectively (Table 1). The number of more severe dengue cases increased after implementation of the program (Table 2). The mean maximum hematocrit levels (Hct) (excluding GIB cases) were 43.56, 46.34 and 45.22 in 2006, 2007 and 2008, respectively ($p=0.04$). The mean albumin levels were 2.87, 2.34 and 2.54 in 2006, 2007 and 2008, respectively ($p=0.03$). Albumin was < 3.5 g% in 35 (83.3%), 34 (82.5%) and 52 (92.1%) in 2006, 2007 and 2008, respectively ($p=0.03$) but the complications decreased (Table 3). Significant GIB, renal

failure, fluid overload and severe liver dysfunction also decreased in frequency over time (Table 3). Three patients in 2006 developed hepatic encephalopathy and 2 required exchange transfusion. Two patients in 2008 developed hepatic encephalopathy and recovered fully with supportive treatment only. There were no significant differences in the number of cases with AST/ALT levels $>1,000$ u and $>5,000$ u (Table 2). The median AST/ALT levels in DSS patients for 2006, 2007 and 2008 were 362/117, 224/79 and 256/103 U/l, respectively. There were no differences in case fatality rates by year. The case fatality rate for 2008 was 0.06%.

DISCUSSION

During the program for strengthening DHF case management the number of DF, DHF and DSS cases at Buri Ram Hospital and referred patients increased each year. This trend represents inadequate control of dengue transmission. The number of referred patients with DSS increased each year. This may be explained by the different doctors rotating through the local hos-

pitals, differences in dengue virus virulence in each year [serotype 2 in Southeast Asia has the highest virulence (Pancharoen, 2002), differences in the viruses infecting each patient (Halstead, 1998; Libraty *et al*, 2002; Wang *et al*, 2006) or it may reflect the quality of care at the local hospitals.

Referred DSS patients has complications, including prolonged shock, volume overload from inappropriate IV fluid administration, concealed bleeding, delayed diagnosis or delayed treatment (Kalayana-Navooj, 1999; Singhis *et al*, 2007). These findings emphasize improving early diagnosis and proper management of dengue patients is important to reduce preventable complications which could lead to death. Prolonged shock is a major risk for multi-organ failure (Nimmannitya *et al*, 1978).

A dengue care team, clinical practice guidelines for early diagnosis, prevention of shock, proper initial treatment of shock and an effective referral system are crucial. Patients with multi-organ failure, especially liver and renal dysfunction, have a poor prognosis even when treated at the best tertiary care hospitals with the most experienced physicians (Nimmannitya *et al*, 1978; Kamath and Ranjit, 2006; Tantracheewathorn and Tantracheewathorn, 2007).

The program for strengthening DSS case management is important. The key to success is evaluation team that were sent to every local hospital involved. The dengue team was composed of pediatricians, pediatric nurses and health care officers from the Provincial Health Office, who had experience dealing with dengue patients. Emphasis on using dengue clinical practice guidelines included a DHF monitoring chart. This guideline helped in decision making for proper fluid resuscitation and management to reduce complications, such as pulmonary edema (Kamath and

Ranjit, 2006). A limitation of the study was it was a single center study.

After implementation of the program, there was a reduction in clinical complications, such as significant GIB, liver and renal dysfunction. AST and ALT levels were directly correlated with severity of disease. High levels were correlated with a high risk for spontaneous bleeding (Lum *et al*, 1993; Nguyen *et al*, 1997; Wahid *et al*, 2000; Poovorawan *et al*, 2006). The mean AST and ALT levels decreased during this project, though the difference was not significant. Patients with hepatic encephalopathy requiring total exchange transfusion decreased in number, meaning reduced cost of treatment.

The CFR did not change significantly. In 2006 two patients died from multi-organ failure (prolonged shock from delayed diagnosis) and in 2008 one patient died from respiratory failure due to excessive IV fluid administration. Early diagnosis of dengue patients and proper IV fluid administration need to be emphasized to prevent fluid overload.

The program for strengthening DHF case management improved clinical outcomes. Applying clinical practice guidelines for the whole province, effective consultation and a referral system resulted in a CFR in 2008 of 0.06%, lower than goal of the Ministry of Public Health of Thailand (<0.13%). This project is still running, maintaining a low CFR. This program may be used as a model for other provinces in Thailand with high dengue deaths.

REFERENCES

- Guzman MG, Kouri G. Dengue: an update. *Lancet Infect Dis* 2001; 2: 33-42.
- Halstead SB. Pathogenesis of dengue: challenges to molecular biology. *Science* 1998; 239: 476-81.

- Kalayanarooj S. Diagnosis and management of dengue haemorrhagic fever. Bangkok: Desire Printing, 1998.
- Kalayanavooj S. Standardized clinical management: evidence of reduction of dengue haemorrhagic fever case-fatality rate in Thailand. *Dengue Bull* 1999; 23: 10-7.
- 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: 889-95.
- Libraty DH, Young PR, Pickering D, *et al.* High circulation levels of the dengue virus nonstructural protein NS1 early in dengue illness correlate with the development of dengue hemorrhagic fever. *J Infect Dis* 2002; 186: 1165-8.
- Lum LC, Lam SK, George R, Devi S. Fulminant hepatitis in dengue infection. *Southeast Asian J Trop Med Public Health* 1993; 24: 467-71.
- Ministry of Public Health, Thailand (MOPH). Guidelines for diagnosis and management of dengue haemorrhagic fever. Nonthaburi: MOPH, 1999.
- Nguyen TL, Nguyen TH, Ticu NT. The impact of dengue hemorrhagic fever on liver function. *Res Virol* 1997; 148: 273-7.
- Nimmannitya S, Thisyakorn U, Hemsrichart V. Dengue hemorrhagic fever with unusual manifestations. *Southeast Asian J Trop Med Public Health* 1978; 18: 398-406.
- Nimmannitya S. Clinical manifestations and management of dengue/dengue haemorrhagic fever. In: Thongchareon P, ed. Monograph on dengue/dengue haemorrhagic fever. New Delhi: WHO Regional Office for South-East Asia, 1993: 48-54, 55-61.
- Nimmannitya S. Dengue haemorrhagic fever: Diagnosis. In: DJ Gubler, G Kuno, eds. Dengue and dengue haemorrhagic fever. London: CAB International, 1997: 133-45.
- Pancharoen C, Kulwichit T, Tantavichien T, Thisyakorn U, Thisyakorn C. Dengue infection: A global concern. *J Med Assoc Thai* 2002; 85: S25-33.
- Poovorawan Y, Hatagalung Y, Chongsrirawat V, Bouduille I, Bock HL. Dengue virus infection a major cause of acute hepatic failure in Thai children. *Ann Trop Paediatr* 2006; 26: 17-23.
- Ranjit S, Kisson N, Jayakumar I. Aggressive management of dengue shock syndrome may decrease mortality rate: a suggested protocol. *Pediatr Crit Care Med* 2005; 6: 412-9.
- Singhis, Kisson N, Bansal A. Dengue and dengue hemorrhagic fever: management issues in an intensive care unit. *J Pediatric (Rio J)* 2007; 83(2 suppl): S22-S35.
- Tantracheewathorn T, Tantracheewathorn S. Risk factors of dengue shock syndrome in Children. *J Med Assoc Thai* 2007; 90: 272-7.
- Vachvanichsanong P, Dissaneevate P, Lim A, McNeil ED. Childhood acute renal failure: 22-year experience in a university hospital in southern Thailand. *Pediatrics* 2006; 118: e786-791.
- Wahid SF, Sanusi S, Zawawi MM, Ali RA. A comparison of the pattern of liver involvement in dengue hemorrhagic fever with classic dengue fever. *Southeast Asian J Trop Med Public Health* 2000; 31: 259-63.
- Wang WK, Chen HI, Yang CF, Hsien SC, *et al.* Slower rates of clearance of viral load and virus-containing immune complexes in patients with dengue hemorrhagic fever. *Clin Infect Dis* 2006; 43: 1023-30.
- WHO. Dengue haemorrhagic fever: diagnosis, treatment and control. Geneva: WHO, 1997.
- Wills BA, Nguyen MD, Ha TL, Dong TH, *et al.* Comparison of three fluid solutions for resuscitation in dengue shock syndrome. *N Engl J Med* 2005; 353: 877-89.