Risk Factors of Dengue Shock Syndrome in Children

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Background: *Dengue shock syndrome (DSS) is a major public health problem with high morbidity and mortality, especially in a case of prolonged shock with subsequently massive bleeding. The morbidity and mortality from DSS can be decreased by early diagnosis of shock and adequate replacement of plasma loss. Therefore, determination of risk factors of DSS is crucial for early detection and proper management of shock.*
Objective: *To determine the risk factors of dengue shock syndrome in children.*
Material and Method: *Medical records of 110 patients with dengue hemorrhagic fever (DHF) and 55 with DSS admitted at BMA Medical College and Vajira Hospital between January 2003and December 2005 were collected by simple random sampling. Clinical data including age, sex, signs and symptoms, and laboratory data (before defervescence) of patients with DHF and DSS were comparatively analyzed. Risk factors of DSS were determined by Mantel-Haenzel test, simple and multiple logistic regression analysis.*
Results: *Of the 165 children, 110 were in the DHF group (grade I, 72 children; grade II, 38 children) and 55 were in the DSS group (grade III, 53 children; grade IV, 2 children). The age, sex, nutritional status, and duration of fever between both groups were not statistically different. Risk factors of DSS were bleeding, secondary dengue infection, and hemoconcentration of more than 22% from baseline hematocrit (adjusted OR (95%CI): 5.1 (1.5-17.1), 21.8 (5.3-90.8), 15.5 (4.4-54.6), respectively).*
Conclusion: *Risk factors of DSS are bleeding, secondary dengue infection, and hemoconcentration of more than 22%. Patients with DHF who have one of these risk factors should be closely observed for early signs of shock, as prompt and adequate fluid replacement can prevent the progression of shock.*

Keywords: *Dengue shock syndrome, Dengue hemorrhagic fever, Risk factors, Children*

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Dengue virus infection, caused by any of four serotypes of dengue viruses (DEN 1-4), is the major public health problem in Southeast Asia and Western Pacific countries, including Thailand. Severity of the disease ranges from asymptomatic and undifferentiated fever to dengue fever (DF) or dengue hemorrhagic fever (DHF) with plasma leakage that can lead to hypovolemic shock (dengue shock syndrome, DSS)[1-3]. In patients with DSS, if detection and management of shock is delayed, the morbidity and mortality from prolonged shock or massive bleeding is high. The severity of the disease can be modified by early diagnosis and adequate replacement of plasma loss[1,2]. Therefore, a study to determine risk factors of DSS is crucial.

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A documented risk factor of DSS was primary infection with dengue virus serotype 1, 3, or 4 followed by a secondary infection with dengue virus serotype 2[4,5]. However, the recognition of dengue titer or secondary infection is not helpful for prediction and management of shock as it usually occurs after defervescence or shock. Very few studies determine risk factors of DSS before defervescence or shock[6-9]. Some of these studies[6,7] were descriptive studies with inadequate sample size, thus inappropriate to demonstrate risk factors of DSS. The authors conducted the present study in a case-control design with adequate sample size to determine the risk factors before defervescence of DSS in children.

Material and Method

The present case-control study was approved by the Ethical Committee of Bangkok Metropolitan

Administration. Medical records of 110 patients with dengue hemorrhagic fever and 55 patients with DSS admitted to BMA Medical College and Vajira Hospital between January 2003 and December 2005 were collected by simple random sampling. Inclusion criteria were children 15 year old or under who were compatible with definitions of DHF (DHF grade I and II) or DSS (DHF grade III and IV)[1,2]. All patients were tested by the Dengue Specific IgM and IgG Detection Kit (Do-Test Dengue Rapid ; Do-Test Co., Ltd., Thailand). The patient was interpreted as primary dengue infection when the test revealed positive dengue Ig M only or secondary dengue infection when both dengue Ig M and Ig G were positive. The patients with underlying hematologic diseases or other simultaneous infections were excluded. Data collection included age, sex, clinical signs, and symptoms and laboratory data (before defervescence). Complete blood count was repeated daily during admission.

Case definition for dengue hemorrhagic fever[1,2]: All of the following must be present:

1. Fever, or history of acute fever, lasting 2-7 days;

2. Hemorrhagic tendencies (evidenced by at least one of the following; a positive tourniquet test, petechiae, ecchymoses, purpura, bleeding from the mucosa, gastrointestinal tract, injection sites or other locations);

3. Thrombocytopenia (platelet count $\leq$ 100,000 /mm^3);

4. Evidence of plasma leakage (manifested by at least one of the following; a rise of hematocrit $\geq$ 20% from baseline, a drop in the hematocrit $\geq$ 20% from baseline after volume replacement, pleural effusion, ascites, or hypoproteinemia).

Case definition for dengue shock syndrome[1,2]: Four criteria of DHF must be present, plus evidence of circulatory failure manifested by restlessness, cold clammy skin, rapid weak pulse, and pulse pressure < 20 mmHg or hypotension for age (systolic blood pressure < 80 mmHg if < 5 years old or < 90 mmHg if $\geq$ 5 years old).

Grading severity of dengue hemorrhagic fever[1,2]: DHF is classified into 4 grades of severity

Grade I: DHF which hematologic manifestation is a positive tourniquet test and/or easy bruising;

Grade II: Spontaneous bleeding in addition to the manifestations of grade I;

Grade III: Circulatory failure manifested by a rapid, weak pulse and pulse pressure < 20 mmHg or hypotension for age with the presence of cold, clammy skin and restlessness;

Grade IV: Profound shock with undetectable blood pressure or pulse.

Sample size

The authors determined a sample size using the following equation

$$n_1 = \frac{(Z_{\alpha/2}\sqrt{2PQ} + Z_{\beta}\sqrt{P_1Q_1 + P_0Q_0})^2}{(P_1 - P_0)^2}$$

$Z_{\alpha/2}(\alpha = 0.05) = 1.96$

$Z_{\beta}(\beta = 0.2) = 0.842$

P_0 = Rate of secondary dengue infection in children = 70%[4] = 0.7

$Q_0 = 1\text{-}P_0 = 0.3$

OR = Odds ratio of secondary dengue infection as a risk factor of DSS = 3.5-66.1[5]

$P_1 = P_0R / [1 + P_0(R\text{-}1)] = 0.891$, $Q_1 = 0.109$

$P = (P_1 + P_0) / 2 = 0.796$, $Q = 0.204$

After substituting the constant into the equation, the number of cases of DSS (n_1) was 69.

$n = (C + 1)\, n_1 / 2C$

control (DHF grade 1 and grade 2): case (DSS) = 2: 1, C = 2

Therefore, the number of case and control were at least 52 and 104, respectively.

Statistical analysis

Statistical analysis was performed by SPSS version 11.5. Categorical data were expressed as percent and compared between the two groups by Chi-square test or Fisher's exact test. Continuous data were expressed as mean $\pm$ SD, median, range and compared between the two groups by student's t-test or Mann-Whitney U test. Risk factors of DSS were determined by Mantel-Haenzel test, and simple and multiple logistic regressions. The results were presented as crude Odds ratio (OR), adjusted OR, and 95% confidence interval (95%CI). A p-value < 0.05 was considered statistically significant.

Results

Of the 165 children, 110 were categorized as DHF group (grade I, 72 children; grade II, 38 children) and 55 as DSS group (grade III, 53 children; grade IV, 2 children). The mean age of the patients was 10.3 $\pm$ 3.3 years (0.5-14.9 years). Clinical characteristics of both

groups of children are shown in Table 1. Dehydration, hepatomegaly, bleeding, pleural effusion, and ascites were found in the DSS group more than the DHF group ($p < 0.05$). Bleeding manifestations were seen in 37 DHF patients (epistaxis 24, gum bleeding 9, hematemesis 4, and melena 2) and 32 DSS patients (epistaxis 18, gum bleeding 6, hematemesis 7, melena 3, and ecchymosis 1). Although some patients had more than one site of bleeding, no severe or continuous bleeding was found.

Laboratory data of both groups were compared in Table 2. Patients in the DSS group had higher Hb, Hct, per cent of hemoconcentration, and white blood cell count (WBC) but lower platelet count than those in the DHF group ($p < 0.05$). Lymphocyte count, atypical lymphocyte count, serum sodium, alanine aminotransferase (ALT), aspartate aminotransferase (AST), prothrombin time (PT), and partial thromboplastin time (PTT) were not statistically different between both groups.

Table 3 shows that factors associated with DSS by univariated analysis were dehydration, hepatomegaly, bleeding, pleural effusion, ascites, Hb > 14 g/dL, Hct > 42%, hemoconcentration > 22%, WBC $\leq$ 5,000 /mm^3, platelet count $\leq$ 50,000 /mm^3, and secondary dengue infection. However, after adjustment for confounding variables, factors that remained associated with DSS were bleeding, secondary dengue infection, and hemoconcentration > 22%. Secondary dengue infection was the strongest risk factor (adjusted OR 21.8, 95%CI 5.3-90.8).

Discussion

Risk factors of DSS in the present study were bleeding, hemoconcentration more than 22%, and

Table 1. Clinical characteristics of dengue hemorrhagic fever (DHF) and dengue shock syndrome (DSS)

	Total n = 165	DHF n = 110	DSS n = 55	p
Age, yr[+]	10.3±3.3	10.6±3.2	9.8±3.5	0.19
Sex: male (%)	85 (51.5)	58 (52.7)	27 (49.1)	0.66
Duration of fever, day[+]	5.4±1.0	5.4±1.0	5.33±1.0	0.65
Ingestion of aspirin or NSAIDs (%)	3 (1.8)	2 (1.8)	1 (1.8)	1.00
Body weight, kg[+]	35.8±15.5	35.7±14.5	35.9±17.4	0.96
Nutritional status[++]				0.67
:normal (W/A of 90-120%), (%)	70 (42.4)	46 (41.8)	24 (43.6)	
:PEM (W/A <90%), (%)	52 (31.5)	37 (33.6)	15 (27.3)	
:obesity (W/A >120%), (%)	43 (26.1)	27 (24.5)	16 (29.1)	
Maximal temperature,^oC[+]	38.9±0.9	38.8±0.8	39.0±0.9	0.3
Dehydration (%)	98 (59.4)	57 (51.8)	41 (74.5)	0.009*
Altered sensorium (%)	0	0	0	-
Headache (%)	99 (60.0)	67 (60.9)	32 (58.2)	0.81
Respiratory symptoms (%)	68 (41.2)	46 (41.8)	22 (40.0)	0.82
Vomiting (%)	116 (70.3)	77 (70.0)	39 (70.9)	0.9
Diarrhea (%)	28 (17.0)	18 (16.4)	10 (18.2)	0.77
Abdominal pain (%)	101 (61.2)	63 (57.3)	38 (69.1)	0.14
Hepatomegaly (%)	50 (30.3)	24 (21.8)	26 (47.3)	0.001*
Splenomegaly (%)	0	0	0	-
Jaundice (%)	0	0	0	-
Bleeding (%)[+++]	69 (41.8)	37 (33.6)	32 (58.2)	0.003*
Positive tourniquet test (%)	136 (82.4)	90 (81.8)	46 (83.6)	0.77
Pleural effusion (%)	21 (12.7)	3 (2.7)	18 (32.7)	<0.001*
Ascites (%)	18 (10.9)	3 (2.7)	15 (27.3)	<0.001*

[+] mean ± SD, * $p < 0.05$, PEM; Protein energy malnutrition

[++] Nutritional status was classified by per cent of the weight for age (W/A) compared to the National Growth References for Thai children[10]

[+++] Bleeding included skin bleeding (ecchymosis), bleeding from mucosa (epistaxis, bleed per gum), gastrointestinal bleeding (hematemesis, melena), and concealed hemorrhage. Petechiae and a positive tourniquet test were excluded

Table 2. Laboratory data within 24 hours before defervescence of dengue hemorrhagic fever (DHF) and dengue shock syndrome (DSS)

	Total n = 165	DHF n = 110	DSS n = 55	p
Hemoglobin, gm/dL[+]	14.3±2.1	14.0±2.3	14.9±1.5	0.004*
Hemoglobin > 14 g/dL (%)	81 (49.1)	43 (39.1)	38 (69.1)	<0.001*
Hematocrit, %[+]	42.2±4.5	41.0±4.1	44.6±4.2	<0.001*
Hematocrit > 42% (%)	82 (49.7)	44 (40.0)	38 (69.1)	<0.001*
Hemoconcentration, %[+]	19.8±8.7	16.0±6.8	27.3±7.2	<0.001*
Hemoconcentration > 22% (%)	83 (50.3)	32 (29.1)	51 (92.7)	<0.001*
WBC, cells/mm^3[+]	3,657.5±2,022.8	3,370.7±1,733.7	4,230.9±2,420.1	0.02*
WBC ≤ 5,000 cells/mm^3 (%)	141 (85.5)	100 (90.9)	41 (74.5)	0.005*
Lymphocyte count, %[+]	40.5±14.9	41.1±14.5	39.3±15.9	0.48
Atypical lymphocyte count, %[+]	5.6±5.1	6.6±6.1	4.9±4.5	0.09
Platelets count, cells/mm^3[+]	60,484.9±35,498.3	66,827.3±36,212.6	47,800.0±30,565.3	0.001*
Platelets count ≤ 50,000 cells/mm^3 (%)	83 (50.3)	47 (42.7)	36 (65.5)	0.006*
Secondary dengue infection (%)	89 (53.9)	40 (36.4)	49 (89.1)	<0.001*
Serum sodium,mmol/L[+]	134.6±3.9	134.9±4.0	134.2±3.7	0.36
Hyponatremia, %	51 (45.9)	29 (45.3)	22 (46.8)	0.88
Alanine aminotransferase, IU/L[++]	169.5 (26.0-854.0)	151 (36-594)	203 (26-854)	0.76
Aspartate aminotransferase, IU/L[++]	85.5 (11.0-470.0)	44 (11-399)	88 (12-470)	0.33
Prothrombin time, s[+]	12.8±3.1	12.4±1.3	13.0±3.6	0.57
Partial thromboplastin time, s[+]	55.6±14.4	52.5±11.3	57.0±15.6	0.4

[+] mean ± SD, [++] median (range), * $p < 0.05$

- Per cent of hemoconcentration was calculated as the difference of hematocrit value within 24 hours before defervescence and baseline hematocrit, divided by the baseline value, multiplied with 100
- Alanine aminotransferase, aspartate aminotransferase, prothrombin time and partial thromboplastin time were measured in 35 patients (11 DHF and 24 DSS)

Table 3. Univariate and multivariate analysis of factors associated with dengue shock syndrome (DSS)

	DHF n = 110 (%)	DSS n = 55 (%)	Crude OR	95%CI of crude OR	Adjusted OR[+]	95%CI of adjusted OR[+]	p
Dehydration (%)	57 (51.8)	41 (74.5)	2.6	1.3-5.5	2.2	0.7-6.7	0.17
Hepatomegaly (%)	24 (21.8)	26 (47.3)	3.2	1.6-6.4	1.3	0.4-4.2	0.69
Bleeding (%)	37 (33.6)	32 (58.2)	2.7	1.4-5.3	5.1	1.5-17.1	0.008*
Pleural effusion (%)	3 (2.7)	18 (32.7)	17.4	4.8-62.3	7.9	0.3-243.5	0.24
Ascites (%)	3 (2.7)	15 (27.3)	13.4	3.7-48.7	1.6	0.1-45.9	0.79
Hemoglobin > 14 g/dL (%)	43 (39.1)	38 (69.1)	3.5	1.8-6.9	3.6	0.4-34.5	0.27
Hematocrit > 42% (%)	44 (40.0)	38 (69.1)	4.4	2.2-8.8	0.1	0.01-1.3	0.09
Hemoconcentration > 22% (%)	32 (29.1)	51 (92.7)	14.3	6.5-31.7	15.5	4.4-54.6	<0.001*
WBC ≤ 5,000 cells/mm^3 (%)	100 (90.9)	41 (74.5)	3.4	1.4-8.3	0.5	0.1-1.7	0.25
Platelets count ≤ 50,000 cells/mm^3 (%)	47 (42.7)	36 (65.5)	0.2	0.1-0.5	-	-	-
Secondary dengue infection	89 (53.9)	40 (36.4)	14.3	5.6-36.3	21.8	5.3-90.8	<0.001*

[+] adjusted for dehydration, hepatomegaly, bleeding, pleural effusion, ascites, hemoglobin > 14 g/dL, hematocrit > 42%, hemoconcentration > 22%, WBC ≤ 5,000 cells/mm^3 and secondary dengue infection, * $p < 0.05$

secondary dengue infection. It was well documented that secondary dengue infection was the risk factor of DSS[4,5], but after searching the references available on MEDLINE and Thai Index Medicus, the authors found that the present study is the first study to demonstrates that bleeding and hemoconcentration of more than 22% are also risk factors of DSS (adjusted OR (95%CI): 5.1 (1.5-17.1) and 15.5 (4.4-54.6), respectively). Gender and malnutrition were not risk factors of DSS in the present study, as in the report of Hung NT et al[9], but in contrast to the report of Kalayanarooj S et al[8]. The mean ages of DHF and DSS in the present study were not statistically significant, similar as Narayanan M et al[11].

Hemorrhagic manifestations in DHF are usually mild. Petechiae and a positive tourniquet test, which indicate increased capillary fragility, are the most common hemorrhagic manifestations in DHF. Massive bleeding that requires blood transfusion is less common and usually occurs after the onset of shock[1-3]. The present study found that bleeding in the early course of the disease before defervescence, including epistaxis, bleeding per gum, hematemesis, and melena, was one of the risk factors of DSS. This is because these patients tended to have more severe bleeding during defervescence that increased the risk of shock. Bleeding in the early course of the disease should alarm the clinicians that the DHF patients are at risk of shock.

Hemoconcentration $\geq$ 20% from baseline is one of the diagnostic criteria of DHF[1,2]. Furthermore, the present study also found that hemoconcentration $\geq$ 22% is one of the risk factors of DSS. Plasma leakage in DHF appears to be selective into serous space especially pleural and abdominal cavities. The leakage subsequently causes an elevation of hematocrit and can lead to hypovolemic shock in cases of extensive volume loss[1-3]. Therefore, frequent Hct determinations are essential because they reflect the extent of plasma leakage and the adequacy of volume replacement.

Elevated liver enzymes (AST, ALT) associated with severity of diseases reported by Pancharoen C et al[12] and Mohan B et al[13] and prolonged PT and PTT in patients with protracted shock described by Mitrakul C[14] were not found in the present study. This is because the present study was focused on clinical manifestations and laboratory data before defervescence or shock. Elevation of liver enzymes and prolonged PT and PTT in patients with DHF usually occurred after defervescence or shock[12-14], so these parameters were not significantly changed in the present study.

The present study is the first study emphasizing that after control of the confounding factors, the risk factors of DSS were bleeding, secondary dengue infection, and hemoconcentration of more than 22%. Recognition of these risk factors made the doctors aware of the early signs of shock including restlessness, cold clammy skin, rapid weak pulse, pulse pressure < 20 mmHg, or hypotension for age. Although the plasma leakage and bleeding cannot be prevented, the progression of DSS can be prevented by close observation for early signs of shock and prompt and adequate replacement of plasma leakage.

Conclusion

Risk factors of DSS are bleeding, secondary dengue infection, and hemoconcentration in more than 22%. Patients with DHF who have one of these risk factors should be closely observed for early signs of shock. Prompt and adequate fluid replacement can prevent the progression of shock .

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ปัจจัยเสี่ยงของการเกิดภาวะช็อกของไข้เลือดออกเดงกีในเด็ก

ทวีวงศ์ ตันตราชีวธร, สุภาพรรณ ตันตราชีวธร

***ภูมิหลัง**: ไข้เลือดออกเดงกีที่ช็อกเป็นปัญหาทางสาธารณสุขที่สำคัญ มีการเสียชีวิตและภาวะแทรกซ้อนสูงโดยเฉพาะในผู้ป่วยที่ช็อกเป็นเวลานานและมีเลือดออกอย่างรุนแรง การวินิจฉัยช็อกได้ตั้งแต่ระยะแรก และการให้สารน้ำทดแทนพลาสมาที่สูญเสียไปอย่างเพียงพอ สามารถลดภาวะแทรกซ้อนและการเสียชีวิตจากไข้เลือดออกเดงกีที่ช็อกได้ ดังนั้นการทราบปัจจัยเสี่ยงของภาวะช็อกจึงมีความสำคัญช่วยให้วินิจฉัยและรักษาช็อกได้ตั้งแต่ระยะแรก*

***วัตถุประสงค์**: ศึกษาปัจจัยเสี่ยงของภาวะช็อกในผู้ป่วยไข้เลือดออกเดงกีในเด็ก*

***วัสดุและวิธีการ**: สุ่มตัวอย่างเวชระเบียนของผู้ป่วยไข้เลือดออกเดงกี 110 ราย และไข้เลือดออกเดงกีที่ช็อก 55 ราย ซึ่งรับไว้รักษาที่วิทยาลัยแพทยศาสตร์กรุงเทพมหานครและวชิรพยาบาล ระหว่างมกราคม พ.ศ. 2546-ธันวาคม พ.ศ. 2548 โดยวิธี simple random sampling เปรียบเทียบข้อมูลทางคลินิก ได้แก่ อายุ เพศ อาการ อาการแสดง และผลการตรวจทางห้องปฏิบัติการ ระยะก่อนไข้ลงของผู้ป่วยไข้เลือดออกเดงกีและไข้เลือดออกเดงกีที่ช็อก หาปัจจัยเสี่ยงของการเกิดช็อกของไข้เลือดออกเดงกีโดยวิธี Mantel-Haenzel test, simple และ multiple logistic regression*

***ผลการศึกษา**: ผู้ป่วยเด็ก 165 ราย เป็นกลุ่มไข้เลือดออกเดงกี 110 ราย (เกรด I, 72 ราย; เกรด II, 38 ราย) และกลุ่มไข้เลือดออกเดงกีที่ช็อก 55 ราย (เกรด III, 53 ราย; เกรด IV, 2 ราย) อายุ เพศ ภาวะโภชนาการ และระยะเวลาของไข้ระหว่างผู้ป่วยสองกลุ่มแตกต่างกันอย่างไม่มีนัยสำคัญทางสถิติ ปัจจัยเสี่ยงของไข้เลือดออกเดงกีที่ช็อก ได้แก่ การมีเลือดออก การติดเชื้อทุติยภูมิ และค่าฮีมาโตคริตเพิ่มขึ้นมากกว่าร้อยละ 22 จากค่าฮีมาโตคริตแรกรับ (adjusted OR (95%CI): 5.1 (1.5-17.1), 21.8 (5.3-90.8), 15.5 (4.4-54.6) ตามลำดับ)*

***สรุป**: ปัจจัยเสี่ยงของไข้เลือดออกเดงกีที่ช็อก ได้แก่ การมีเลือดออก การติดเชื้อทุติยภูมิ และค่าฮีมาโตคริต เพิ่มขึ้นมากกว่าร้อยละ 22 ผู้ป่วยไข้เลือดออกเดงกีที่มีปัจจัยเสี่ยงเหล่านี้ควรได้รับการสังเกตอาการแสดงเริ่มแรกของภาวะช็อกอย่างใกล้ชิด เนื่องจากการให้สารน้ำทดแทนอย่างเพียงพอในทันทีสามารถป้องกันการเกิดช็อกได้*