Fluid Replacement in Dengue Shock Syndrome: A Randomized, Double-Blind Comparison of Four Intravenous-Fluid Regimens

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Dengue hemorrhagic fever and dengue shock syndrome (DSS) are major causes of childhood morbidity and mortality in many tropical countries. Increased intravascular permeability leading to shock is the cardinal feature of DSS. Fluid resuscitation to counteract massive plasma leakage is the mainstay of treatment. A double-blind, randomized trial comparing four intravenous-fluid regimens for acute resuscitation of 50 children with DSS was conducted. Colloids (dextran 70 or the protein digest gelafundin 35,000) restored cardiac index and blood pressure and normalized hematocrit more rapidly than crystalloids (Ringer's lactate or 0.9%-weight/volume saline). Dextran 70 provided the most rapid normalization of the hematocrit and restoration of the cardiac index, without adverse effects, and may be the preferred solution for acute resuscitation in DSS. Further large-scale double-blind trials are required to provide an evidence-based approach to the management of DSS.

Dengue fever is an acute mosquito-borne tropical febrile illness caused by one of four serotypes of the dengue virus. In its severe forms it is characterized by hemorrhagic diathesis and a tendency toward development of a shock syndrome that may be fatal [1]. Severe dengue is usually a disease of childhood. Dengue is the most important vector-borne viral infection of humans: >100 million cases are reported annually, and up to 2.5 billion people are at risk of infection in tropical and subtropical regions of Africa, Asia, and the Americas. Dengue hemorrhagic fever (DHF) has been graded according to severity by criteria adopted by the World Health Organization (WHO) [2]. Dengue shock syndrome (DSS; DHF grades III and IV) is the major cause of hospital admission of children in many parts of Southeast Asia, particularly during the rainy season.

See editorial response by Halstead and O'Rourke on pages 795–6.

A sudden marked increase in vascular permeability is the cardinal feature of DSS; shock is thought to result from leakage of plasma into the extravascular compartment, although the cause and extent of the increased permeability remain unresolved [2–4]. Dengue virus can infect endothelial cells, although the virus has not been demonstrated in endothelium in vivo. Light and electron microscopic studies on endothelial cells from fatal cases of DSS showed nonspecific changes and an absence of structural damage [5].

Typically, DSS develops suddenly, following defervescence. Plasma volumes, as determined by injection of ^{131}I-albumin, fall during the febrile period and reach a nadir during the first 2 days of convalescence, as the fever subsides [6]. The loss of plasma results in hemoconcentration and a reduction in circulating-blood volume, leading to peripheral vasoconstriction [7] and narrowing of the pulse pressure. Systemic vascular resistance is increased and the cardiac index is reduced [7], whereas in other systemic infections the opposite is found (i.e., low systemic vascular resistance and high cardiac index; H. T. T. Chau, unpublished data). Most patients have tender hepatomegaly, and ascites and pleural effusions are common. In untreated patients severe hypotension may follow, which can be fatal if intravenous fluids are not given.

There are no specific medications for dengue infections. Administration of crystalloid solutions (Ringer's lactate or 0.9% w/v "normal" saline) to patients with shock is usually effective in restoring circulating-blood volume, but large volumes are often required [8, 9]. More refractory cases may require the use of colloid solutions. There have been no previous randomized comparisons to assess the optimal fluid replacement regimen in DSS. The administration of colloids containing molecules that escape slowly from the circulation could theoretically overcome shock more quickly and effectively, and this might be beneficial in preventing recurrence of shock and reducing the requirement for large volumes of intravenous fluid and thus the risk of fluid overload. In order to address this, we conducted a randomized and blinded compar-

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Ethical approval was given and scientific review was performed by the Scientific and Ethical Committee of the Centre for Tropical Diseases. Informed consent was obtained from the patients or their parents or guardians.

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ison of the therapeutic responses to four intravenous solutions in the treatment of DSS in Vietnam.

Patients and Methods

Study site. The study was carried out in the Pediatric Intensive Care Unit at the Centre for Tropical Diseases, Ho Chi Minh City, Vietnam, an infectious diseases hospital that serves as the referral center for southern Vietnam.

Patients. Children between the ages of 5 and 15 years who had DSS and had not received intravenous fluid therapy during their current illness were eligible for enrollment in the study. All patients were admitted between July and November 1995, the height of the dengue season in southern Vietnam. Clinical diagnosis of DHF was made on the basis of (1) a history of fever, (2) hemorrhagic phenomena, including a positive tourniquet test, and (3) a raised hematocrit value and exclusion of alternative diagnoses by clinical criteria and appropriate laboratory investigations. In our experience this clinical presentation is highly specific for DHF. With use of this case definition, the clinical diagnosis of grade-III DHF in 95% of patients (205 of 215) was correct when compared to subsequent MacELISA findings (B. Wills, unpublished data).

DSS was defined as DHF with either low pulse pressure ($<$20 mm Hg) or unrecordable blood pressure, along with clinical signs of circulatory insufficiency such as cold extremities and thready pulse.

Informed consent to enrollment was obtained from the parent or guardian of the patient.

Procedures. On admission of a patient to the study, the history and clinical examination findings were recorded on a standard form and venous blood was taken to determine the hematocrit and full blood cell count and for serological and biochemistry tests (including determinations of lactate and glucose values). The patients were randomized to receive one of four fluids for resuscitation: 0.9% w/v saline (sodium [154 mmol/L] and chloride [154 mmol/L] in a plasma isotonic solution); Ringer's lactate solution (sodium [147 mmol/L], potassium [4 mmol/L], calcium [2.3 mmol/L], and chloride [156 mmol/L]); dextran 70 (60 g of dextran [molecular mass, 70,000 Da] in 0.9% w/v saline); or gelafundin, a polymerisate of degraded succinylated gelatin with a mean molecular mass of 35,000 Da (30 g of succinylated gelatin containing sodium [142 mmol/L], calcium [1.4 mmol/L], and chloride [80 mmol/L]). All fluids were manufactured by B. Braun Pharmaceuticals (Penang, Malaysia).

The randomization procedure involved opening a numbered opaque envelope to obtain a treatment-pack number. The envelopes were randomized in blocks of 10. This pack was then taken from the ward's supply. Ten such packs were kept on the ward at any one time. Each pack consisted of a 500-mL container of the study fluid. Each container 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.

An intravenous cannula was inserted and the fluid infused at a constant rate of 20 mL/kg for the first hour, followed by 10 mL/kg for the subsequent hour.

Vital signs were recorded every 30 minutes until blood pressure was stabilized, then every 4 hours. Patients were monitored by means of a cardiac monitor (Merlin; Hewlett Packard, Palo Alto, CA) while hemodynamically unstable (pulse pressure of $\leqslant$20 mm Hg, systolic blood pressure of $\leqslant$120 mm Hg, or pulse rate of $\geqslant$100/min). If the clinical responses were considered unsatisfactory, the treating physician could break the randomization and change the intravenous fluid. Blood for hematocrit was taken immediately before the infusion was started and at 60 minutes, 120 minutes, and at the time of discharge from the hospital. At the same time-points, cardiac output was measured noninvasively with use of a Doppler ultrasound technique (Sigma HCVD 44; Kontron Instruments, Montigny-Le-Bx, France): stroke volume was calculated as the product of the velocity-time integral and the internal cross-sectional area of the aortic root, multiplied by the heart rate to give the cardiac output. Cardiac index was calculated by dividing the cardiac output by the body surface area (calculated from height and weight with use of standard formulae).

Each measurement was performed in duplicate, and the measurements were recorded on videotape for checking by a second ultrasonographer, blinded to the clinical details. The same ultrasonographer, using the same machine, made all original measurements.

At the end of the 2-hour infusion, the study fluid was withdrawn. Further intravenous infusions were given on an open basis according to WHO guidelines, if and when the attending physician thought this was indicated [8]. All further infusions, the type of fluid used, and any further episodes of shock were all documented.

Blood pressure and pulse were measured at least every 2 hours, and hematocrit at least twice a day until recovery. WBC, platelet, and reticulocyte counts were measured both on admission and on discharge from the hospital. Serum was taken for serological confirmation of acute dengue infection with use of the PanBio dengue fever rapid immunochromatographic test (PanBio Ltd., Windsor, Queensland, Australia), which immunochromatographically demonstrates IgM and IgG antibodies to dengue viruses with a sensitivity of 100% and a specificity of 88% [10].

The a priori definition of clinical improvement was recovery from shock (pulse pressure, $\geqslant$20 mm Hg), and the main clinical outcome variables were duration of shock and number of episodes of shock. Improvements in cardiac output and hematocrit values and requirements for further fluid resuscitation were secondary outcome measures.

Table 1. Hemodynamic variables: mean baseline values and changes 2 hours after administration of each of the four fluid types.

Parameter	Fluid type	No. of recipients	Baseline value (95% CI)	Comparison of baseline values (P value)*	Change at peak dose (95% CI)	Post hoc pairwise comparisons of effects of fluid types over time: Bonferroni-corrected P values			Overall effect of fluid type over time (P value)†
						Ringer's lactate	Gelafundin	Dextran 70	
Hematocrit (%)	0.9% Saline	12	49.1 (45.9–52.3)	.74	−6.6‡ (−3.9–−9.3)	.99	.99	.03	.0008
	Ringer's lactate	13	50.2 (45.3–52.3)		−5.4‡ (−3.3–−7.6)		.99	.006	
	Gelafundin	13	46.8 (43.9–49.8)		−7.1§ (−4.7–−9.5)			.035	
	Dextran 70	12	48.3 (44.2–52.4)		−12.8§ (−9.2–−16.3)				
Pulse rate (beats/min)	0.9% Saline	12	116 (109–123)	.10	−12.3# (−1.4–−23.2)	.99	.99	.99	.41
	Ringer's lactate	13	124 (114–134)		−11.7‡ (−5.0–−18.3)		.99	.66	
	Gelafundin	13	127 (121–134)		−11.6‡ (−1.6–−21.7)			.99	
	Dextran 70	12	120 (114–125)		−20.4‡ (−11.0–−29.8)				
Pulse pressure (mm Hg)	0.9% Saline	12	18.3 (15.9–20.8)	.44	+8.3§ (5.9–10.80)	.99	.07	.67	.039
	Ringer's lactate	13	17.3 (15.3–19.3)		+10.4‡ (5.7–15.1)		.40	.99	
	Gelafundin	13	14.6 (9.8–19.5)		+16.9§ (10.7–23.2)			.98	
	Dextran 70	12	16.4 (11.8–20.9)		+11.8§ (7.8–15.9)				
Cardiac index (L/min · m^2)	0.9% Saline	12	2.25 (2.01–2.45)	.78	+0.77§ (0.60–0.94)	.66	.99	.07	.01
	Ringer's lactate	13	2.30 (2.02–2.58)		+0.51‡ (0.23–0.80)		.99	.01	
	Gelafundin	13	2.24 (1.89–2.59)		+0.79‡ (0.39–1.2)			.40	
	Dextran 70	12	2.10 (1.75–2.45)		+1.3§ (0.89–1.6)				

* Significance of one-way ANOVA comparing the four groups at baseline.
† Significance of effect of the interaction of time (baseline and at 2 h) and fluid type (0.9% saline, Ringer's lactate, gelafundin, or dextran 70) in a repeated-measures ANOVA model.
‡ $P < .001$.
§ $P < .0001$ (comparison between baseline and peak values for each fluid type).
# $P < .01$.

Statistics. One-way analysis of variance (ANOVA) or the Kruskal-Wallis test was used to compare baseline continuous variables between the four groups. Changes in variables between groups over time were assessed with repeated-measures ANOVA (SuperANOVA; Abacus Concepts, Berkeley, CA). When pairwise comparisons were made, P values were adjusted for multiple comparisons with use of the Bonferroni method. All outcome measures were stipulated a priori. For selected outcome variables, the fluid types were pooled into two a priori groups, crystalloid (saline 0.9% and Ringer's lactate) and colloid (dextran 70 and gelafundin), and assessed.

Results

Baseline variables. Fifty patients were studied over a 5-month period: 12 each in the saline and dextran 70 groups and 13 each in the Ringer's lactate and gelafundin groups. The mean age (±SD) was 8.2 years (±2.5 years) and did not differ between fluid groups. Although there were more boys than girls (33 vs. 17), this sex difference did not vary between groups. All 50 patients had serological evidence suggestive of acute secondary dengue infection, as assessed by the PanBio dengue fever immunochromatographic test. All patients recovered fully without any prescribed antimicrobial therapy; thus, an alternate diagnosis (malaria, typhoid fever, or leptospirosis) was extremely unlikely. No viral isolation was attempted for these patients.

All patients were in shock on admission (pulse pressure, ⩽20 mm Hg), had raised hematocrit values, and were classified as having DHF grade III on the basis of WHO criteria (table 1). Pleural effusions were present clinically in 76% (38) of the 50 patients on admission, and there was no difference in their incidence between the treatment groups. There were no significant differences in other clinical or laboratory parameters between the four treatment groups. The plasma lactate value was raised in all patients on admission (mean [95% CI], 3.7 mmol/L [3.0–4.5]) and was not significantly different between treatment groups.

Acute responses. With administration of all fluid types there were significant falls in mean pulse rate. The mean (range) changes in pulse rate (beats/min) at 2 hours were as follows: 0.9% saline, −12.3 (−1.4 to −23.2); Ringer's lactate, −11.7 (−5 to −18.3); gelafundin, −11.6 (−1.6 to −21.7); and dextran 70, −20.4 (−11 to −29.8).

The mean (range) increases in pulse pressure (mm Hg) were as follows: 0.9% saline, +8.3 (+5.9 to +10.8); Ringer's lactate, +10.4 (+5.7 to +15.1); gelafundin, +16.9 (+10.7 to +23.2); and dextran 70, +11.8 (+7.8 to +15.9). Pairwise

Table 2. Mean baseline values and changes 2 hours after administration of each fluid type.

Parameter	Fluid type	*n*	Baseline value (95% CI)	Comparison of baseline values (*P* value)*	Change at peak dose (95% CI)	Effect of fluid type over time (*P* value)†
Hematocrit (%)	Crystalloid	25	49.6 (47.4–51.8)	.53	−6.1‡ (−4.5–−7.7)	.01
	Colloid	25	47.5 (45.3–49.7)		−9.7‡ (−7.4–−11.9)	
Pulse rate (beats/min)	Crystalloid	25	120 (114–126)	.34	−12§ (−6.2–−17.8)	.37
	Colloid	25	124 (119–128)		−15.8‡ (−9.2–−22.5)	
Systolic blood pressure (mm Hg)	Crystalloid	25	98.8 (94–103.5)	.03	+5.0 (9.7–0.31)	.005
	Colloid	25	88.6 (79.5–97.7)		+20.4‡ (12.3–24.5)	
Diastolic blood pressure (mm Hg)	Crystalloid	25	81.0 (76.1–86.0)	.04	−4.2 (−9.4–+1.0)	.07
	Colloid	25	73.4 (66.0–80.8)		+11 (−2.5–24.5)	
Pulse pressure (mm Hg)	Crystalloid	25	17.8 (16.3–19.3)	.15	+9.4‡ (6.9–12.0)	.02
	Colloid	25	15.4 (12.3–18.5)		+14.6‡ (0.7–2.0)	
Cardiac index (L/min · m^2)	Crystalloid	25	2.27 (2.11–2.44)	.47	+0.64‡ (0.47–0.80)	.02
	Colloid	25	2.18 (1.95–2.41)		+1.0‡ (0.73–1.3)	

* Significance in Student's *t* test comparing the two groups at baseline.
† Significance of effect of the interaction of time (baseline and at 2 h) and fluid type (crystalloid or colloid) in a repeated-measures ANOVA model.
‡ $P < .0001$ (comparison between baseline and peak values for each fluid type).
§ $P < .001$.

analysis did not show any one fluid to be superior to the others (table 2).

In all groups there was a marked increase in mean cardiac index. The mean (range) increases in cardiac index (L/min · m^2) at 2 hours were as follows: 0.9% saline, +0.77l (+0.6 to +0.94); Ringer's lactate, +0.51 (+0.23 to +0.8); gelafundin, +0.79 (+0.39 to +1.2); and dextran 70, +1.3 (+0.89 to +1.6). Dextran 70 was associated with a significantly greater increase than Ringer's lactate ($P = .01$).

Mean hematocrit values fell significantly at 2 hours following infusion in all four groups, by 16% of baseline levels (baseline mean hematocrit, 48.6%; after 2 hours, 40.6%). Infusion of dextran 70 was associated with a significantly greater relative fall in mean hematocrit value at 2 hours than that with each of the other fluid types (table 1 and figure 1). There was no significant difference between the other fluids.

In a pooled comparison of crystalloids and colloids, patients who received colloid infusions had greater increases in mean hematocrit, systolic blood pressure, pulse pressure, and cardiac index values than did crystalloid recipients (table 3 and figure 2).

Subsequent responses. There were no differences between the four groups in the occurrence of shock after the study period or in the requirements for further infusions of crystal-

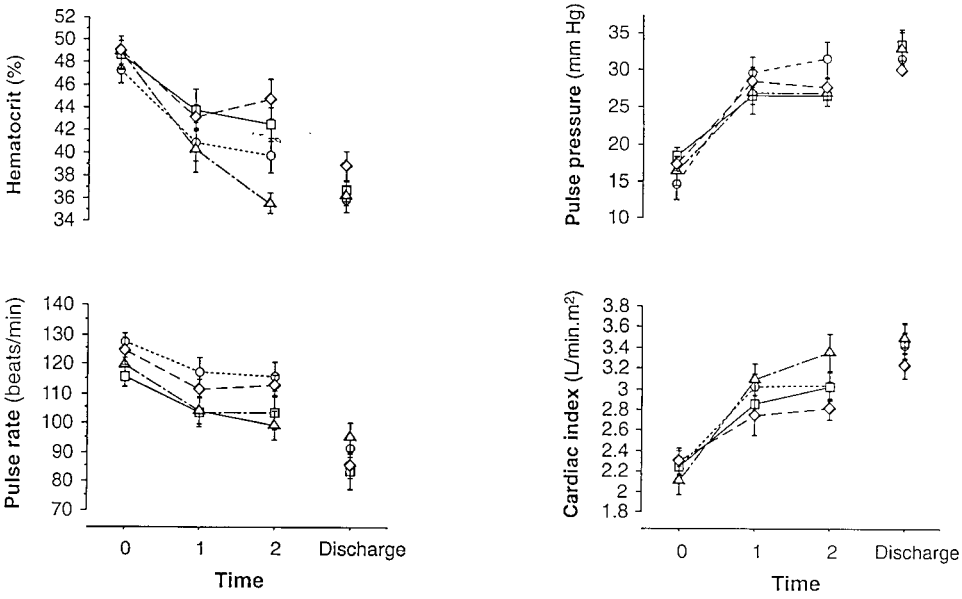

Figure 1. Changes in the hematocrit, pulse rate, pulse pressure, and cardiac index values over time (hours) in each treatment group (*dashes/diamonds*, Ringer's lactate; *straight line/squares*, 0.9% saline; *dots/circles*, gelafundin; and *dots/dashes/triangles*, dextran 70). Data points are means ± SE.

Table 3. Further outcome variables.

Parameter	Fluid type	*n*	Values: median (range)	*P* values: Comparison of 4 groups*	Post hoc pairwise comparisons of effects of fluid types (Bonferroni-corrected): Ringer's lactate	Gelafundin	Dextran 70
Further colloid infusions (mL)	0.9% Saline	12	0 (0–400)	.70	.99	.99	.99
	Ringer's lactate	13	0 (0–400)			.99	.99
	Gelafundin	13	0 (0–600)				.99
	Dextran 70	12	0 (0–4,300)				
Further crystalloid infusions (mL)	0.9% Saline	12	0 (0–800)	.16	.30	.22	.90
	Ringer's lactate	13	200 (0–1,060)			.99	.99
	Gelafundin	13	200 (0–1,540)				.99
	Dextran 70	12	125 (0–1,000)				
No. of episodes of shock	0.9% Saline	12	1 (1–2)	.46	.99	.70	.67
	Ringer's lactate	13	1 (1–3)			.40	.99
	Gelafundin	13	1 (1–3)				.98
	Dextran 70	12	1 (1–3)				
Hours in shock	0.9% Saline	12	1.5 (1–18)	.36	.99	.99	.99
	Ringer's lactate	13	5 (1–18.5)			.99	.99
	Gelafundin	13	7 (1–29.5)				.99
	Dextran 70	12	2.8 (1–20)				

* Significance in Kruskall-Wallis test comparing the four recipient groups.

loids or colloids (table 3). There were no treatment-attributable side effects reported during the study; in particular, there was no increased bleeding tendency noted clinically in any group, and no dermatological problems were noted. None of the physicians felt it necessary to break the code and change fluid management. No patients required diuretic therapy for clinically detected fluid overload. All patients made a full recovery following supportive fluid therapy alone and were discharged to home.

Hematologic variables. There were no significant changes in mean platelet count, reticulocyte count, and WBC count between admission and discharge, and there was no difference between the four fluid groups in this respect (table 4). Mean hematocrit values decreased over the hospital stay in all four fluid groups, though there was no significant difference in the extent of these decreases between groups.

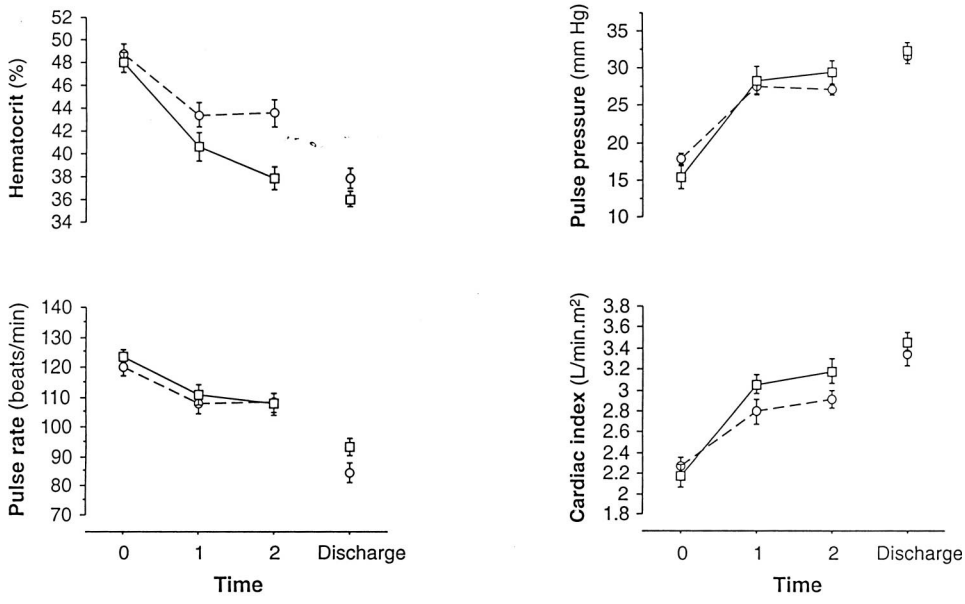

Figure 2. Changes in the hematocrit, pulse rate, pulse pressure, and cardiac index values over time (hours), by fluid type (*dashes/circles*, crystalloid; *straight line/squares*, colloid). Data points are means ± SE.

Table 4. Hematologic variables: mean baseline values and changes at discharge in recipients of the four fluid types.

Parameter	Fluid type	Baseline value (95% CI)	Comparison of baseline values (*P* value)*	Change at peak dose (95% CI)	*P* values: Post hoc pairwise comparisons of effects of fluid types over time (Bonferroni-corrected): Ringer's lactate	Gelafundin	Dextran 70	Overall effect of fluid type over time†
Platelet count ($\times 10^9$/L)	0.9% Saline	35 (13–58)	.06	+32 (−19–+84)	.99	.99	.99	.52
	Ringer's lactate	30 (23–37)		+35‡ (12–58)		.99	.99	
	Gelafundin	46 (28–64)		+16 (−13–+44)			.91	
	Dextran 70	23 (14–31)		+46 (4.8–88)				
Reticulocytes (%)	0.9% Saline	0.32 (0.16–0.48)	.74	+0.16 (0.03–0.45)	.99	.99	.99	.56
	Ringer's lactate	0.27 (0.16–0.38)		+0.39 (0.01–0.77)		.99	.99	
	Gelafundin	0.26 (0.14–0.38)		+0.2 (0–0.4)			.99	
	Dextran 70	0.22 (0.08–0.36)		+0.2 (0–0.4)				
Hematocrit (%)	0.9% Saline	49.1 (45.9–52.3)	.60	+12.4§ (9.2–13.9)	.99	.99	.99	.75
	Ringer's lactate	50.2 (45.3–52.3)		+10.1# (6.4–15.1)		.99	.99	
	Gelafundin	46.8 (43.9–49.8)		+11.4§ (7.4–15.3)			.99	
	Dextran 70	48.3 (44.2–52.4)		+12.5§ (8.4–16.7)				
WBCs ($\times 10^9$/L)	0.9% Saline	6.3 (4.4–8.3)	.57	+1.3 (−3.7–+1.4)	.99	.99	.99	.74
	Ringer's lactate	5.6 (3.9–7.27)		+0.3 (−1.7–+2.2)		.99	.99	
	Gelafundin	6.2 (3.5–8.9)		+0.6 (−1.6–+2.8)			.99	
	Dextran 70	5.5 (3.3–7.75)		−0.45 (−2.4–+1.4)				

* Significance in one-way ANOVA comparing the four groups at baseline.
† Significance of effect of the interaction of time (baseline and at 2 h) and fluid type (0.9% saline, Ringer's lactate, gelafundin, or dextran 70) in a repeated-measures ANOVA model.
‡ $P < .01$.
§ $P < .0001$ (comparison between baseline and peak values for each fluid type).
# $P < .001$.

Discussion

Dengue fever is the most common cause of pediatric hospital admission during the rainy season in many parts of Southeast Asia, but there are few data from controlled trials on the most appropriate treatment regimen. The general introduction of intensive intravenous fluid replacement in DSS more than 25 years ago led to a marked reduction in the mortality rate in the best pediatric centers, from ~20% to 2%. However, there has been no consensus on which intravenous fluid should be used. The widely quoted WHO guidelines of 1974, updated in 1986, 1994, and 1997, recommend that Ringer's lactate or isotonic saline solution (20 mL/kg) be infused as quickly as possible. For cases of continued or profound shock (pulse pressure of <10 mm Hg), the WHO recommendations state that colloids may be substituted at dosages of 10–20 mL/(kg · h) [8, 9].

One of the major management difficulties in DSS is to correct hypovolemia rapidly, without precipitating volume overload. This is particularly difficult in peripheral health care facilities, where, in Vietnam and many other tropical countries, most patients with DHF initially present. Iatrogenic fluid overload, coupled with the ongoing endothelial leak, may also contribute to the risk of death in cases of DHF. It is unclear whether colloids would provide a wider therapeutic window in cases of DSS.

Crystalloids have a considerably shorter intravascular residence time than colloids and may precipitate pulmonary edema if the systemic increase in capillary permeability also affects the pulmonary microcirculation [11]. Pulmonary edema has been observed in several autopsy studies of fatal dengue, often following extensive fluid resuscitation [5, 12].

There has been much debate about the optimal means of fluid replacement in a number of diverse conditions, but there is little evidence on which to base firm recommendations [13–19]. In one prospective study of trauma patients, colloids were shown to stabilize the hemodynamic profile faster and required significantly lower resuscitation volumes than did those patients resuscitated with crystalloids. Of particular interest was the significantly increased incidence of adult respiratory distress syndrome in those treated with Ringer's lactate [13]. In other examples of hypovolemic circulatory collapse, it has been suggested that colloids may be superior to crystalloids as replacement fluids, causing less fluid overload and pulmonary edema. Conversely, one recent meta-analysis suggested that mortality is increased among critically ill patients treated

with colloids [20], whereas a second contemporary review reached the opposite conclusion [21].

Most patients recruited into controlled trials have been adults undergoing cardiac or aortic surgery or with septic shock. It may not be possible to extrapolate the results from such patients to the specific situation in children with DSS. The effects of a fluid infusion in cases of DSS are dependent on the extent to which the fluid can remain within the intravascular space and the osmotic pressure generated. This will be influenced by the molecular mass of the infusate, the size of the presumed "pore" in or around the endothelial cells, and in the case of colloids, by the colloid osmotic pressure.

Dextran 70 has an average molecular mass of 70,000 Da; the molecular mass of gelafundin is 35,000 Da. These solutions have a longer intravascular residence time than the crystalloids, and by increasing the colloid osmotic pressure, they may draw extravasated fluid back into the intravascular compartment. It has been estimated that 2–4 times the volume of crystalloids may need to be infused to achieve the same degree of resuscitation [14]. However, in DSS the extra volume of crystalloid required to achieve adequate cardiovascular stability may exacerbate the ongoing fluid leakage.

The management of DSS is a delicate balancing act between adequate resuscitation and overzealous replacement, often in circumstances where full monitoring is not available. In this study of 50 children with DSS there were potentially important differences in the immediate hemodynamic response following treatment with different fluid-replacement regimens. Dextran 70 was associated with a significantly faster improvement in hematocrit values and cardiac output than were the other three solutions. When results with dextran 70 and gelafundin were pooled, the two colloid solutions caused significant improvement in hematocrit, blood pressure, and cardiac index values, in comparison with those associated with the crystalloid solutions.

These data suggest that cardiovascular stability can be better restored in grade-III DHF by the use of colloids. Early use of colloids in grade-III DHF may reduce the volume of fluid that is required to achieve cardiovascular stability and potentially may lessen the risks of subsequent fluid overload and pulmonary edema. There would be major cost implications of such a conclusion. The differential cost of the fluids studied in this trial are considerable; in Vietnam, the cost in United States dollars for a single 500-mL bottle of each fluid is as follows: 0.9% saline, $0.50; Ringer's lactate, $2.00; dextran 70, $8.00; and gelafundin, $5.00.

There were no evident differences between 0.9% saline and the more complex and expensive Ringer's lactate in this small trial. There would seem to be no reason to use this or any other quasi-"physiological" fluid in acute resuscitation for dengue shock. It is possible that with large controlled trials a subset of patients may be identified who would benefit particularly from an initial infusion of colloid, i.e., potentially those with grade-III DHF with a pulse pressure of $\leqslant$10 on admission.

This study was not designed to identify such a subset or demonstrate significant differences in episodes of recurring shock, requirement for further fluids, or death. Whilst it would not be appropriate on the basis of this study to change current recommendations, the findings do suggest that there may be important differences between crystalloids and colloids. The question of which fluid regimen is optimal in terms of cost-effectiveness for DSS should be addressed in large-scale randomized, controlled trials, and treatment recommendations should be made on the basis of the results.

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References

1. Nimmanitaya S, Halstead SB, Cohen SN, Margiotta MR. Dengue and Chikungunya virus infection in man in Thailand. I. Observations on hospitalised patients with hemorrhagic fever. Am J Trop Med Hyg **1969**;18:954–71.
2. Halstead S. Dengue viruses. In: Gorbach SL, Barlett JG, Blacklow NR, eds. Infectious diseases. Philadelphia: WB Saunders, **1992**:1830–41.
3. Innis BL. Dengue and dengue hemorrhagic fever. In: Porterfield JS, ed. Exotic viral infections. London: Chapman & Hall, **1995**:103–46.
4. Kurane I, Ennis FA. Immunopathogenesis of dengue virus infections. In: Gubler DJ, Kuno G, eds. Dengue and dengue hemorrhagic fever. Oxon, United Kingdom: CAB International, **1997**:273–90.
5. Bhamarapravati H, Tuchinda P, Boonyapaknavik V. Pathology of Thailand hemorrhagic fever: a study of 100 autopsy cases. Ann Trop Med Parasitol **1967**;61:500–10.
6. Suwanik R, Tuchinda P, Tuchinda S, et al. Plasma volume and other fluid space studies in Thai hemorrhagic fever. J Med Assoc Thailand **1967**; 50:48–66.
7. Pongpanich B, Kumponpant S. Studies of dengue hemorrhagic fever. V. Hemodynamic studies of clinical shock associated with dengue hemorrhagic fever. J Pediatr **1973**;83:1073–7.
8. Technical Advisory Committee. Dengue hemorrhagic fever: diagnosis, treatment, prevention, and control. Geneva: World Health Organization, **1997**.
9. Nimmanitya S. Workshop on the epidemiology and laboratory diagnosis of dengue fever, dengue hemorrhagic fever, and Japanese encephalitis. Geneva: World Health Organization, **1994.**
10. Vaughn DW, Nisalak A, Kalayanarool S, et al. Evaluation of a rapid immunochromatographic test for diagnosis of dengue virus infection. J Clin Microbiol **1998**;36:234–8.
11. Shoemaker WC, Kram HB. Crystalloid and colloid fluid therapy in resuscitation and subsequent ICU management. In: Kox WJ, Gamble J, eds. Fluid resuscitation. London: Bailliere Tindall, **1995**:509–44.
12. Burke T. Dengue hemorrhagic fever: a pathological study. Trans R Soc Med Hyg **1968**;62:682–92.
13. Modig J. Effectiveness of dextran 70 versus Ringer's lactate in traumatic shock and adult respiratory syndrome. Crit Care Med **1986**;14:454–7.
14. Skowronski GA. Hypovolaemic shock. In: Oh TE, ed. Intensive care manual. 3rd ed. London: Butterworths, **1990**:371–4.
15. Shoemaker WC. Comparison of the relative effectiveness of whole blood transfusions and various types of fluid therapy in resuscitation. Crit Care Med **1976**:4:71–8.

16. Virgilio RW, Rice CL, Smith DE, et al. Crystalloid vs. colloid resuscitation. Is one better? A randomised clinical study. Surgery **1979**;85:129–39.
17. Hauser CJ, Shoemaker WC, Turpin I, et al. Oxygen transport responses to colloids and crystalloids in critically ill surgical patients. Surg Gynecol Obstet **1980**;150:811–6.
18. Haupt MT, Rackow EC. Colloid osmotic pressure and fluid resuscitation with hetastarch, albumin, and saline. Crit Care Med **1982**;10:159–62.
19. Rackow EC, Falk JL, Fein A, et al. Fluid resuscitation in circulatory shock: a comparison of the cardiorespiratory effects of albumin, hetastarch, and saline solutions in patients with hypovolemic and septic shock. Crit Care Med **1983**;11:839–50.
20. Cochrane Injuries Group Albumin Reviewers. Human albumin administration in critically ill patients: systematic review of randomised trials. BMJ **1998**;317:235–9.
21. Hankeln KB, Beez M. Hemodynamic and oxygen transport correlates of various volume substitutes in critically ill in-patients with various aetiologies of haemo-dynamic instability. Int J Intensive Care **1998**; 5:8–14.