

## **Clinical Characteristics and Outcomes of Dengue-infected Children Admitted to the Chiang Mai University Hospital During an Outbreak in 2008**

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### **Abstract**

**Objective** To assess clinical characteristics, outcomes, and hospital costs of dengue-infected children, who were admitted to Chiang Mai University (CMU) Hospital during an outbreak in 2008.

**Methods** All serologically confirmed dengue-infected children, who were admitted to CMU Hospital between January 1 and December 31, 2008 were reviewed retrospectively.

**Results** A total of 130 children were included in the study. The median age was 12.2 years (interquartile range: 9.7-13.9). Seventy-eight children (60%) were males. Twenty children (15.4%) were classified as having dengue fever, 99 (76.1%) as having dengue hemorrhagic fever (DHF), and 11 (8.5%) as having dengue shock syndrome (DSS). The three most common presenting symptoms were acute fever (98.5%), nausea/vomiting (66.9%), and myalgia (55.4%). Hepatomegaly, hypotension, pleural effusion, and ascites were found more common in children with DSS than in those without it ( $p < 0.05$ ). Children with DSS stayed significantly longer in hospital than those without it (7.1 vs. 3.3 days,  $p < 0.01$ ). The mean hospital cost per admission was 10 times higher among children with DSS than those without it (US\$ 181.9 vs. US\$ 1,873.0,  $p < 0.001$ ). The overall mortality rate was 1.5%.

**Conclusion** Children with DSS showed higher clinical severity, longer hospital stay, and poorer outcomes than those without it. Prompt diagnosis and treatment definitely helps reduce morbidity, mortality and hospital costs. **Chiang Mai Medical Journal** 2011;50(4):95-104.

**Keywords:** dengue infection, clinical characteristics, outcomes, cost, children

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Dengue viral infection is the most significant mosquito-transmitted viral disease in humans worldwide. More than 2.5 billion people in approximately 110 countries are at risk for this disease.<sup>(1)</sup> Annually, 50-100 million people become infected, of which 250,000-500,000 develop dengue fever (DF), dengue hemorrhagic fever (DHF), and dengue shock syndrome (DSS).<sup>(2-4)</sup> The fatality case rate averages less than 1%, when prompt diagnosis and proper management of the disease is carried out.<sup>(3)</sup> Dengue viral infection most often occurs in children aged 5-9 years;<sup>(5)</sup> although the peak age has shifted to 10-14 years in recent years.<sup>(6-8)</sup>

Most patients with dengue viral infection are usually asymptomatic or have mild clinical syndromes. Among children who develop clinical symptoms, Kalayanarooj *et al*<sup>(9)</sup> found that fever (100%), anorexia (85%), and vomiting (70%) were the most common clinical presentations, and pleural effusion (42.9%) and bleeding manifestations (13%) the most common signs. Similarly, Wichmann *et al*,<sup>(10)</sup> reported that fever (100%), vomiting (59.0%), and nausea (57.0%) were the most common presenting manifestations, and hepatomegaly (40.0%) and bleeding manifestations (21.0%) the most common signs. Generally, patients with secondary dengue infection usually develop more severe illness than those with primary infection, due to the influence of enhancing antibodies.<sup>(8)</sup> The Thai study by Wichmann *et al*, demonstrated that children with secondary dengue infection were at a significantly higher risk of having DHF/DSS than DF (OR: 3.63;  $p < 0.001$ ).<sup>(10)</sup>

Dengue viral infection increases hospital costs, especially among patients with highly severe illness.<sup>(11)</sup> Previous studies conducted in Thailand and Vietnam found that both

direct and indirect costs of illness for patients with DHF and DSS were significantly higher than those for patients with DF alone.<sup>(12, 13)</sup>

In 2008, the Thai Ministry of Public Health reported an outbreak of dengue viral infection in Chiang Mai, with an incidence of 255.6 per 100,000 population.<sup>(14)</sup> We therefore aimed to determine any differences or similarities to previous studies of dengue infections in children by assessing the clinical characteristics and outcomes of dengue-infected children, who were admitted to Chiang Mai University (CMU) Hospital during the outbreak.

## METHODS

### Study area and population

We collected data retrospectively of serologically confirmed dengue-infected children, who were aged less than 15 years and admitted to CMU Hospital between January 1 and December 31, 2008.

### Data collection

Demographic data, clinical characteristics, laboratory results, treatment, and outcomes were extracted from the medical records. The study protocol was approved by the research ethics committee of CMU.

### Case definition

We applied the case definition from the 1997 guideline of the World Health Organization,<sup>(2)</sup> in which DF is defined as an asymptomatic, non-localizing febrile illness or acute febrile viral infection; DHF is characterized by four major clinical manifestations that include high fever, hemorrhagic phenomena, hepatomegaly, and signs of circulatory failure; and DSS is classified as DHF with hypovolemic shock from plasma leakage.<sup>(2)</sup>

## Laboratory Tests

Anti-dengue antibodies (IgM and IgG) were measured by the Enzyme-Linked Immunoabsorbant Assay (ELISA) test (Euro-immune AG, Lübeck, Germany). Primary and secondary dengue infection was defined by an anti-dengue IgM-to-IgG ratio of  $\geq 1.8$  and  $< 1.8$ , respectively.<sup>(15)</sup> A complete blood count (CBC) and platelet count were performed, and levels of serum glutamic oxaloacetic transaminase (SGOT), serum glutamic pyruvic transaminase (SGPT), albumin, and total bilirubin were assessed.

All testing was carried out at the central laboratory of CMU Hospital and blood samples were tested on the day of hospital admission.

## Statistical analysis

Differences in clinical characteristics, laboratory data, and outcomes of dengue-infected children were analyzed. Statistical analyses were performed using version 13 of the Statistical Package for Social Science software (SPSS Inc., Chicago, IL, USA). Continuous variables were compared using analysis of variance (ANOVA). Categorical variables were compared using Chi-square analysis or Fisher's exact test, as appropriate. A two-sided p-value of  $< 0.05$  was considered to be statistically significant.

## RESULTS

### Demographic data

A total of 130 dengue-infected children were included in this study. Seventy-eight children (60%) were males. The median age of all the children was 12.2 years (interquartile range [IQR]: 9.7-13.9). Twenty children (15.4%) were classified as having DF, 99 (76.1%) as having DHF, and 11 (8.5%) as having DSS. Based on the serological tests, 107 children (82.3%) were classified as having secondary dengue infection (Table 1). More children with DSS were reported as having underlying diseases than those without it ( $p = 0.06$ ).

### Clinical characteristics

A history of acute fever ( $T \geq 38.0$  °C) was the most common presenting symptom (98.5%), followed by nausea/vomiting (66.9%) and myalgia (55.4%). Skin rash (17.7%) was relatively uncommon. Mild bleeding (71.5%), tachycardia (60.8%) and hepatomegaly (30.0%) were the three most common signs. The tourniquet test was performed on 75 children, of which 54 (72.0%) were positive. More children with DSS were found to have hepatomegaly (72.7% vs. 21.7%;  $p < 0.01$ ), pleural effusion (45.5% vs. 1.0%;  $p < 0.01$ ), and ascites (36.4% vs. 0%;

**Table 1.** Demographic data of dengue-infected children admitted to CMU Hospital

	DF (n=20)	DHF (n=99)	DSS (n=11)	Total (n=130)	p-value
Male gender	10 (50.0)	62 (62.6)	6 (54.5)	78 (60.0)	0.53*
Age (years)	10.7 (8.5-12.2)	12.9 (10.3-14.0)	12.2 (8.7-13.7)	12.2 (9.7-13.9)	0.33†
Underlying diseases	0 (0)	12 (12.1)	3 (27.3)	15 (11.5)	0.06‡
Secondary infection	15 (75.0)	82 (82.8)	10 (90.9)	107 (82.3)	0.52‡

Note: Data are shown in number (%) or median (IQR).

a Such as hemolytic disease, congenital heart disease, congenital CNS anomaly, and epilepsy.

\* By Chi-square test; † By ANOVA test; ‡ By Fisher's exact test

$p < 0.01$ ), than children without it (Table 2).

### Laboratory results

The mean hematocrit level on admission was 39.4% (SD: 6.4), with no significant difference between the non-DSS and DSS groups ( $p=0.52$ ). One hundred and nine children (83.9%) had leukopenia [white blood cell (WBC) count  $<5 \times 10^3/\text{cumm}$ ] with a mean of  $3.6 \times 10^3/\text{cumm}$ . Children with DSS tended to have a higher WBC count than those without it ( $p = 0.08$ ). Eighty-two children (63.1%) had thrombocytopenia (platelet count  $<100 \times 10^3/\text{cumm}$ ) with a mean platelet count of  $92.3 \times 10^3/\text{cumm}$ . The mean platelet count in the DHF and DSS group was significantly lower than that in the DF group ( $p < 0.01$ ). Children with DSS had significantly higher levels of both SGOT and SGPT than

those without it ( $p < 0.01$  and  $p = 0.02$ , respectively). Furthermore, children with DSS had significantly lower albumin levels than those without it ( $p < 0.01$ ) (Table 3).

### Outcomes

The mean length of hospital stay was 3.6 days (SD: 2.4). Children with DSS had a significantly longer mean hospital stay than those without it (7.1 vs. 3.1 days;  $p < 0.01$ ). Twelve children (9.2%) were admitted to the Pediatric Intensive Care Unit (PICU), and among them, 10 were in the DSS group and 2 the non-DSS group ( $p < 0.01$ ) (Table 4). All the dengue-infected children received either oral (7.7%) or intravenous (92.3%), hydration during hospitalization. Thirteen children (10.0%) required platelet transfusion to correct the bleeding from thrombo-

**Table 2.** Clinical characteristics of dengue-infected children admitted to CMU Hospital

Characteristics	DF (n=20)	DHF (n=99)	DSS (n=11)	Total (n=130)	p-value
Presenting symptoms					
• Fever	20 (100)	97 (98.0)	11 (100)	128 (98.5)	NS†
• Nausea/vomiting	12 (60.0)	66 (66.7)	9 (81.8)	87 (66.9)	0.46*
• Myalgia	9 (45.0)	58 (58.6)	5 (45.5)	72 (55.4)	0.43*
• Headache	9 (45.0)	48 (48.5)	4 (36.4)	56 (43.1)	0.89*
• Abdominal pain	10 (50.0)	35 (35.4)	7 (63.6)	52 (40.0)	0.12*
• Rash	1 (5.0)	20 (20.2)	2 (18.2)	23 (17.7)	0.32†
Physical signs					
• Bleeding	11 (55.0)	72 (72.7)	10 (90.9)	93 (71.5)	0.09*
• Positive tourniquet test	11/15 (73.3)	39/56 (69.6)	4/7 (57.1)	54/75 (72.0)	0.22†
• Tachycardia	12 (60.0)	56 (56.6)	11 (100)	79 (60.8)	0.20*
• Hepatomegaly	3 (15.0)	28 (28.3)	8 (72.7)	39 (30.0)	<0.01*
• Abnormal neurological signs	0 (0)	8 (8.1)	3 (27.3)	11 (8.5)	0.04†
• Hypotension	0 (0)	2 (2.0)	9 (81.8)	11 (8.5)	<0.01†
• Pleural effusion	0/10 (0)	2/48 (4.2)	5/11 (45.5)	7/69 (8.7)	<0.01†
• Ascites	0 (0)	0 (0)	4 (36.4)	4 (3.1)	<0.01†

Note: Data are shown in number (%)

\* By Chi-square test; † By Fisher's exact test

**Table 3.** Laboratory results of dengue-infected children admitted to CMU Hospital

Laboratory parameters	DF (n=20)	DHF (n=99)	DSS (n=11)	Total (n=130)	p-value
Hematocrit (%)	38.7±2.3	39.7±6.6	37.6±8.7	39.4±6.4	0.52*
Leukocyte count ( $\times 10^3/\text{cumm}$ )	3.3±2.4	3.3±2.1	7.2±4.6	3.6±2.7	0.08*
Platelet counts ( $\times 10^3/\text{cumm}$ )	145.6±57.6	85.5±60.9	57.1±71.0	92.3±65.3	<0.01*
Total bilirubina (mg/dL)	0.4±0.1	1.1±1.6	0.8±0.6	1.0±1.4	0.66*
Albumina (g/dL)	3.9±0.4	3.7±0.6	2.7±0.5	3.5±0.7	<0.01*
SGOTb (U/L)	125±85.9	308.3±585.8	1927.1±3277.5	547.8±1477.2	<0.01*
SGPTb (U/L)	70.7±66.1	111.7±154.4	492.7±709.0	168.3±333.7	<0.01*

Note: Data are shown in number (%) or mean ± SD.

\* By ANOVA test; † By Fisher's exact test; a Albumin and total bilirubin were reported in 54 cases.

b SGOT and SGPT were reported in 63 cases.

**Table 4.** Outcomes and hospital costs of dengue-infected children admitted to CMU Hospital

Outcomes	DF (n=20)	DHF (n=99)	DSS (n=11)	Total (n=130)	p-value
PICU admission (persons)	0 (0)	2 (2.0)	10 (90.9)	12 (9.2)	<0.01†
Length of hospital stay (days)	3.1±1.4	3.4±1.8	7.1±5.0	3.6±2.4	<0.01*
Deaths (persons)	0 (0)	0 (0)	2 (18.2)	2 (1.5)	<0.01†
Hospital cost per admission (US\$)	155.2±83.9	208.6±285.5	1873.0±2082.18	341.2±786.1	<0.001*

Note: Data are shown in number (%) or mean ± SD.

\* By ANOVA test; † By Fisher's exact test

cytopenia. Eight children (6.2%) required fresh frozen plasma transfusion to correct coagulopathy. Eleven children (8.5%) were admitted to the hospital in a state of shock. The mean hospital cost per admission was US\$ 341.2 (SD: 786.1). The mean hospital cost for children with DSS (US\$ 1,873.0) was significantly higher than that of children with DF (US\$ 155.2) and DHF (US\$ 208.6) ( $p < 0.001$ ).

Among the children with DSS, nine (81.8%) fully recovered and two (1.5%) from the total of 130 died from massive hemorrhage and acute renal failure from prolonged shock. No patients were readmitted for any complications after 1 week of discharge.

## DISCUSSION

We reported 130 dengue-infected children, who were admitted to CMU Hospital during an outbreak in Chiang Mai in 2008. Most of the children presented with the classical clinical characteristics of dengue infection. The median age of our dengue-infected children was 12.2 years, with the highest incidence being among those aged from 11-15 years. The three most common presenting symptoms were acute fever (98.5%), nausea/vomiting (66.9%), and myalgia (55.4%). Children with DSS stayed in the hospital significantly longer than those without it (7.1 vs. 3.3 days,  $p < 0.01$ ). The mean hospital cost among children with DSS was 10 times higher than that among those without it (US\$ 181.9 vs. US\$ 1,873.0,  $p < 0.001$ ). The mortality rate was 1.5%.

Similar to previous studies,<sup>(5-7,16)</sup> this study found that the median age of dengue-infected children shifted to adolescent age. A study by Nimmannitya found that the median age of Thai dengue-infected children was 3.8, 5.6 and 7.4 years in the 1960s, 1970s, and 1980s, respectively.<sup>(5)</sup> Furthermore, Kittigul *et al*, and the Thai Department of Communicable Disease found that the median age of Thai dengue-infected children had shifted to 10-14 years in recent decades.<sup>(6-7)</sup> The shifting of age might be related to changes in where dengue virus transmission takes place, e.g. from households to schools,<sup>(17)</sup> changes in age structure of the Thai population,<sup>(16)</sup> an effective mosquito-control program in households,<sup>(10)</sup> and the temporary effect of cross-protection from Japanese encephalitis virus vaccination.<sup>(18)</sup> We propose that similar phenomena to those are responsible for the shifting median age (12.2 years) in our study sample as well.

Most children in our study presented with the classic symptoms and signs of dengue infection, which were similar to previous studies from Thailand and other Asian countries.<sup>(6,19-23)</sup> We found that fever (98.5%), nausea/vomiting (66.9%), and myalgia (55.4%) were the three most common presenting symptoms. These findings are similar to those in studies by Kalayanarooj *et al*,<sup>(19)</sup> Wichmann *et al*,<sup>(10)</sup> and Kittigul *et al*.<sup>(6)</sup>

In addition, we found that the incidences of abnormal neurological signs ( $p = 0.04$ ), hepatomegaly ( $p = 0.003$ ), hypotension ( $p < 0.001$ ), pleural effusion ( $p < 0.001$ ), and ascites ( $p < 0.001$ ) were significantly higher among children with DSS than those without it. Kalayanarooj *et al*,<sup>(19)</sup> found that pleural effusion (42.9%) and bleeding manifestations (13%) were the most common signs. They reported further that pleural effusion was more common in DHF/DSS than DF groups (84.0% vs. 7.0%). Similar results were reported also by Wichmann *et al*,<sup>(10)</sup> and Kittigul *et al*.<sup>(6)</sup>

In terms of association between secondary dengue infection and the severity of illness, Wichmann *et al*,<sup>(10)</sup> found that children with secondary dengue infection were at significantly higher risk of DHF/DSS than DF (OR: 3.63;  $p < 0.001$ ). However, no such association occurred in our study ( $p = 0.52$ ).

The tourniquet test is a simple clinical procedure that is now used as standard screening for dengue infection. However, it seems to have low sensitivity and specificity in enabling differentiation between DF and DHF.<sup>(23)</sup> In our study, tourniquet tests were positive in 73.3% of DF cases, 69.6% of DHF cases, and 57.1% of DSS cases without any significant differences between the groups. Similar results were reported by Wichmann *et al*, who found that tourniquet

tests were positive in 59% of DF cases, 77% of DHF cases, and 78% of DSS cases.<sup>(10)</sup> These findings support the notion that the tourniquet test may not be able to differentiate accurately between DF, DHF, and DSS. Physicians should interpret the tourniquet test in combination with clinical findings in order to increase its sensitivity to and specificity of acute dengue infection.<sup>(22, 23)</sup>

In this study, the laboratory results found that the mean hematocrit level and mean platelet count was 39.4% and  $92.3 \times 10^3$  cumm, respectively, which were almost the same values as those reported in previous studies.<sup>(10, 19)</sup> The mean hematocrit level among children with DSS was no different when compared to those without it, whereas, the mean platelet counts among children with DSS were significantly lower than in those without it. These results were not the same as those reported by Wichmann *et al.*, who found that children with DSS had a significantly higher level of hematocrit and significantly lower number of platelet counts than those without it.<sup>(10)</sup> With regard to hepatic enzymes, children with DSS had significantly higher levels of transaminases than those without it.<sup>(10, 19, 24-25)</sup>

The outcomes of dengue-infected children depend on the early recognition and appropriate management of the disease.<sup>(26)</sup> A delay in diagnosis and treatment leads to significant morbidity and mortality. In our study, children with DSS had a significantly longer hospital stay than those without it ( $p < 0.01$ ). The mortality rate of our children was 1.5%, all of which came from the DSS group. This percentage was around 10 times higher than the overall mortality rate of Thai dengue-infected patients (0.1%),<sup>(14)</sup> maybe because our hospital is a tertiary center serving more severe cases that are referred from

other hospitals nearby. Regarding the mean hospital cost of children with DSS, it was not surprising to find it at around 10 times higher than that for children without DSS. As shown in previous studies, children with DSS generally have more severe symptoms and need intensive care during their admission.<sup>(11-13)</sup> Thus, physicians should provide prompt diagnosis and treatment for these patients in order to reduce hospital costs.

This study firstly highlighted the characteristics, outcomes, and hospital costs among children with DSS in comparison to those without it in a tertiary care hospital during the 2008 outbreak. Secondly, we created awareness among health care workers and showed the need to provide prompt diagnosis and treatment by using clinical manifestations, along with the tourniquet test, in order to reduce morbidity, mortality, and hospital costs among this group of patients.

Our study, however, had some limitations. Firstly, it was performed in a single tertiary center, so the findings may not represent the overall picture concerning dengue infections among children nationwide. Secondly, we did not include factors that might influence the severity of illness among these children such as ecological data, environmental factors, and family information, as well as daily activities which would provide important information for devising further preventive strategies.

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## อาการทางคลินิกและผลการรักษาของเด็กไทยเลือดออกที่เข้ารับการรักษาในโรงพยาบาลราชนาครเชียงใหม่ในช่วงการระบาดปี พ.ศ. 2551

ทวิศิษยา สุจิตรักษ์, พ.บ., เพณณิชาท์ โอบฟอร์ดอร์เฟอร์, พ.บ.  
สาขาวิชาโรคติดเชื้อ ภาควิชาการเวชศาสตร์ คณะแพทยศาสตร์ มหาวิทยาลัยเชียงใหม่

### บทคัดย่อ

วัตถุประสงค์ เพื่อประเมินลักษณะทางคลินิกผลการรักษา และค่าใช้จ่ายของเด็กติดเชื้อไทยเลือดออกที่เข้ารับการรักษาในโรงพยาบาลราชนาครเชียงใหม่ในช่วงการระบาดของโรคในจังหวัดเชียงใหม่ ปี พ.ศ. 2551

วิธีการศึกษา ทบทวนวรรณบีบีนเด็กทุกรายที่ได้รับการยืนยันการติดเชื้อไทยเลือดออกจากผลตรวจทางน้ำเหลือง และเข้ารับการรักษาในโรงพยาบาลราชนาครเชียงใหม่ ในช่วงเดือนมกราคม ถึงเดือนมีนาคม พ.ศ. 2551

ผลการศึกษา เด็กจำนวนทั้งหมด 130 ราย เข้าร่วมในการศึกษานี้ ค่ามัธยฐานของอายุคือ 12.2 ปี (ระหว่างอายุ 9.7-13.9 ปี) เป็นเพศชาย 78 ราย (ร้อยละ 60) ผู้ป่วยจำนวน 20 ราย (ร้อยละ 15.4) ได้รับการวินิจฉัยเป็นโรคไข้เดงก์ ผู้ป่วยจำนวน 99 ราย (ร้อยละ 76.1) ได้รับการวินิจฉัยเป็นโรคไข้เลือดออก และผู้ป่วยจำนวน 11 ราย (ร้อยละ 8.5) ได้รับการวินิจฉัยเป็นโรคไข้เลือดออกที่มีภาวะช็อก อาการน้ำสำลัก 3 อันดับคือ ไข้ (ร้อยละ 98.5) คลื่นไส้อาเจียน (ร้อยละ 66.9) และปวดกล้ามเนื้อ (ร้อยละ 55.4) ในผู้ป่วยเด็กที่ได้รับการวินิจฉัยเป็นโรคไข้เลือดออกที่มีภาวะช็อกจะพบความผิดปกติของระบบประสาท ตับโต น้ำในช่องเยื่อหุ้มปอด และน้ำในช่องห้องมากกว่าผู้ป่วยเด็กที่ได้รับการวินิจฉัยเป็นโรคไข้เดงก์และไข้เลือดออกอย่างมีนัยสำคัญทางสถิติ ( $p < 0.05$ ) เด็กที่ได้รับการวินิจฉัยเป็นโรคไข้เดงก์และไข้เลือดออกที่มีภาวะช็อกต้องเข้ารับการรักษาในโรงพยาบาลนานกว่าเด็กที่ไม่มีภาวะช็อก อย่างมีนัยสำคัญทางสถิติ ( $7.1$  วัน เทียบกับ  $3.3$  วัน,  $p < 0.01$ ) ค่าเฉลี่ยของค่าใช้จ่ายในโรงพยาบาลในกลุ่มเด็กที่ได้รับการวินิจฉัยว่าเป็นโรคไข้เลือดออกที่มีช็อกสูงถึง  $10$  เท่าของเด็กกลุ่มที่ไม่มีภาวะช็อก อัตราตายโดยรวม คิดเป็นร้อยละ  $1.5$ .

สรุป เด็กที่ได้รับการวินิจฉัยเป็นโรคไข้เลือดออกที่มีภาวะช็อกจะมีอาการทางคลินิกรุนแรงกว่า และต้องเข้ารับการรักษาในโรงพยาบาลนานกว่าเด็กที่ไม่มีภาวะช็อก ดังนั้น การวินิจฉัยและรักษาอย่างทันท่วงที จะสามารถช่วยลดอัตราการป่วย อัตราการตายและค่าใช้จ่ายในโรงพยาบาลเชียงใหม่เวชสาร 2554;50(4):95-104.

คำสำคัญ: ไข้เลือดออก อาการทางคลินิก ผลการรักษา ค่าใช้จ่าย เด็ก