MAJOR ARTICLE

Acute Management of Dengue Shock Syndrome: A Randomized Double-Blind Comparison of 4 Intravenous Fluid Regimens in the First Hour

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Dengue hemorrhagic fever is an important cause of morbidity among Asian children, and the more severe dengue shock syndrome (DSS) causes a significant number of childhood deaths. DSS is characterized by a massive increase in systemic capillary permeability with consequent hypovolemia. Fluid resuscitation is critical, but as yet there have been no large trials to determine the optimal fluid regimen. We undertook a randomized blinded comparison of 4 fluids (dextran, gelatin, lactated Ringer's, and "normal" saline) for initial resuscitation of 230 Vietnamese children with DSS. All the children survived, and there was no clear advantage to using any of the 4 fluids, but the longest recovery times occurred in the lactated Ringer's group. The most significant factor determining clinical response was the pulse pressure at presentation. A comparison of the colloid and crystalloid groups suggested benefits in children presenting with lower pulse pressures who received one of the colloids. Further large-scale studies, stratified for admission pulse pressure, are indicated.

Dengue is the most widely distributed mosquito-borne viral infection of humans, affecting an estimated 100 million people worldwide each year. It is endemic in parts of Asia and the Americas and has been increasingly reported from many tropical countries in recent years [1–3]. Dengue hemorrhagic fever (DHF) and dengue shock syndrome (DSS) are among the leading causes of pediatric hospitalization in Asia, with up to 500,000 cases reported annually to the World Health Organization (WHO) [4]. Mortality rates from <1% to 5% are usually quoted for DHF/DSS from centers experienced in fluid resuscitation [4, 5], but rates up to 44% have occasionally been reported with regard to established shock [6, 7].

There are 4 serotypes of dengue virus, all of which may produce either a nonspecific febrile illness, dengue fever (DF) or may result in the more severe manifestation of DHF. The pathophysiology of DHF is not clear, but the main feature differentiating it from DF is an increase in vascular permeability, resulting in leakage of fluid from the intravascular compartment to the extravascular space [1, 3, 8]. In some cases there is a massive loss of fluid and shock develops, usually between the third and fifth days of illness. Narrowing of

Received 27 December 1999; revised 2 June 2000; electronically published 15 January 2001.

Financial support: The Wellcome Trust of Great Britain.

Ethical approval and scientific review were provided by the Scientific and Ethical Committees of the Dong Nai Paediatric Hospital and the Centre for Tropical Diseases of Ho Chi Minh City. Informed consent was obtained from the parents or guardians of the patients.

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Clinical Infectious Diseases 2001; 32:204–13

1058-4838/2001/3202-0005$03.00

the pulse pressure is recognized as one of the earliest manifestations of shock, and occurs before the development of hypotension. The mainstay of treatment is prompt, vigorous fluid resuscitation [9–11]. If appropriate volume resuscitation is started at an early stage, shock is usually reversible; in very severe cases, and in those in whom the resuscitation is inadequate, patients may progress to irreversible shock and death. In the majority, however, the capillary leakage resolves spontaneously by the sixth day of illness and is followed rapidly by full recovery [1, 9, 10]. In the 24–48 h period following initial resuscitation, there may be recurrent episodes of shock, presumably reflecting the severity of the ongoing capillary leakage.

Guidelines for diagnosis of both DF and DHF are published by the WHO [9, 10]. DHF has been classified into the following 4 grades of severity (table 1): grades I and II involve only mild capillary leakage, insufficient to result in the development of shock, and are differentiated by the absence (grade I) or presence (grade II) of spontaneous bleeding; in grade III circulatory failure occurs, manifested by a rapid, weak pulse, with narrowing of the pulse pressure to ⩽20 mm Hg; in grade IV shock is severe, with no detectable pulse or blood pressure. DHF grades III and IV are collectively referred to as DSS. For patients with DSS, the WHO recommends immediate volume replacement with isotonic crystalloid solutions, followed by the use of plasma or colloid solutions (specifically, dextran) for profound or continuing shock.

For many years there has been controversy over whether crystalloid or colloid solutions should be used for volume replacement in the treatment of shock [12–14]. This debate is of particular importance in situations in which shock is accompanied by capillary leakage, when resuscitation may readily be complicated by the development of severe fluid overload [15, 16]. Even in the setting of a well-equipped intensive care unit (ICU), the care of such patients is often fraught with difficulties; most children with DSS live in parts of the world where there is no access to sophisticated intensive care and health care personnel must manage the delicate balance between maintaining an effective circulation while avoiding fluid overload.

The WHO recommendations for treatment were originally proposed in 1975 [17], following the marked rise in morbidity and mortality associated with DHF in Southeast Asia during the 1960s [18]. It is surprising that given the critical importance of volume replacement in the management of DSS, there have been no large-scale studies carried out to determine the optimal fluid regimen, and the current WHO guidelines have remained virtually unchanged. Largely as a result of the ongoing debate over whether crystalloids or colloids should be used for volume resuscitation, alternative synthetic colloid solutions have been developed in the past 20 years, some of which may have relevance for the management of DSS. In this study we addressed the issue of optimal early fluid resuscitation in DSS with use of 4 of the fluids commonly available in this part of Asia. In many hospitals in southern Vietnam, standard management is with lactated Ringer's solution, with dextran solutions reserved for refractory or recurrent shock. Gelatin solutions are becoming more widely available and are used empirically in some centers [19].

Emergency management in the first hour has become recognized as critical to the outcome in many situations [20–22]. We have assessed both the immediate therapeutic response to crystalloid and colloid therapy and whether the use of one of the colloid solutions at first presentation might influence the likelihood of further episodes of shock during the period of ongoing capillary leakage.

PATIENTS AND METHODS

Study design. The study was a randomized, double-blind trial comparing the efficacy of 4 different fluid regimens in the initial management of DSS in children. The 4 solutions were dextran 70 (Onkovertin 70), 3% gelatin (Gelafundin), lactated Ringer's, and "normal" saline (all fluids were supplied by B. Braun).

The study took place from September 1996 through September 1997 on the ICU of Dong Nai Paediatric Hospital, a specialist children's hospital situated 40 km from Ho Chi Minh

Table 1. WHO guidelines for the diagnosis of dengue haemorrhagic fever (DHF) and dengue shock syndrome (DSS).

DHF grade	Duration of fever, d	Hemorrhage	Thrombocytopenia: platelets/mm^3	Increased vascular permeability
I	>2, ⩽7	Positive tourniquet test only	⩽100,000	Plasma leakage[a]
II	>2, ⩽7	Spontaneous bleeding[b]	⩽100,000	Plasma leakage[a]
III (DSS)	>2, ⩽7	Positive tourniquet test and/or spontaneous bleeding[b]	⩽100,000	Plasma leakage[a] and circulatory failure with pulse pressure ⩽20 mm Hg or hypotension for age
IV (DSS)	>2, ⩽7	Positive tourniquet test and/or spontaneous bleeding[b]	⩽100,000	Plasma leakage[a] and profound shock with undetectable pulse and blood pressure

[a] As demonstrated by any of the following: elevation of the admission hematocrit to ⩾20% above the expected mean for age, sex, and population; reduction of the hematocrit to ⩾20% of the baseline value after fluid resuscitation; and clinical signs of plasma leakage, such as pleural effusion or ascites.
[b] For example, skin petechiae, bruising, or mucosal/gastrointestinal bleeding.

City, in southern Vietnam. The ICU has 15 beds, staffed by an average of 5 nurses and 3 doctors at any time. There are no facilities for ventilation, and invasive monitoring is carried out only in exceptional circumstances.

Patients. Children aged from 1 to 15 years who presented to the hospital with clinically diagnosed DHF grade III or IV were eligible for enrollment in the study, provided they had not received any iv fluid therapy and a parent or guardian gave informed consent. Those with severe hemorrhagic manifestations at presentation for whom transfusion seemed likely to become necessary were excluded, as were children with chronic disorders. Each day the first 3 children meeting the criteria were enrolled. A member of the emergency department staff initially assessed each child as suitable for study enrollment, and then a study team member, who did not have access to the clinical details, was consulted by telephone regarding bed availability on the ICU. If a bed was available, the child was transferred to the ICU, a full history and examination findings were recorded on standard forms, and the next sequential randomization envelope was opened. A venous blood sample was taken for determination of hematocrit and full blood cell count (with a manual platelet count), and a serum sample was stored for subsequent serological confirmation of dengue, in conjunction with a second sample obtained on the day of discharge.

Randomization. The randomization envelopes were opaque and contained only a treatment pack number. The envelopes had been randomized in blocks of 10. Each treatment pack consisted of three 500-mL containers of 1 of the study fluids; each bottle was covered in opaque black insulating tape to ensure that the treating medical and nursing staff did not know which fluid was being administered. All containers looked identical except for the pack number on the outside. Ten such packs were kept on the ward at any one time. A sealed envelope containing the identity of the study fluid was attached to each child's notes.

Management. Children with DHF grade III received the relevant study fluid at a rate of 20 mL/kg for the first hour, while those with DHF grade IV received 20 mL/kg over 15 min, followed by a second bolus of 20 mL/kg over the following hour. Following this initial management, all patients received lactated Ringer's solution according to a standard reducing protocol, based on the WHO guidelines for management of DSS [10]. However, if the patient's pulse and blood pressure failed to improve or deteriorated subsequently, such that the pulse pressure dropped below 20 mm Hg again, additional boluses of dextran 70 were given at the discretion of the study doctors. In all other respects, standard supportive care was given. For those patients who developed symptomatic fluid overload, frusemide was prescribed (0.5–1.0 mg/kg per dose). Ultrasound scanning is not available at the facility, so it was not possible to quantify the degree of fluid overload for individual children. A few children with marked respiratory signs underwent chest radiography. In all cases pleural effusions were found to be the cause of the respiratory distress, and no child had radiological evidence of pneumonia.

Pulse, blood pressure, and respiratory rate were monitored every 15 min for the first hour, every 30 min for the second hour, hourly for the remainder of the first 24 h, and subsequently as clinically indicated. Hematocrit was determined at baseline, at 1, 2, 6, and 12 h after enrollment in the study, and thereafter as necessary. A strict record was kept of the type, volume, and rate of administration of all fluids after administration of the initial study fluid, and the frequency and volume of urine output.

The diagnosis of dengue was confirmed serologically in 1 of 2 laboratories (either the Institute of Health and Community Medicine, Universiti Malaysia, Sarawak, Malaysia, or the Department of Virology, Armed Forces Research Institute of Medical Sciences, Bangkok, Thailand) with use of conventional capture ELISA techniques. Criteria for serodiagnosis were as described previously [23, 24].

Statistical analysis. The following outcome measures were defined prospectively, to be compared among the 4 different fluid-recipient groups. The primary outcome measures were the initial pulse pressure recovery time, used as a marker of recovery from shock, and the occurrence and timing of subsequent episodes of shock. The pulse pressure recovery time was defined as the time from the start of fluid therapy until the pulse pressure reached $\geqslant$30 mm Hg. A child was considered to have developed "reshock" if, in association with tachycardia and coolness of extremities, the pulse pressure narrowed to $\leqslant$20 mm Hg, having previously reached a level of $\geqslant$30 mm Hg. The time elapsed from the start of fluid therapy to the first episode of "reshock" was recorded. Secondary outcome measures included the drop in hematocrit and pulse rate after the first hour, the total volume of dextran 70 required after the first hour, the total volume of iv fluid administered until full recovery, and the development of any complications of fluid therapy.

The analysis was conducted on an intention-to-treat basis. Normally distributed variables were compared between groups with use of one-way analysis of variance, followed by unpaired *t* tests. For variables that were not normally distributed the groups were compared with the Kruskal-Wallis test, followed by the Mann-Whitney *U* test. For the post hoc pairwise comparisons, the *P* value was adjusted with use of the Bonferroni correction. Differences between proportions were tested by means of the χ^2 test. Multiple logistic regression analysis was performed to adjust for any confounders. Statistical computations were performed with the program SPSS for Windows, version 7.5 (SPSS).

RESULTS

A total of 230 patients were recruited into the study over 1 year; 222 of these had DHF grade III and the remaining 8 had DHF grade IV. Of the 230 patients, 205 (89%) had serologically confirmed dengue, and 10 (4%) had findings suggestive of dengue (significant elevation of dengue IgG level in a single acute sample, but without a diagnostic level of dengue IgM). Samples from the remaining 15 children were inadequate for analysis. In view of the small number of children with DHF grade IV who received treatment with a different regimen, we focused this report on the 222 children with DHF grade III. All of the patients presenting with grade IV DHF made a good recovery without serious complications.

Demographic information, clinical features at presentation, and preliminary laboratory data for all children with DHF grade III are shown in table 2. The numbers of children in each group were similar, with similar proportions of males and females. Children presenting with shock earlier in the course of the illness might be expected to have more severe disease; there were no differences between the study groups in the numbers developing shock on illness days 3 and 4, as distinct from days 5 and 6.

Pulse pressures at presentation with shock were not normally distributed within the overall study group and were skewed toward the higher end of the range (20 mm Hg). Despite randomization, the small number of children with very low pulse pressures at presentation with shock (≤10 mm Hg) were not equally distributed between the 4 fluid-recipient groups. The variable, "pulse pressure at shock," was therefore dichotomized into 2 categories considered to be clinically relevant and likely to reflect disease severity: pulse pressure that was unmeasurable or ≤10 mm Hg, and pulse pressure of >10 and ≤20 mm Hg. The proportion of subjects with pulse pressure at shock ≤10 mm Hg was significantly different between the 4 groups, with relatively few in the dextran group. There was also a difference in the mean pulse rate at presentation with shock, with the dextran group having the lowest values. Thus, an unequal distribution of more severely ill patients seems to have occurred by chance between the 4 fluid-recipient groups.

The platelet counts at shock were also significantly different between the 4 groups. These differences seem unlikely to be clinically relevant; many children manifested some evidence of clinical bleeding on admission, but in the vast majority spontaneous petechiae in the skin were the only abnormality.

The remaining clinical features and laboratory data were similar between the groups. None of the patients were withdrawn from the study after randomization or received the incorrect fluid.

Outcome. There were no deaths in any of the groups, and all patients made a full recovery with fluid therapy and general supportive care alone. In no case was the randomization code broken before completion of the study. Six children had allergic reactions, developing fever and chills shortly after completing colloid therapy (5 received gelatin and 1 received dextran). In all cases the symptoms resolved promptly with administration of paracetamol, and there was no cardiovascular compromise. Two of these children did experience episodes of "reshock" later during the hospital course but responded to conventional treatment. One child in the gelatin group had a severe epistaxis requiring transfusion of blood (10 mL/kg), and another child in the dextran group developed a large hematoma at a site of minor trauma. A total of 35 patients (15.7%), equally distributed between the 4 fluid-recipient groups, required treatment with frusemide for 1 or 2 days after recovery from shock. No other complications or adverse effects were documented.

Differences between fluid treatment groups. The results of treatment on the main outcome variables are shown in table 3. In the majority of children the pulse pressure returned to normal within 1 hour, and all but 1 child recovered from the initial episode of shock within 3 h. There was a small but significant difference ($P = .03$) in the median pulse pressure recovery times between the 4 fluid-recipient groups. After Bonferroni adjustment, the only significant difference observed was between dextran and "normal" saline ($P = .036$). The longest recovery times overall were in the lactated Ringer's group; significantly more children in this group (11 children [20%], $n = 55$) than in the other 3 groups (3–4 children [5.4%–7.1%], $n = 56$; $P = .022$) took >1 h to recover. Among the children who recovered slowly, the clinical response to resuscitation was considered to be inadequate in 14 children, in the majority of cases because the pulse pressure was still ≤20 mm Hg at 1 h. Most of these children (10 patients) had received lactated Ringer's solution. All required resuscitation with dextran solution (15–30 mL/kg) in addition to the study fluid for successful resolution of the first episode of shock. However, the majority of children requiring dextran solution at this stage also had evidence of more severe disease, with a pulse pressure at onset shock of ≤10 mm Hg (see below on the importance of pulse pressure in assessing the severity of shock). There were no differences in the "reshock" rate between the 4 groups. In addition, there was no difference in the time from the onset of resuscitation to the first episode of "reshock."

Elevation of the hematocrit level at shock reflects the severity of hemoconcentration. Subsequent changes in the hematocrit level are used to monitor the progress of patients with DSS. The mean hematocrit at presentation with shock was similar in all the groups. The mean reduction in hematocrit after the initial resuscitation was significantly different between the four groups ($P < .001$), with the maximum reduction in the group treated with dextran. There was also a significant difference in the mean volume of dextran required after the first hour ($P = .035$); those initially treated with dextran required the

Table 2. Demographic, clinical and laboratory data at presentation with shock, in 222 children with grade III dengue hemorrhagic fever who received one of four treatment solutions.

Feature	Solution administered					P
	All patients (*n* = 222)	Dextran 70 (*n* = 55)	Gelatin (*n* = 56)	Lactated Ringer's (*n* = 55)	"Normal" saline (*n* = 56)	
Demographic						
Boys/girls	94/128	24/31	24/32	26/29	20/36	.659
Age, y						
Mean ± SD	7.7 ± 3.1	7.9 ± 3.5	7.5 ± 3.0	8.3 ± 3.2	7.3 ± 2.7	.281
Range	2–15	2–15	3.5–13	4–15	2–14	
1–4, no. (%)	38 (17.1)	9 (16.4)	13 (23.2)	7 (12.7)	9 (16.1)	.319
5–9, no. (%)	117 (52.7)	28 (50.9)	25 (44.6)	28 (50.9)	36 (64.3)	
10–14, no. (%)	67 (30.2)	18 (32.7)	18 (32.2)	20 (36.4)	11 (19.6)	
Clinical						
Patients with shock, no. on day 3 or 4/no. on day 5 or 6	108/114	26/29	28/28	26/29	28/28	.983
Patients with history of fever, no.	222	55	56	55	56	
Temperature, °C						
Mean ± SD	37.2 ± 0.3	37.1 ± 0.3	37.2 ± 0.4	37.1 ± 0.2	37.2 ± 0.4	.519
Range	37–39	37–38.4	37–39	37–37.9	37–38	
Pulse, beats/min[a]						
Mean ± SD	113.9 ± 14.3	110.3 ± 15.3	114.4 ± 13.4	113.2 ± 14.7	117.7 ± 13.3	.038[b]
Range	78–140	78–140	80–140	80–140	80–140	
Pulse pressure ⩽10 mm Hg, no. (%)	51 (23)	4 (7.3)	17 (30.4)	16 (29.1)	14 (25)	.014[b]
Patients with clinical bleeding, no. (%)	184 (82.9)	49 (89.1)	49 (87.5)	41 (74.5)	45 (80.4)	.152
Liver size cm[c]						
Mean ± SD	1.7 ± 0.6	1.6 ± 0.6	1.7 ± 0.6	1.8 ± 0.6	1.8 ± 0.6	.674
Range	0.5–3	0.5–3	1–3	1–3	0–3	
Laboratory						
Hematocrit, %						
Mean ± SD	49.1 ± 3.5	48.1 ± 3.8	49.2 ± 3.4	49.1 ± 3.6	49.7 ± 3.3	.058
Range	39–60	41–60	41–55	41–58	39–59	
Platelet count, cells/mm^3						
Mean ± SD	62,118 ± 18,780	69,345 ± 24,772	62,696 ± 16,138	59,000 ± 16,529	57,364 ± 14,077	.029[b]
Range	30,000–160,000	30,000–160,000	30,000–120,000	30,000–110,000	34,000–88,000	
Patients with platelet count ⩽100,000 cells/mm^3, no. (%)	215 (96.8)	51 (92.7)	55 (98.2)	54 (98.2)	55 (98.2)	—[d]
WBC count, cells/mm^3						
Mean ± SD	6380 ± 1181	6534 ± 1193	6332 ± 1772	6380 ± 1611	6276 ± 2144	.873
Range	3200–17,000	4000–12,800	3200–12,000	4000–12,000	4000–17,000	

[a] In 6 patients the pulse at shock was too rapid and weak to count accurately; thus *n* = 216 for the whole study group (A, 55; B, 56; C, 50; D, 55).
[b] Significant *P* value.
[c] Number of cm below the right costal margin, in the midclavicular line.
[d] Differences too small for valid statistical comparison.

least support subsequently. Finally, there was a significant difference in the reduction in pulse rate after initial resuscitation ($P = .023$), with the greatest reduction in the group treated with gelatin. Amongst the other secondary outcome measures, there were no significant differences between the 4 groups.

The pulse pressure at presentation with shock was identified as a potential confounder, being unequally distributed between the 4 fluid-recipient groups; thus, we considered the effect of this on the main outcome variables. A pulse pressure of ⩽10 mm Hg on admission was associated with a 6.7-fold increase

Table 3. Effect of treatment group on selected clinical and laboratory parameters.

Outcome variable	Solution administered					P
	All patients (*n* = 222)	Dextran 70 (*n* = 55)	Gelatin (*n* = 56)	Lactate Ringer's (*n* = 55)	"Normal" saline (*n* = 56)	
Primary						
PPRT, h median (range)	0.75 (0.25–7)	0.50 (0.25–3)	0.50 (0.25–2)	0.75 (0.25–7)	0.75 (0.25–3)	.030[a]
PPRT >1 h, no. (%) of patients	21 (9.5)	3 (5.5)	3 (5.4)	11 (20)	4 (7.1)	.022[a]
"Reshock" rate, no. (%) of patients	63 (28.4)	16 (29.1)	15 (26.8)	16 (29.1)	16 (28.6)	.992
Time to first episode of "reshock" (*n* = 63)						
Mean h ± SD	11.7 ± 5.5	15 ± 6.8	11.4 ± 4	10 ± 4.1	10.3 ± 5.6	.068
Range	1.5–23	2.5–23	3–17	3–16	1.5–23	
Secondary						
Decrease in hematocrit at 1 h, %						
Mean ± SD	8.4 ± 3.8	11.5 ± 3.3	9.7 ± 3.0	5.7 ± 2.8	6.5 ± 2.9	<.001[a]
Range	−2 to 19	2 to 19	0 to 16	−2 to 13	0 to 17	
Decrease in pulse at 1 h, beats/min						
Mean ± SD	15.1 ± 10.1	14.9 ± 9.9	18.5 ± 11.3	13.2 ± 9.2	13.5 ± 8.9	.023[a]
Range	20–44	−20 to 36	0–44	−10 to 36	0–40	
Total volume of iv fluid infused, mL/kg						
Mean ± SD	134.1 ± 20.6	134.3 ± 22.1	135 ± 23.5	134.2 ± 19.9	132.9 ± 16.6	.954
Range	89–212	89–189	93–212	103–182	106–172	
Requirement for dextran after first hour, no. (%) of patients	69 (31.1)	17 (30.9)	15 (26.8)	20 (36.4)	17 (30.4)	.749
Volume of dextran after first hour, mL/kg (*n* = 69)[b]						
Mean ± SD	28.3 ± 12.7	22.1 ± 6.1	30.7 ± 11.6	33.5 ± 14.3	26.3 ± 14.3	.035[a]
Range	10–69	10–37.5	14.5–57	15–64	15–69	
Required frusemide, no. (%) of patients	35 (15.7)	5 (9.1)	10 (17.9)	8 (14.5)	12 (21.4)	.328

NOTE. PPRT, pulse pressure recovery time.

[a] Significant *P* value.

[b] In 6 patients the pulse at presentation with shock was too rapid and weak to count accurately; thus *n* = 216 for the whole study group (A, 55; B, 56; C, 50; D, 55).

in risk (95% CI, 2.9–15.7; $P < .001$) of not recovering from shock within 1 h and a 1.7-fold increase in risk (95% CI, 1.1–2.6; $P = .033$) of developing "reshock" (table 4). Patients in this "severe" group were more likely both to require dextran and to require a greater volume of dextran, after the initial resuscitation. Children whose pulse pressure took >1 h to recover had a much higher "reshock" rate (62%) than those whose pulse pressure was normal by 1 h (25%; $P < .001$), an effect which persisted after adjustment for admission pulse pressure (OR, 4.0; 95% CI, 1.5–10.8; $P = .006$).

To adjust for this confounding effect, logistic regression analysis was carried out to determine the relationship between pulse pressure at presentation with shock, type of resuscitation fluid, and the pulse pressure recovery time (table 5). A pulse pressure of ⩽10 mm Hg at presentation with shock remained strongly associated with a recovery time of >1 h (OR, 9.7; 95% CI, 3.4–27.7; $P < .001$), independent of the type of fluid used for resuscitation. Comparing the different fluid-recipient groups and controlling for admission pulse pressure, we found a significant difference in the number of children whose recovery took >1 h, between those who received lactated Ringer's solution and those who received gelatin (OR, 5.7; 95% CI, 1.4–23.6; $P = .017$). Differences between lactated Ringer's solution and "normal" saline were equivocal, and all other comparisons between fluid-recipient groups showed no significant difference.

Crystalloids versus colloids. Among children presenting with a pulse pressure of ⩽10 mm Hg, there were significant differences between those who received a colloid and those who received a crystalloid solution for primary resuscitation, in both the median pulse pressure recovery time and the proportion whose recovery took >1 h (table 6). Of the 8 patients with grade IV DSS (who received more aggressive initial resuscitation), 3 received a colloid solution and 5 received a crystalloid solution. The trend toward improved outcome with colloids is also apparent within this small group. The median pulse pres-

Table 4. Effect of pulse pressure at presentation with shock on pulse pressure recovery time, "reshock" rate, and requirement for dextran after the first hour.

Variable	All groups, PP ⩽10 mm Hg (n = 51)	All groups, 10 > PP ⩽20 mm Hg (n = 171)	P[a]
PPRT, h median (range)	1 (0.25–7)	0.50 (0.25–3)	<.001
PPRT >1 h, no. (%) of patients	14 (27.5)	7 (4.1)	<.001
"Reshock" rate, no. (%) of patients	21 (41.2)	42 (24.6)	.033
Requirement for dextran after first hour, no. (%) of patients	25 (49.0)	44 (25.7)	.003
Volume of dextran used after first hour, mL/kg (n = 69)			
Mean ± SD	33.7 ± 16.0	25.2 ± 9.3	
Range	15–69	10–52	.02

NOTE. PP, pulse pressure; PPRT, pulse pressure recovery time.
[a] All P values were significant.

sure recovery time in the 3 patients treated with a colloid was half an hour (range, 0.5–0.75 h), and 2 children developed "reshock," while among those receiving 1 of the crystalloids, it was 1 h (range, 0.25–2.75 h), and 4 children developed "reshock."

The crystalloid group required, on average, twice the volume of dextran (mean ± SD, 43.3 ± 5 mL/kg) after the initial resuscitation than did the colloid group (20.5 ± 9.2 mL/kg). The combined results must be interpreted with caution, however, since the study was not designed to combine the fluid-recipient groups, and the effect of one fluid may be overemphasized in this way.

DISCUSSION

In this study we found the most significant factor predicting the clinical response to resuscitation in DSS was the width of the pulse pressure at presentation. Children with a pulse pressure of ⩽10 mm Hg on admission were more likely to have prolonged shock and to experience subsequent episodes of shock than were those presenting with higher pulse pressures. The preliminary analysis suggested a difference in outcome related to the fluid treatment group, but despite blinding and randomization, there were differences in severity between the treatment groups. Of all the fluids, Ringer's lactate performed the least well. For children receiving this fluid, recovery times were longer, initial therapy was more likely to be considered a failure, and dextran was more likely to be required for treatment of the initial episode of shock than for children in the other three groups. The greater number of children with profound shock in the group may explain this.

Table 5. Logistic regression analysis.

Independent variable	OR (95% CI)	P
Pulse pressure ⩽10 vs. >10	9.71 (3.41–27.68)	<.001[a]
Group C vs. group A	2.43 (0.57–10.3)	.228
Group C vs. group B	5.76 (1.36–23.59)	.017[a]
Group C vs. group D	3.50 (0.95–12.89)	.060
Group A vs. group B	2.33 (0.40–13.74)	.348
Group A vs. group D	1.44 (0.27–7.59)	.666
Group B vs. group D	0.62 (0.12–3.09)	.558

NOTE. Outcome is pulse pressure recovery time >1 hour. A, dextran group; B, gelatin group; C, Ringer's lactate group; D, "normal" saline group.
[a] Significant P value.

Conventionally, the cutoff for a diagnosis of grade III DHF is a pulse pressure of ⩽20 mm Hg, with no detectable pulse or blood pressure signifying DHF grade IV [10]. Within the DHF grade III group there is a gradient of worsening severity, reflected by narrowing of the pulse pressure. Most children with DSS present shortly after becoming symptomatic, at a time when the pulse pressure is ~20 mm Hg. A minority present at a later stage, either because of explosive disease or because relatives have failed to recognize the severity of the disease or have difficulties arranging transportation. In such situations the plasma volume is severely depleted and the pulse pressure very narrow by the time the child presents. Outcome is determined largely by severity at presentation. In the past, DHF grade III has been regarded as a homogeneous entity. This study suggests that the majority of patients with this diagnosis have mild to moderate shock, likely to respond well to conventional treatment, but that a small but important minority have more serious disease, merit very careful monitoring, and may require more aggressive management from the outset.

Theoretically, colloid solutions offer some advantages over crystalloid solutions, because they provide volume expansion over and above the actual fluid volume infused [25, 26]. The colloid molecules increase plasma oncotic pressure and reverse the net flux of fluid out of the intravascular compartment. The magnitude of this effect is determined by the average molecular weight of the distributed colloid molecule; the duration of the effect reflects the circulation residence time. Synthetic colloids

Table 6. Comparision of selected outcome variables for children receiving colloid versus crystalloid solutions for initial resuscitation, stratified by pulse pressure at shock.

Variable	PP < 10 mm Hg			10 > PP ⩽ 20 mm Hg		
	Colloids (n = 21)	Crystalloids (n = 30)	P	Colloids (n = 90)	Crystalloids (n = 81)	P
PPRT, median h (range)	0.75 (0.25–2)	1.00 (0.25–7)	.01[a]	0.5 (0.25–3)	0.75 (0.25–3)	.107
PPRT >1 h, no. (%) of patients	2 (9.5)	12 (40)	.037[a]	4 (4.4)	3 (3.7)	.99[b]
"Reshock" rate, no. (%) of patients	8 (38.1)	13 (43.3)	.932	23 (25.6)	19 (23.5)	.883
Requirement from dextran after first hour, no. (%) of patients	8 (38.1)	17 (56.7)	.307	24 (26.7)	20 (24.7)	.905
Volume of dextran used after first hour, mL/kg (n = 69)						
Mean ± SD	34.1 ± 13.7	33.5 ± 17.3	.933	23.4 ± 6.8	27.3 ± 11.4	.187
Range	15–57	15–69		10–40	15–52	

NOTE. PP, pulse pressure; PPRT, pulse pressure recovery time.

[a] Significant P value.

[b] Fisher's exact test.

are polydisperse, with a range of molecules of different molecular weights in one solution; larger molecules remain within the circulation longer, but smaller molecules exert a greater osmotic effect. Thus, dextran 70, with an average molecular weight of 70,000 and a maximum molecular weight of 125,000, increases plasma volume by up to 150% of the volume infused, with a significant volume expansion that persists for 6 hours [27, 28]. Gelatin solutions have an average molecular weight of 35,000 and a narrow range, giving a volume effect of ~110%, which lasts for ~2 h [27, 28]. Conversely, in patients with increased vascular permeability, colloid molecules may themselves leak into the interstitium and exert a reverse osmotic effect, thereby drawing out intravascular fluid and worsening the situation [15]. The plasma volume–expanding capacity of crystalloid solutions is related to the sodium concentration: 154 mM for "normal" saline and 131 mM for lactated Ringer's solution. They have no added volume effect and are likely to be lost from the circulation very quickly [26].

In this study, lactated Ringer's solution, the standard fluid used for management of DSS in many hospitals in southern Vietnam and one of the fluids recommended by the WHO for dengue resuscitation, performed the least well. There are theoretical risks of worsening tissue acidosis and lactate accumulation when large infusions of lactated Ringer's solution are administered [28–30]. However, this seems unlikely to be the explanation here, since all patients received lactated Ringer's solution as standard management after the initial resuscitation, and those randomized to receive this treatment for primary resuscitation received only 20 mL/kg more than the average amount received by all patients (105 mL/kg). It seems more likely that the higher sodium content of "normal" saline over that in lactated Ringer's solution explains the difference in outcome between patients who received the 2 crystalloid solutions. There is little published information directly comparing the 2 crystalloids in shock resuscitation, and the available data relate predominantly to surgical cases or trauma [31]. Findings in animal models, together with some human data, do suggest that small boluses of hypertonic (7.5%) saline solutions could offer advantages over more conventional resuscitation with crystalloids in cases of hemorrhagic shock [32]. One important implication from the study is that "half-normal" saline solution containing 75 mM of sodium, another of the fluids currently recommended by WHO in the form of 5% glucose solution diluted 1:2 in physiological saline [10, 11], is likely to be inferior to "normal" saline for resuscitation in DSS.

In terms of secondary outcome variables, both dextran and gelatin solutions appeared to have significant advantages, but differences in admission severity between the groups may compromise the comparisons. Any benefit associated with gelatin solution in the subgroup of children with very severe shock would be expected to be more pronounced with dextran solution, but the dearth of severe patients in the dextran group might have obscured this. There was no difference in the development of symptomatic fluid overload between the fluid-recipient groups, a critical factor in terms of choosing the most appropriate fluid for resuscitation. Of the 6 allergic reactions, 5 occurred following treatment with gelatin solution. The allergic potential of gelatin, as well as all synthetic colloids, is well recognized [26, 28].

In conclusion, we have been unable to demonstrate a clear benefit of any 1 of the 4 fluids in the treatment of 222 children with DHF grade III, in this first large, randomized, blinded trial of fluid resuscitation in DSS. For the majority of patients with less severe disease, the type of fluid used for resuscitation may not actually matter. Of the 4 fluids evaluated, lactated Ringer's solution performed the least well, which suggests that

the simple, widely available 0.9% saline may be the crystalloid fluid of choice for resuscitation of the majority of patients with DSS. There are indications that in an important subgroup of the more severely ill patients, identifiable by their narrow admission pulse pressure, early treatment with colloid solutions improves outcome. In the analysis of the colloid and crystalloid fluid groups combined, the subgroup with the lowest pulse pressures at presentation improved significantly more quickly if they received one of the colloid solutions, whereas among the children with higher pulse pressures there was no difference in outcome between the groups. In a smaller study carried out recently at the Centre for Tropical Diseases in Ho Chi Minh City, there was also some evidence of greater improvements in hematocrit, pulse pressure, and cardiac index amongst children with DSS who received a colloid rather than a crystalloid solution for initial resuscitation [33].

The WHO classification of DHF considers a pulse pressure of ≤20 mm Hg as the arbitrary demarcation between DHF grades II and III. We would like to suggest that a further demarcation of ≤10 mm Hg might be usefully employed to indicate those children with severe DHF III. This group and, by extension, patients who present with grade IV DHF must be monitored very carefully and may merit early intervention with colloids. Further large trials, with stratification by pulse pressure at admission, are indicated if an effect is to be identified. Assuming a 20% incidence of late recovery from shock (>1 h) within the crystalloid group, a comparison of a single crystalloid with a single colloid, with stratification for admission severity, would require 438 cases to detect a 10% difference in shock recovery time with 95% confidence and 80% power.

Given the scale of the problem (in 1998 almost 120,000 cases of DHF were reported to the WHO from southern Vietnam alone [34]) a significant effect in the subgroup of patients with the most severe disease may be very important at a national or regional level.

Acknowledgments

We are very grateful to the director and staff of the Dong Nai Paediatric Hospital for help and support during the study. All fluids were kindly provided by B. Braun. In addition, we are most grateful to Dr. M. J. Cardosa and the staff of the Institute of Health and Community Medicine, Universiti Malaysia, Sarawak, Malaysia, and to Dr. T. Endy and the staff of the Department of Virology, Armed Forces Research Institute of Medical Sciences, Bangkok, Thailand, for their help with serological confirmation of dengue infection.

Finally, we would like to pay tribute to Dr. Cao Xuan Thanh Phuong, who died tragically in October after a short illness. Her hard work, energy, and enthusiasm will be greatly missed by all of her friends and colleagues.

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