VOLUME REPLACEMENT IN INFANTS WITH DENGUE HEMORRHAGIC FEVER/DENGUE SHOCK SYNDROME

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Abstract. Volume replacement was studied prospectively in 208 infants with dengue hemorrhagic fever/dengue shock syndrome (DHF/DSS). The mean volume of intravenous fluid used was 110.4 mL/kg administered over a mean period of 25.8 hours. The mean volumes of intravenous fluid replacement in infants with DSS was significantly higher than in those with non-shock DHF (129.8 mL/kg versus 102.1 mL/kg; \( P = 0.001 \)). Patients with DSS had significantly higher proportional requirements for dextran and blood transfusions than non-shock infants. Recurrent shock, prolonged shock, and acute respiratory failure were recorded in 8, 6, and 13 patients, respectively. Four patients with DSS died of severe complications. Intravenous fluid replacement with special care to avoid fluid overload requires careful attention to established indications for use of colloidal solutions and blood transfusions. To improve case fatality rates, special efforts need to be directed to infants with DHF/DSS accompanied by severe complications.

INTRODUCTION

Dengue infections result in a disease continuum that includes syndromes varying in severity and prognosis. These include dengue fever (DF), dengue hemorrhagic fever (DHF), and dengue shock syndrome (DSS), the most severe form of DHF. All are caused by dengue viruses that belong to the family Flaviviridae as four serotypes (DEN-1, DEN-2, DEN-3 and DEN-4). In the past 15 years, there has been a dramatic increase in the global incidence of dengue and DHF/DSS. More than 2.5 billion people are now at risk in more than 100 countries worldwide, and every year approximately 50 million infections occur, including 500,000 cases of DHF and DSS. Nearly 95% of cases are among children less than 15 years of age, with ≥ 5% of all DHF/DSS cases occur in infants. In contrast to DHF/DSS cases in children older than one year of age, which occur during secondary dengue virus infections, almost all of DHF/DSS cases in infants occur during primary dengue virus infections.

The main hallmark that differentiates DHF from DF is clinically significant vascular permeability usually between the third and the sixth days of illness, which results in plasma leakage from the intravascular compartment to extravascular spaces. In less severe cases (non-shock DHF grades I and II), plasma leakage is mild to moderate, and many patients recover spontaneously or shortly after administration of intravenous fluid. In more severe cases (DSS grades III and IV), there are large plasma losses, hypovolemic shock ensues, and it can progress rapidly to profound shock. The patient in shock may die within 12–24 hours if appropriate treatment is not promptly administered. Volume replacement is the mainstay of treatment of DHF/DSS. The current World Health Organization (WHO) guidelines for volume replacement were based on the studies of DHF/DSS in children. Early and effective replacement of plasma loss with crystalloid, colloidal solutions results in favorable outcome in most patients. In a recent randomized double-blind comparison of four intravenous fluids (dextran, gelatin, Ringer’s lactate [RL], and saline) for initial resuscitation of 230 Vietnamese children older than one year of age with DSS, there was no clear advantage to using any of the four fluids. The most significant factor determining clinical response was the pulse pressure at presentation.

Case fatality rates of DHF/DSS in children of < 1% to 5% have been reported from centers experienced in fluid resuscitation. DHF/DSS is less common in infancy but when it does occur the risk of dying is higher than in older children. Volume replacement in infants with DHF/DSS is a challenging management problem. There are few published studies on this topic. In attempt to support evidence-based management of DHF/DSS infants with the goal of reducing mortality in this group, we present our experience with volume replacement in infants with DHF/DSS.

MATERIALS AND METHODS

Study design. This was part of a prospective study on DHF in infants that had focused on clinical and immunologic aspects and management. The study period was from August 1997 to December 2002 at the Department of Dengue Hemorrhagic Fever of Children’s Hospital No. 1 in Ho Chi Minh City, a tertiary referral pediatric hospital in southern Vietnam. The Department of Dengue Hemorrhagic Fever has 85 in-patient beds and is staffed with 10 doctors and 25 nurses.

Patients. Two hundred seventy-two infants less than 12 months of age admitted to the Department of Dengue Hemorrhagic Fever with clinical diagnosis of DHF according to the 1997 criteria of the WHO were recruited into the study after parental or guardian informed consent was obtained.

Dengue virus infections in the patients were studied by 1) viral envelope and membrane (E/M)-specific capture IgM enzyme-linked immunosorbent assay (ELISA) and/or nonstructural protein 1 serotype-specific IgG ELISA at the Center for
Disease Control, Department of Health in Taipei, Taiwan, or 2) capture IgM ELISA at the Pasteur Institute in Ho Chi Minh City, Vietnam.

Of 272 infants hospitalized with DHF a positive IgM-capture ELISA result was obtained in 245 infants. Among these infants 182 had non-shock DHF (grade I, 1 infant; grade II, 181 infants) and 63 had DSS (grade III, 54 infants; grade IV, 9 infants). The nutritional status and clinical and immunologic aspects of these infants have been previously reported. Serologic testing showed that almost all of the patients (95.3%) had primary dengue virus infections. Intravenous fluid therapy was indicated in 208 infants: 145 infants with non-shock DHF and 63 infants with DSS. We focused on fluid management in these 208 infants. Ethical approval of the study was obtained from the Scientific and Ethical Committee of Children’s Hospital No. 1 in Ho Chi Minh City.

Investigations and observations. A full history, physical examination findings, management, and subsequent progress were recorded on a standard data form for each patient. For infants receiving intravenous fluid therapy, a fluid balance sheet was used to record the type, rate, and quantities of fluid administered, and to calculate the volume of intravenous fluid per kilogram of body weight given per 24 hours.

On admission, a venous blood sample was obtained for determination of hematocrit and complete blood cell count, and a serum sample was stored for virus isolation or serologic confirmation of dengue virus infection, in conjunction with a second sample collected on the day of discharge. Complete blood cell counts (H-2000 counter; Careside Inc., Culver City, CA) were determined in the hospital laboratory. Chest radiographic and/or ultrasound examinations were conducted as clinically required.

Management. Treatment of non-shock DHF was supportive and symptomatic. Management of DHF/DSS patients in the study principally followed the current WHO guidelines for volume replacement with some adaptations. Intravenous fluid therapy was indicated when the patient had one or more of the signs/symptoms: repeated vomiting, rapid liver enlargement, hematemesis, melena, lethargy, a high degree of hemocoagulation, and a rapidly rising hematocrit. Ringer’s lactate with or without 5% dextrose was started at a rate of 6–7 mL/kg of body weight/hour, then adjusted according to the patient’s clinical condition, vital signs, hematocrit, and urine output. For patients with DSS, plasma losses were immediately replaced with electrolyte or, in case of profound shock, colloidal solutions. Use of intravenous fluid was necessary to replace further plasma losses to maintain effective circulation for 24–48 hours. For patients with DSS grade III, RL was started at a rate of 15–20 mL/kg/hour, while those with DSS grade IV (profound shock) received RL at a rate of 20 mL/kg over a 15-minute period, followed by colloidal solution (dextran 40 or dextran 70) at a rate of 10–20 mL/kg/hour. Pulse, blood pressure (BP), and respiratory rate were recorded every 15–30 minutes until shock was overcome. When the condition of the patient did not improve with RL infusion (vital signs were still unstable [shock persists]), dextran was used at a rate of 15–20 mL/kg/hour. A blood transfusion was only indicated in patients with severe bleeding. Infants receiving intravenous fluid therapy were closely observed around the clock until it was certain that danger has passed. Frequent recording of vital signs and hematocrit was important for evaluating treatment results. Hematocrit was determined every two to four hours and thereafter every four hours until stable. A fluid balance sheet was used to record the type, rate, and quantity of fluid administered (input), and to calculate the amount of intravenous fluid per kilogram of body weight given per 24 hours to determine whether there had been sufficient volume replacement and to avoid fluid overload. The frequency and volume of urine (output) were also recorded.

Intravenous fluid therapy was stopped when the patient’s condition had been stable for more than 24 hours, or there was any sign/symptom of fluid overload. In the convalescent phase, usually between the seventh and the ninth days of illness, some patients had signs of fluid overload because of excessive intravenous therapy and reabsorption of extravascular plasma from the interstitial compartment. For those patients who developed symptomatic fluid overload, furosemide was given (0.5–1 mg/kg/dose).

Data and statistical analysis. The outcome measures were the total volume of intravenous fluid infused; the requirement for dextran; blood transfusion; duration of intravenous fluid therapy; development of any complications related to fluid therapy, such as recurrent shock, prolonged shock, and respiratory failure; and death. Other complications of DHF/DSS such as dengue encephalopathy, gastrointestinal (GI) bleeding, and associated pneumonia were also noted. These outcome measures were compared between two groups of the patients (non-shock DHF versus DSS). An infant had developed recurrent shock if he or she had tachycardia, coolness of the extremities, and a decrease in BP to ≤ 20 mm of Hg while BP had previously reached ≥ 30 mm of Hg even though they had received adequate fluid according to the guidelines for volume replacement. Prolonged shock was when an infant in shock did not improve after receiving ≥ 60 mL/kg of intravenous fluid or the patient was still in shock after ≥ 6 hours of intravenous fluid therapy. Dengue encephalopathy was when an infant with DHF/DSS had mental disturbances (lethargy, stupor, restlessness, coma); neurologic signs and symptoms (headache, vomiting, convulsions, hemiparesis, tetraparesis, hyperreflexia); and cerebrospinal fluid examination with normal levels of protein, glucose, negative gram stain and bacterial culture. Coinfection with bacterial pneumonia was when a patient had cough, tachypnea, reuctions, the presence of crackles, and suggestive radiologic findings (scattered infiltrates to dense lobar pneumonia).

The statistical significance of differences in normally distributed data was compared using analysis of variance. The Kruskal-Wallis test for two groups was used when the variances in the samples differed. Differences between proportions were tested by the chi-square test or Fisher’s exact test. Statistical analyses were performed with Epinfo 2000, version 1.1 (Centers for Disease Control and Prevention, Atlanta, GA). Multivariate logistic regression analysis was performed with SPSS statistical package version 12.0 for Windows (SPSS Inc., Chicago, IL). A P value < 0.05 was considered statistically significant.

RESULTS

Clinical findings of 208 DHF/DSS patients. Clinical and laboratory findings on patients are shown in Table 1. The mean age of the patients was 6.7 months (range = 1–11). The mean age of infants with DSS was significantly higher than that of infants with non-shock DHF (7.3 vs 6.5 months;
P = 0.003). There were no significant differences in the date of admission from the onset of fever, duration of fever, and peak temperature between non-shock DHF and DSS groups (mean = 4.0 days versus 4.3 days [P = 0.07]; 5.2 days versus 5.3 days [P = 0.7]; and 39.0°C versus 38.8°C [P = 0.7], respectively, Table 1). Compared with infants with non-shock DHF, infants with DSS had a larger liver size below right costal margin (mean = 3.6 cm versus 2.8 cm [P = 0.001]). Gastrointestinal bleeding and dengue encephalopathy were noted in 14 (5.7%) and 16 (7.7%) patients, respectively. The proportions of GI bleeding and dengue encephalopathy were similar between infants in the non-shock DHF and DSS groups (P = 0.4, and P = 0.1; Table 1).

Pulse rate in the critical phase in patients with DSS was faster than that in patients with non-shock DHF (mean = 142 versus 136 beat/minute [P = 0.006]; Table 2). Systolic BP in the critical phase of patients with DSS was significantly lower than that of patients with non-shock DHF, while diastolic BP was similar in the two groups (mean = 83.7 versus 92.4 mm Hg [P = 0.001], and 62.4 versus 59.3 mm Hg [P = 0.06], respectively, Table 2). Pulse rate, systolic BP, and diastolic BP in the convalescent phase in both two groups returned to the normal ranges (Table 2). Compared with infants with non-shock DHF, infants with DSS had a significantly higher respiratory rate in the acute and convalescent phases of illness (mean = 46.0 versus 39.7 breaths/minute [P = 0.001] and 48.9 versus 42.5 breaths/minutes [P = 0.001]; Table 2).

**Laboratory findings.** The mean peak hematocrit and increase in hematocrit in all patients was 40.5% (range = 30–60%) and 36% (range = 10–68%), respectively. Peak hematocrit level and increase in hematocrit were significantly higher in DSS group than that in non-shock DHF group (mean = 43.6% versus 39.2% [P = 0.001] and 44.1% versus 32.4% [P = 0.001], respectively, Table 1). The mean time to reach the peak hematocrit level was 4.7 days (range = 3–7). The mean lowest platelet count of all patients was 61.5 x 10^3/mm^3 (range = 14–190 x 10^3 cells/mm^3), and infants with DSS had a significantly lower mean platelet count compared with those with non-shock DHF (mean = 54.9 x 10^3 versus 64.3 x 10^3 cells/mm^3 [P = 0.03]). The mean time for platelets to reduce to the lowest level in all patients was 4.9 days (range = 3–8).

**Intravenous fluid replacement.** The intravenous fluid therapy and clinical outcome for 208 infants with DHF/DSS in the study are summarized in Figure 1. The mean volume of intravenous fluid used was 110.4 mL/kg (range = 27.5–243 mL/kg) administered over a mean period of 25.8 hours (range = 6–72). The mean volume of intravenous fluid replacement in infants with DSS was significantly higher than that in those with non-shock DHF (129.8 versus 102.1 mL/kg [P = 0.001]). The mean duration of intravenous fluid administration and the time to normalize the hematocrit level from the start of intravenous fluid therapy for both the non-shock DHF and DSS groups did not differ significantly (mean = 25.9 versus 25.7 hours [P = 0.5] and 29.9 versus 30 hours [P = 0.9]; Table 3).
Administration of colloidal solution (dextran 40 or dextran 70) was indicated in 48 infants (23%). The proportion of infants with DSS requiring dextran infusion (35 infants, 55.5%) was significantly higher than that of infants with non-shock DHF (13 infants, 8.9%) \((P = 0.001)\). The mean volume of dextran administered was 55.1 mL/kg \((range = 13–119 \text{ mL/kg})\); this was correlated with severity of the disease \((P = 0.01; \text{Table 3})\). Twenty-eight infants (13.4%), five of whom had severe GI bleeding, received a transfusion of fresh whole blood \((FWB; \text{mean } 38.7 \text{ mL/kg, range } 12–140 \text{ mL/kg})\). Compared with patients with non-shock DHF, patients with DSS had a higher requirement for FWB \((26.9\% \text{ versus } 7.5\%; \text{Table 3})\). However, the mean volume of FWB administered did not different between the groups \((P = 0.1)\). Seventeen \((8.1\%)\) patients needed furosemide for symptoms of fluid overload. The requirement for furosemide was related to severity of the disease \((4.8\% \text{ in the non-shock DHF group versus } 15.8\% \text{ in DSS group} \ [P = 0.007])\). In most of these cases furosemide was used for fluid overload because of re-absorption of extravasated plasma from the intestinal compartment in the convalescent phase of the illness.

For the subgroup of patients with DSS grade IV \((nine\) cases) admitted in the late stage of DSS, all patients required infusion of dextran and intensive care with close monitoring. However, there were no differences in the mean volume of intravenous fluid administered; the volume of dextran, FWB, or the duration of fluid replacement between the subgroups of DSS grade IV and grade III \((P = 0.5, P = 0.4, P = 0.5, \text{and } P = 0.7, \text{respectively, Table 4})\).

**Complications related to intravenous fluid therapy.** Recurrent shock was recorded in eight patients and prolonged shock was noted in six patients. All eight patients with recurrent shock had a second episode of shock at a mean \((SD)\) time of 6.2 \((2.9)\) hours \((range = 3–11)\) from beginning of intravenous fluid therapy. Each of these patients responded well to dextran solution. Of six patients with prolonged shock, four had DSS grade III and two had DSS grade IV. Two patients with prolonged shock died. Patients with prolonged shock required careful fluid management with catheters inserted to monitor central venous pressure and correction of severe metabolic acidosis. Nevertheless, there were no significant differences in the total volume of intravenous fluid administered, or of dextran, FWB, or the duration of fluid replacement in the patients with prolonged shock compared with other DSS patients \((P = 0.5, P = 0.09, P = 0.6, \text{and } P = 0.6, \text{respectively, Table 4})\).

Thirteen patients \((three\) patients with non-shock DHF and 10 with DSS, 6.2%) developed acute respiratory failure between day 4 and day 7 after onset of illness \((day 4–5 = 4 \text{ patients}; \text{day 6–7} = 9 \text{ patients})\).
day 6–7 = 9 patients). Among patients with acute respiratory failure, fluid overload was diagnosed in two patients on day 5 and day 6 of illness. Fluid overload resulting from reabsorption of extravasated plasma from the interstitial compartment in the convalescent phase (day 6–7) was considered the most likely cause of respiratory failure in another five patients. Respiratory failure was associated with prolonged shock, dengue encephalopathy, GI bleeding, and coinfection with pneumonia in five, three, three, and six patients, respectively. All of these patients were treated with oxygen delivered by nasal cannula (five patients) or nasal continuous positive airway pressure (NCPAP, eight patients). Furosemide was used in seven patients. Cefotaxim was prescribed for pneumonia. Univariate analysis showed that factors related to acute respiratory failure included a total volume of intravenous fluid infused > 140 mL/kg, a requirement for dextran, prolonged shock, GI bleeding, and coinfection with pneumonia (Table 5). Multivariate logistic analysis identified prolonged shock and coinfection with pneumonia as significantly associated with acute respiratory failure (P = 0.01 and P = 0.001, respectively, Table 5).

**Results of treatment.** All but four patients recovered after receiving fluid replacement and good nursing care. Of the patients who died, two had prolonged shock, three had encephalopathy, two had respiratory failure, and three had massive GI bleeding. Clinical characteristics and laboratory findings for these four patients have been reported. Compared with survivors, fatal cases had higher rates of severe complications such as prolonged shock, encephalopathy, respiratory failure, and massive GI bleeding (P = 0.04, P = 0.001, P = 0.02, and P = 0.001, respectively, Table 6). Thrombocytopenia in fatal patients was greater than that in surviving patients (P = 0.007; Table 6).

**DISCUSSION**

We describe attributes of the clinical course and management of DHF/DSS that occur in a unique immunologic group, infants less than one year of age who experience severe disease during their initial dengue infection. Their only known risk factor for severe dengue is the pre-natal acquisition of maternal antibodies to dengue virus. As in older children, the onset of DHF/DSS coincides with defervescence, a time when T cells are actively terminating cellular infection and generating cytokines. Virus infection, viremia, or cytokines

<table>
<thead>
<tr>
<th>Variable</th>
<th>All infants (n = 208)</th>
<th>Infants with nonshock DHF (n = 145)</th>
<th>Infants with DSS (n = 63)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total volume of iv fluid infused, mean mL/kg ± SD (range)</td>
<td>110.4 ± 33.6 (27.5–243)</td>
<td>102.1 ± 28.4 (27.5–211.7)</td>
<td>129.8 ± 36.9 (50–243)</td>
<td>0.001†</td>
</tr>
<tr>
<td>Requirement for dextran, no. (%) of infants</td>
<td>48 (23)</td>
<td>13 (8.9)</td>
<td>35 (55.5)</td>
<td>0.001‡</td>
</tr>
<tr>
<td>Volume of dextran, mean mL/kg ± SD (range)</td>
<td>55.1 ± 25.9 (13–119)</td>
<td>39.4 ± 16.2 (13–65)</td>
<td>60.9 ± 26.5 (20–119)</td>
<td>0.01†</td>
</tr>
<tr>
<td>Requirement for FWB, no. (%) of infants</td>
<td>28 (13.4)</td>
<td>11 (7.5)</td>
<td>17 (26.9)</td>
<td>0.001‡</td>
</tr>
<tr>
<td>Volume of FWB, mean mL/kg ± SD (range)</td>
<td>38.7 ± 32.5 (12–140)</td>
<td>27.3 ± 18.2 (13–68)</td>
<td>44.7 ± 38.1 (12–140)</td>
<td>0.1†</td>
</tr>
<tr>
<td>Duration of iv fluid administration, mean hours ± SD (range)</td>
<td>25.8 ± 8.8 (6–72)</td>
<td>25.9 ± 8.1 (8–53)</td>
<td>25.7 ± 10.2 (6–72)</td>
<td>0.5†</td>
</tr>
<tr>
<td>Requirement for furosemide, no. (%) of infants</td>
<td>29.9 ± 12.9 (12–72)</td>
<td>29.9 ± 13.2 (12–72)</td>
<td>30.0 ± 12.7 (12–72)</td>
<td>0.9†</td>
</tr>
<tr>
<td>Time to normalize hematocrit, mean hours ± SD (range)</td>
<td>17 (8.1)</td>
<td>7 (4.8)</td>
<td>10 (15.8)</td>
<td>0.007‡</td>
</tr>
<tr>
<td>Length of hospital stay, mean days ± SD (range)</td>
<td>5.7 ± 2.6 (1–19)</td>
<td>5.7 ± 2.5 (2–16)</td>
<td>5.5 ± 2.7 (1–19)</td>
<td>0.3†</td>
</tr>
</tbody>
</table>

* FWB = fresh whole blood.
† Nonshock DHF group vs. DSS group by Kruskal-Wallis test.
‡ Nonshock DHF group vs. DSS group by chi-square test.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Infants with DSS grade III (n = 54)</th>
<th>Infants with DSS grade IV (n = 9)</th>
<th>DSS infants without prolonged shock (n = 57)</th>
<th>DSS infants with prolonged shock (n = 6)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total volume of iv fluid infused, mean mL/kg ± SD (range)</td>
<td>128.7 ± 46.9 (50–215)</td>
<td>66.6 ± 32.5 (20–105)</td>
<td>55.6 ± 24.1 (20–119)</td>
<td>80.5 ± 33.6 (20–119)</td>
<td>0.01, 0.06†</td>
</tr>
<tr>
<td>Requirement for dextran, no. (%) of infants</td>
<td>26 (48.1)</td>
<td>9 (100)</td>
<td>29 (50.8)</td>
<td>6 (100)</td>
<td>0.01, 0.06†</td>
</tr>
<tr>
<td>Volume of dextran, mean mL/kg ± SD (range)</td>
<td>57.8 ± 25.6 (20–105)</td>
<td>66.6 ± 32.5 (20–119)</td>
<td>55.6 ± 24.1 (20–100)</td>
<td>80.5 ± 33.6 (20–100)</td>
<td>0.4, 0.09‡</td>
</tr>
<tr>
<td>Requirement for FWB, no. (%) of infants</td>
<td>14 (25.9)</td>
<td>3 (33.3)</td>
<td>13 (22.8)</td>
<td>4 (66.6)</td>
<td>0.9, 0.3‡</td>
</tr>
<tr>
<td>Volume of FWB, mean mL/kg ± SD (range)</td>
<td>39.8 ± 31.7 (12–131)</td>
<td>67.3 ± 64.6 (16–140)</td>
<td>49.9 ± 42.3 (12–140)</td>
<td>27.7 ± 10.3 (17–37)</td>
<td>0.5, 0.6‡</td>
</tr>
<tr>
<td>Duration of iv fluid administration, mean hours ± SD (range)</td>
<td>25.5 ± 8.5 (6–48)</td>
<td>27.1 ± 17.7 (8–72)</td>
<td>25.8 ± 10.4 (6–72)</td>
<td>24.1 ± 7.8 (6–72)</td>
<td>0.7, 0.6‡</td>
</tr>
</tbody>
</table>

* FWB = fresh whole blood.
† DSS grade III vs. DSS grade IV by Kruskal-Wallis test for comparison of the means and chi-square test for comparison of the proportions.
‡ DSS infants with prolonged shock vs. DSS infants without prolonged shock by Kruskal-Wallis test for comparison of means and chi-square test for comparison of the proportions.
and chemokines are thought to damage endothelial cells and platelets, which results in the opening of endothelial pores and leads to the extravasation of fluid, hypovolemia, and in some cases, shock. As is evident in this study, clinically significant hypovolemia that required administration of intravenous fluids is essential to the management of patients who may not be in frank shock. We detail treatment regimens in infants with evidence of vascular leakage with and without shock and compare the physiologic status of infant DHF/DSS with that of children greater than one year of age, a group who acquire severe disease during a second dengue infection, which has been extensively documented.

The percentage of non-shock DHF infants requiring intravenous fluid therapy in the present study was 79.6%. This is higher than that of non-shock DHF in children ≥ 1 year of age who were admitted at the same time to the Department of Dengue Hemorrhagic Fever (25–33%).10 According to the WHO guidelines (1997), the amount of intravenous fluid is usually equal to daily fluid maintenance plus a 5% deficit over a 24–48-hour period. Daily fluid maintenance is calculated as 100 mL/kg for the first 10 kg of body weight, 50 mL/kg for the second 10 kg of body weight, and 20 mL/kg for body weight greater than 20 kg.2 Thus, an infant with a body weight of 10 kg will require 150 mL/kg of intravenous fluid. The estimate for infants was higher than the amount actually administered to non-shock DHF cases (mean = 102.1 mL/kg) over the mean time of 25.9 hours. All non-shock DHF infants recovered; only 13 patients (7.1%) required dextran with the mean volume of 39.4 mL/kg, and 11 patients (6%) required FWB transfusions with the mean volume of 27.3 mL/kg.

Volume replacement is the mainstay of treatment of DSS. Early and effective replacement of lost plasma with electrolyte solution, plasma, or plasma expanders results in a favorable outcome. Nimmanitya18 reported 487 cases of DSS treated at Bangkok Children’s Hospital. In these patients, 61% were successfully treated with crystalloid solution (Ringer’s lactate/acetate solution) and in 22% there was a need for colloidal solution (dextran 40). Approximately 15% of the shock cases had significant bleeding that required blood transfusion and some in this group received other blood components, e.g., concentrated platelets, fresh frozen plasma, and cryoprecipitate.18 In another study, 44.6% of 240 DSS patients at the Department of Dengue Hemorrhagic Fever, Children’s Hospital No.1 in Ho Chi Minh City needed dextran 40 (Chi PB and Huyen NTD, unpublished data). In the present study, all 63 DSS patients received intravenous infusion, 27 (42.8%) patients received only RL, 35 (55.5%) patients received dextran plus RL, and 17 (26.9%) patients needed FWB because of GI bleeding or internal bleeding. Special care must be taken to manage intravenous fluids administered to infants. Fluids account for a greater proportion of body weight in infants than in children and minimum daily requirements are correspondingly higher. Infants have lower intracellular fluid reserves than older children and adults. Moreover, capillary beds are intrinsically more permeable in infants than those in older children or adults. Both early cardiovascular compromise and significant fluid overload are more likely to occur if capillary leaks occur in these circumstances. All infants must be treated as high-risk patients who require early intervention with colloids, as in older children with grade IV disease. In the present study, the mean volume of intravenous fluid replacement and dextran in infants with DSS was significantly higher than that given to infants with non-shock DHF (129.8 versus 102.1 mL/kg $[P = \ldots$.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Infants with fatal DSS (n = 4)</th>
<th>Survived infants with DHF/DSS (n = 204)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gastrointestinal bleeding, no. (%) of infants</td>
<td>3 (75)</td>
<td>11 (5.3)</td>
<td>0.001*</td>
</tr>
<tr>
<td>Liver size,† mean cm ± SD (range)</td>
<td>4.7 ± 0.9 (4–6)</td>
<td>3.0 ± 0.9 (1–6)</td>
<td>0.004†</td>
</tr>
<tr>
<td>Respiratory failure, no. (%) of infants</td>
<td>2 (50)</td>
<td>11 (5.3)</td>
<td>0.02*</td>
</tr>
<tr>
<td>Dengue encephalopathy, no. (%) of infants</td>
<td>3 (75)</td>
<td>13 (6.2)</td>
<td>0.01*</td>
</tr>
<tr>
<td>Prolonged shock, no. (%) of infants</td>
<td>2 (50)</td>
<td>4 (6.7)</td>
<td>0.04*</td>
</tr>
<tr>
<td>Lowest platelet count, mean cells $\times 10^9$/mm$^3$ ± SD (range)</td>
<td>25.5 ± 6.4 (20–32)</td>
<td>62.2 ± 32.2 (14–190)</td>
<td>0.007†</td>
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* Infants with fatal DSS vs. surviving infants with DHF/DSS by Fisher exact two-tailed test.
† Below right costal margin.
‡ Infants with fatal DHF vs. surviving infants with DHF/DSS by Kruskal-Wallis test.
0.001] and 60.9 mL/kg versus 39.4 mL/kg \( [P = 0.01] \). It is important to detect early warning signs of shock in infants so that intravenous fluid therapy can be started promptly.18

Prolonged shock was documented in six patients. Prolonged shock led to severe complications such as respiratory failure, massive GI bleeding, metabolic acidosis, multiple organ dysfunctions, and death.7 In the present study, patients with prolonged shock required catheterization to monitor central venous pressure and correction of the metabolic acidosis.

The cause of acute respiratory failure in DHF patients is usually caused by the administration of intravenous fluids too rapidly or for too long a period. Pulmonary edema may occur with the sudden healing of the capillary leak if administration of intravenous fluid continues. With normal capillaries, the body begins the process of readsoorbing fluids from the extra-cellular compartment. Lum and others described acute respiratory distress syndrome in three patients with DHF with prolonged shock and tissue hypoxia when crystalloids were administered too rapidly.19 These patients became hypoxicemic and required positive pressure ventilation. Large pleural effusions and ascites may compress the lungs and limit the movement of the diaphragm, resulting in respiratory distress. The central nervous system may be depressed in patients with dengue encephalopathy, which leads to dysfunction of the respiratory center. Severe pneumonia caused by bacterial superinfection may result in respiratory failure. In the present study, pneumonia in two patients and fluid overload in one patient resulted in respiratory failure in infants with non-shock DHF. Multivariate logistic analysis showed that prolonged shock and coinfection with pneumonia had a strong association with acute respiratory failure \( (P = 0.01 \text{ and } P = 0.001, \text{respectively}) \).

Acute respiratory failure in infants was treated with oxygen by nasal cannula (in five patients), or NCPAP (in eight patients). Cam and others reported that NCPAP improved outcome of respiratory failure in DHF/DSS patients.20 Severe respiratory failure that failed to respond to respiratory support was observed in two out of four fatal cases.

Although DHF/DSS in infants comprises less than 5% of all DHF/DSS cases, mortality rates are higher in infants than in older children.5 In our study, four infants died on day 5 to day 7 after the onset of fever, with the mean time of 29.7 hours after onset of shock. DHF/DSS in infants can quickly result in death. In a hospital-based study in Jakarta, Indonesia, there were 188 DSS patients with overall mortality of 19.7%.10 Those in this study less than one year of age had the highest mortality compared with other groups, but no one more than 10 years of age died. After implementing an improved case management system at the Department of Dengue Hemorrhagic Fever, Children’s Hospital No. 1 in Ho Chi Minh City, we have treated 10,248 DHF/DSS patients of all ages, of whom only 20 have died, resulting in a case fatality rate of 0.19% during the period 1997–2002. However, the case fatality rate remains higher in infants than in older children (0.76% versus 0.15% \( [P = 0.001] \)) (Hung NT and others, unpublished data).

The present study emphasizes that fluid replacement in infants with DHF/DSS is a challenge to good clinical management. Intravenous fluids must be administered with special care to avoid fluid overload. This involves following established procedures for use of colloidal solutions and blood transfusions. To further reduce case fatalities, special emphasis needs to be given to infants with DHF/DSS who have or develop severe complications.

Received August 3, 2005. Accepted for publication November 25, 2005.

Acknowledgments: We thank Tran Tan Tram (former Director of the Children’s Hospital No. 1, Ho Chi Minh City) and Chung-Ming Chang (National Health Research Institutes, Taiwan) for help and support during this study. We also thank the doctors and nurses of the Department of Dengue Hemorrhagic Fever, Children’s Hospital No.1 for providing excellent patient care.

Financial support: This study was supported in part grant NHRI-CNCL9303P from the National Health Research Institutes, Taiwan.

Disclosure: None of the authors have any commercial or other associations that might pose a conflict of interest.

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