Initial fluid resuscitation for children with dengue shock syndrome: a systematic review

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Background: Currently, there is no standard recommendation of fluid resuscitation in dengue hemorrhagic fever (DHF)/dengue shock syndrome (DSS). The types of fluid as initial choice for resuscitation are still questionable. It is important to review what type of fluid is used for clinical outcome improvement.

Objective: To assess the effectiveness and safety of fluid for initial resuscitation of DSS in children.

Methods: Randomized control trials (RCTs) of initial fluid resuscitation in 1-15 years-old DSS children were researched. Characteristics of the study (design, methods of randomization, and withdraws/dropouts), participants (age), intervention (type, dose and duration, and fluid after the ending of intervention), outcomes (types of outcome measures, timing, and adverse events), and results were extracted from three selected RCTs.

Results: Moderate DSS had no significant difference between each type of crystalloids and colloids in volume of rescue colloid and pulse pressure recovery time (PPRT). In severe DSS, colloids had significantly less median PPRT than crystalloids. Additionally, no difference was found in the incidence of allergic reaction from all the RCTs in both moderate and severe DSS.

Conclusion: In moderate DSS, there is no significant difference between crystalloids (Ringer’s lactate solution/normal saline solution) and colloids (dextran/hydroxyethyl starch/gelatin) in the initial fluid resuscitation. The decision in choosing the appropriate type of fluid depends on the physician’s judgment. Some data suggest colloids as the fluid of choice for the initial resuscitation in severe DSS, but there is no significant evidence to support this data. Moreover, any type of colloid is not significantly different from one another. The decision in choosing fluid also depends on the physician’s judgment.

Keywords: Children, dengue hemorrhagic fever, dengue shock syndrome, fluid resuscitation, pulse pressure.

Dengue is one of the most infectious human viral diseases transmitted by arthropod vectors, caused by four viral serotypes in the genus Flavivirus, family Flaviviridae. Its principal vectors are Aedes mosquitoes, such as A. aegypti and A. albopictus. Dengue viral infection ranges in the clinical spectrum from asymptomatic, fever with constitutional symptoms (dengue fever; DF), hemorrhagic manifestation alone, or with shock (dengue hemorrhagic fever (DHF)/dengue shock syndrome (DSS)). DF is self-limited with supportive treatment. DHF/DSS may need aggressive fluid resuscitation and close monitoring to prevent fatal consequences.

The World Health Organization (WHO) scheme classifies symptomatic dengue virus infections into three categories; undifferentiated fever, DF, and DHF. DF is clinically defined as an acute febrile illness with two or more manifestations (headache, retro-orbital pain, myalgia, arthralgia, rash, hemorrhagic manifestations, or leukopenia) and occurs at the same location and time as other confirmed cases of dengue fever. A case must meet all four of the following criteria to be defined as DHF: fever or history of fever lasting two to seven days, hemorrhagic tendency shown by a positive tourniquet test or spontaneous bleeding; thrombocytopenia (platelet count: 100x10^3/mL or less); and evidence of plasma leakage shown either by hemoconcentration with substantial changes in serial measurements of packed-cell volume, or by the development of pleural effusions or ascites, or both [1, 2].
DSS is a medical emergency. Early fluid resuscitation is required to maintain hemodynamic stability and adequate organ perfusion. In current practice, there is no standard recommendation of fluid resuscitation in DHF/DSS. Theoretically, colloids offer more advantages over crystalloids in patients with increased vascular permeability due to their ability to distribute immediately within the intravascular compartment and to increase plasma oncotic pressure [3]. However, the benefit of colloids in this clinical setting is still controversial and several medical institutions still support the initial use of isotonic crystalloids for resuscitation. The WHO recommends rapid administration of normal saline solution (NSS) or Ringer’s lactate solution (RLS) while actively monitoring the hematocrit level, and preserving colloids for refractory or recurrent shock [4].

Both the Thai Ministry of Public Health and Indian Pediatric Advance Life Support guidelines also suggest the use of isotonic crystalloid solution as the first choice for intravenous fluid resuscitation [5, 6]. In this article, we describe the current concept of epidemiology and pathophysiology of DSS, and then assess the effectiveness and safety of fluid for initial resuscitation of DSS in children. With limited medical supplies and labor in primary care centers, general practitioners will benefit from this systematic review to manage efficiently DHF/DSS in a critical setting.

Epidemiology and pathophysiology

Dengue is an important infectious disease, causing major concern for public health in many parts of the world especially in South and Southeast Asia, the Western Pacific, and central and South America. It is now being reported in other tropical regions [7]. Over half of the world’s population lives in areas at risk of infection. Annually there are an estimated 50-100 million cases of DF and 250,000 to 500,000 cases of DHF in the world [8]. This disease is one of the leading causes of hospitalization and death in children in the high prevalent area of dengue infection. World Health Organization reported at least 22,000 deaths in WHO / WPRO (Western Pacific Regional Office)/ SEARO (South-East Asia Regional Office) meeting on DengueNet implementation, December 2003, mainly among children. Most deaths were attributed to inappropriate fluid resuscitation [9]. In Thailand, DHF was first recognized in Bangkok in 1958. Since then, dengue infection incidence has increased from 9/100,000 in 1958 to 189/100,000 in 1998, with the largest reported incidence of 325/100,000 in 1987. Dengue has thus become a severe and intractable public health problem in Thailand [10].

The severity of dengue infection does not relate to age or gender. There were not significant differences in age-specific dengue infection rate observed by Fisher [11]. Bongsebanhu-phubhakdi et al. [12] also found that age and gender of patients did not correlate with severity of dengue infection. As we know, early increasing D-dimer in the febrile stage suggested disseminated intravascular coagulation and secondary fibrinolysis in dengue infection. Positivity of the D-dimer test in dengue-infected patients was more significant for severity prediction [12, 13].

Poor nutritional status had been evaluated whether related to severity of dengue infection. Thisyakorn et al. [14] previously demonstrated that most patients with DHF are not undernourished.

The current global warming crisis presents a challenge. It is evident that global warming and the resulting climate change have a direct relationship with dengue infection. Climate-related natural disasters may enhance the dynamics of human-mosquito contact [15-17]. In considering in global warming, it can be predicted that the rate of dengue viral infection will increase. Furthermore, it will be found in areas not at risk of infection before.

Although both primary and secondary dengue infections can cause DHF, it frequently associates with secondary dengue infection. This has suggested a role for heterologous antibodies in enhancing viral uptake and replication of Fc (Fragment, crystallizable)-receptor bearing cells, so called antibody-mediated immune enhancement [18]. Some hypothesis suggested that the virulence of the serotype of dengue virus play a role in DHF. Another concept was combination of both hypothesis as the accepted cause of DHF [19].

The main mechanisms of DHF/DSS are increasing vascular permeability leading to plasma leakage and bleeding tendency. Changes in blood pressure including diminished cardiac output and low central venous pressure occur as DSS worsen. Shock is not due to congestive heart failure but from venous pooling. With increasing cardiovascular compromise, diastolic pressure rises towards the systolic and pulse pressure narrows. Finally, a decompensation occurs and both pressures disappear abruptly [20].
Methods

We searched for randomized controlled trials (RCTs) of initial fluid resuscitation in children with DSS. We defined DSS by WHO criteria and compared the outcome of initial resuscitation among different types of fluid. We paid attention to children aged 1-15 years. Using our search strategy on electronic databases: Cochrane Library, MEDLINE (1966-2008), ISI Web of Knowledge (1993-2008) and Scopus (1823-2008), we found 568 trials. After two independent reviewers screened titles and abstracts of these papers 17 trials were deemed relevant. We included RCTs that showed outcomes in aspect of requirement of rescue colloid (further colloid needed after finishing each study fluid), volume of rescue colloid used, pulse pressure recovery time, or improvement of hematocrit. The included trials had to show any adverse effects during resuscitation. Difference in dosage, duration, frequency, and rate of administration were not considered. Finally, only three trials from 17 trials were eligible. The procedure of the search is shown in Fig. 1.

The following information was extracted from three RCTs, as shown in Table 1. These are characteristics of the study (design, methods of randomization, and withdraws/dropouts), participants (age), intervention (type, dose and duration, and fluid after the ending of intervention), outcomes (types of outcome measures, timing, and adverse events), and results. Unpublished data were requested from authors when necessary.

We assessed the methodological quality of all three included RCTs with the scale adapted from Cochrane Handbook for Systematic Reviews of Interventions [24]. Additionally, the well-known Jadad five-point scale was used for objectively convenient communication. The statistical analysis was planned for relative risk with 95% confidence interval (CI) and standardized mean difference with 95% CI. However, this could not be performed due to unacceptable methodological and clinical heterogeneity.

![Fig. 1 Result of the search.](image-url)
<table>
<thead>
<tr>
<th>Study</th>
<th>Wills et al. [23]</th>
<th>Ngo et al. [22]</th>
<th>Dung et al. [21]</th>
</tr>
</thead>
<tbody>
<tr>
<td>Participants</td>
<td>Children aged from 2 to 15 years old presenting directly to the hospital with clinical DSS. Participants were grouped into group 1, moderate group (PP &gt; 10 and &lt; or = 20 mmHg); n = 383, and group 2, severe group (PP ≤ 10); n = 129.</td>
<td>Children aged from 1 to 15 years old presenting to the hospital with clinically diagnosed DHF grade III or IV.</td>
<td>Children aged from 5 to 15 years old presenting to the hospital with clinically diagnosed DSS.</td>
</tr>
<tr>
<td>Number</td>
<td>512</td>
<td>230</td>
<td>50</td>
</tr>
<tr>
<td>Location</td>
<td>The pediatric ICU at the Hospital for Tropical Diseases in Ho Chi Minh city, Vietnam.</td>
<td>The ICU of Dong Nai pediatric hospital in Ho Chi Minh city, Vietnam.</td>
<td>Pediatric intensive care unit at the center for tropical diseases, Ho Chi Minh city, Vietnam.</td>
</tr>
<tr>
<td>Exclusion</td>
<td>Not described.</td>
<td>Children were severe hemorrhagic manifestations at presentation for whom transfusion seemed likely to become necessary. Children with chronic disorder.</td>
<td>Not described.</td>
</tr>
<tr>
<td>Interventions</td>
<td>Each child received 15 mL/kg body weight of the allocated fluid over a one-hour period, followed by 10 mL/kg over the second hour.</td>
<td>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 20mL/kg over 15 minutes, followed by a second bolus of 20mL/kg over the following hour. All solutions were infused at a constant rate of 20 mL/kg for the first hour, followed by 10 mL/kg for the subsequent hour.</td>
<td>All solutions were infused at a constant rate of 20 mL/kg for the first hour, followed by 10 mL/kg for the subsequent hour.</td>
</tr>
<tr>
<td>Primary outcomes</td>
<td>Requirement of rescue colloid.</td>
<td>1) Initial pulse pressure recovery time, 2) Occurrence and timing of subsequent episode of shock.</td>
<td>1) Duration of shock, 2) Number of episodes of shock.</td>
</tr>
<tr>
<td>Secondary outcomes</td>
<td>1) Time taken to achieve initial cardiovascular stability, 2) Time taken to achieve sustained cardiovascular stability, 3) Volume of rescue colloid required, 4) Total parenteral fluid required, 5) Pattern change in hematocrit, 6) Number of days in the hospital, 7) Adverse effect: clinical bleeding, severity of vascular leakage, allergic type reaction.</td>
<td>1) Hematocrit level, 2) Pulse rate after first hour of resuscitation, 3) Total volume of dextran, 70 required after first hour of resuscitation, 4) Total volume of intravenous fluid administration until full recovery, 5) Complications of the fluid therapy.</td>
<td>1) Percent change in hematocrit, 2) Cardiac output, 3) Vital status (blood pressure (mmHg), pulse rate (beats/min), body temperature (°C)), 4) Pulse pressure (mmHg).</td>
</tr>
</tbody>
</table>
Results

Requirement of rescue colloid after initial study fluid

This outcome was evaluated in two trials (Wills et al. [23] and Ngo et al. [22]). The requirement of rescue colloid had different measurement for each trial in two points of views, duration after completing initial study fluid and criteria of requirement.

In the study by Wills et al. [23], rescue colloid was distributed in two phases as follows. Initial phase “phase-immediate” after patients did not recover at the end of study fluid, and subsequent phase “phase-later” phase after patients who initially recovered but became worse later. It was founded that number of patients receiving hydroxyethyl starch (HES) that required the initial phase of rescue colloid was significantly less (0 from 129) than dextran (5 from 126) (p=0.05) in moderate group. However, there was no significant difference in the severe group. For subsequent phase, no significant difference was found in both moderate and severe groups. Combining the initial and the subsequent phase of rescue colloid as “any rescue colloid” showed no significant difference in both moderate and severe groups. The results in the study by Wills et al. [23] are shown in Table 2.

The results of the study by Ngo et al. [22] are shown in Table 3. We noted that there was no significant difference in the number of patients who required rescue colloid.

Volume of rescue colloid

The term “volume of rescue colloid” means the volume of rescue colloid over the admission, excluding initial study fluid. This outcome was evaluated as a secondary outcome by Wills et al. [23] and Ngo et al. [22], while it was not evaluated by Dung et al. [21].

The results in the study by Wills et al. [23] are shown in Table 4. The amount of volume of rescue colloid was recorded in all participants, including patients who did not require rescue colloid. The proportion of patients who did not receive rescue colloid was more than a half. As a mentions, the median of total rescue colloid was 0 mL/kg in all types of fluids, and was concluded as no significant difference between each type of fluid in both moderate and severe groups (p-value >0.05).

On the other hand, Ngo et al. [22] showed the significant difference in mean volume of rescue colloid. Those who initially received dextran required the least volume of rescue colloid while RLS group required the most.

Pulse pressure recovery time (PPRT)

Pulse pressure (PP) was measured in all three trials for classification the disease severity as moderate or severe. In addition, PP was a parameter that determined the recovery from shock when it returned to normal level. Grouping DSS patients into “moderate” (PP >10, but <20 mmHg) and “severe” (PP <10 mmHg) groups was done in two trials by Wills et al. [23] and Ngo et al. [22].

<table>
<thead>
<tr>
<th>Table 2. Number (%) of patients required rescue colloid after each type of study fluid [23].</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any rescue colloid*</td>
</tr>
<tr>
<td>6% Dextran70</td>
</tr>
<tr>
<td>Moderate group</td>
</tr>
<tr>
<td>Severe group</td>
</tr>
<tr>
<td>For initial resuscitation*</td>
</tr>
<tr>
<td>Moderate group</td>
</tr>
<tr>
<td>Severe group</td>
</tr>
<tr>
<td>For subsequently resuscitation*</td>
</tr>
<tr>
<td>Moderate group</td>
</tr>
<tr>
<td>Severe group</td>
</tr>
</tbody>
</table>

*Any rescue colloid-fluid needed in initial or subsequent resuscitation. *Initial resuscitation-fluid immediately needed because of patients did not meet the recover criteria after the end of study fluid. *Subsequent resuscitation-further fluid needed after patients who initially recovered but become worse in the later.
Wills et al. [23] used this grouping strategy during the step of population allocation. On the other hand, Ngo et al. [22] found their prior disproportionate allocation that made a result in higher mean PP of dextran group compared to other groups. Then, the patients were regrouped into these groups.

Recovery criteria in three trials by Wills et al. [23], Ngo et al. [22], and Dung et al. [21] are shown in Table 5. We noted that the recovery criteria are difference in each trial for assessing recovery from shock.

According to Dung et al. [21], every patient recovered within the period of the initial study fluid (two hours), so no one was included to account for PPRT. Ngo et al. [22] compared median PPRT between “moderate group” and “severe group” and there was a significant difference between median PPRT in these two groups. Median PPRT was 0.5 (range: 0.25-3) hours in the “moderate group” and one hour (range: 0.25-7 hours) in the “severe group” (p-value <0.001). Their using logistic regression analysis to estimate odd ratios of having PPRT more than one hour in each paired-fluid type with controlled pulse pressure, they found a significant difference between the RLS-gelatin pair (OR=5.7, 95%CI =1.4-23.6, p-value = 0.017). In the study by Wills et al. [23], recovery from shock was categorized into the initial and sustained recovery. It was shown that colloid fluid (dextran and starch) had significantly shorter PPRT in initial recovery, but not in sustained recovery.

### Improvement of hematocrit

In all three RCTs, hematocrit level was measured at different times to determine the effect of each fluid replacement in correcting hemoconcentration. Wills et al. [23] measured hematocrit level at admission, hour 2, hour 6, and then every 12 hours until the time of discharge. Ngo et al. [22] measured hematocrit level at admission, hour 1, hour 2, hour 6, and hour 12. Dung et al. [21] measured hematocrit level at admission, hour 1, hour 2, then twice a day until the time of discharge. In the three studies, baseline hematocrit level was measured at the time of admission. While the patients received fluid treatment, maximum reduction in hematocrit level was calculated and recorded.

### Tables

#### Table 3. Number (%) of patients required rescue colloid after each type of study fluid [22].

<table>
<thead>
<tr>
<th></th>
<th>6% Dextran70</th>
<th>Gelatin</th>
<th>Ringer’s lactate solution (RLS)</th>
<th>0.9% normal saline solution (NSS)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of patient (%)</td>
<td>17 (30.9)</td>
<td>15 (26.8)</td>
<td>20 (36.4)</td>
<td>17 (30.4)</td>
<td>0.749</td>
</tr>
</tbody>
</table>

#### Table 4. Median value (90% range) of volume of rescue colloid after each type of study fluid [23].

<table>
<thead>
<tr>
<th></th>
<th>6% Dextran70</th>
<th>6% HES</th>
<th>Ringer’s lactate solution (RLS)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Moderate group</td>
<td>0 (0-17)</td>
<td>0 (0-26)</td>
<td>0 (0-29)</td>
<td>0.11</td>
</tr>
<tr>
<td>Severe group</td>
<td>0 (0-25)</td>
<td>0 (0-33)</td>
<td>-</td>
<td>0.76</td>
</tr>
</tbody>
</table>

#### Table 5. Recovery criteria in each trial.

<table>
<thead>
<tr>
<th>Trial</th>
<th>Recovery criteria</th>
</tr>
</thead>
</table>
| Wills et al. [23] | Initial: PP $\geq$ 25, SBP $\geq$ 80 mmHg, at least two hours  
                  | Sustained: initial criteria plus definitely not need further intervention |
| Ngo et al. [22]  | PP $\geq$ H30 mmHg                                      |
| Dung et al. [21] | PP $\geq$ 20 mmHg                                      |
In the study by Ngo et al. [22], dextran could significantly reduce hematocrit level more than other fluids (dextran: 11.5±3.3%, gelatin: 9.7±3%, NSS: 6.5±2.9%, RLS: 5.7±2.8%, p-value <0.001). This result was supported by a previous study by Dung et al. [21], in which dextran could similarly reduce hematocrit more than other fluids (dextran: 12.8%, gelatin: 7.1%, NSS: 6.6%, RLS: 5.4%, p-value <0.01).

Wills et al. [23] subgrouped patients into two groups (moderate and severe). In the moderate group, dextran could significantly reduce hematocrit more than other fluids (dextran: 25% reduction, starch: 22% reduction, and RLS: 9% reduction, p-value <0.001). In the severe group, dextran could significantly reduce hematocrit level more than starch (dextran: 28% reduction, starch: 25% reduction, p-value <0.001).

**Adverse effects**

**Severity of vascular leakage**

Wills et al. [23] showed no differences among the fluids in terms of severity of vascular leakage that are represented by clinical fluid overload, ultrasonographic findings, and requirement of diuretics. None of the patients required diuretic therapy for clinically detected fluid overload in the Dung et al. and Ngo et al. studies [21, 22].

**Incidence of allergy reaction**

- **Dextran:** In the study by Wills et al. [23], 15 out of 193 patients had severe reactions (transient high fever and rigors without cardio-respiratory compromise) within six hours after receiving therapy. In the study by Ngo et al. [22], one out of 55 patients developed fever and chills shortly after completing therapy.
- **Starch:** In the study by Wills et al. [23], one out of 191 patients had urticarial rash without fever at the end of the infusion.
- **Gelatin:** In the study by Ngo et al. [22], five out of 56 patients developed fever and chills shortly after completing therapy.
- **Crystalloid:** There was no allergic reaction in the three RCTs [21-23].

**Clinical bleeding**

In the study by Wills et al. [23], no significant differences appeared among all types of fluid with regard to clinical bleedings (minor superficial and major soft tissue). None of the bleedings required transfusion therapy. Ngo et al. [22] showed that one patient receiving dextran developed a large hematoma and one receiving gelatin had severe epistaxis requiring blood transfusion.

**Discussion**

This systematic review has several limitations as follows. All our populations in each trial were Vietnamese people. Hence, our results cannot be generalized to all populations. In addition, all trials were financially supported by the same fluid manufacturing company. Hence, the extrapolation from this paper should be considered carefully.

We did not find any strong evidence to specify which fluid was most appropriate for DSS resuscitation. Let us discuss DSS patients in two groups (moderate and severe).

**Moderate group.** From all RCTs studied, we can safely conclude that there were no differences between each type of crystalloid and colloid in response to intravenous fluid therapy in moderate DSS. However, there were data that supported the idea that RLS had less benefit in some aspects. Ngo et al. [22] demonstrated longer PPRT when using RLS compared to gelatin. Wills et al. [23] found that resuscitation using RLS resulted in longer initial PPRT compared to HES and dextran, but there was no statistical difference in sustained PPRT among each group of fluid replacement. Ngo et al. [22] also showed that percent of hematocrit level reduction at one hour was less in the RLS group compared to the other groups. Dextran claimed more significant benefits than gelatin, normal saline solution (NSS) and RLS because of requiring less volume of rescue colloid. However, other fluids that required more volume than Dextran did not significantly cause more complication from fluid overload [22]. Wills et al. [23] demonstrated that the number of patients who required initial rescue colloid was significantly less in the HES group than in the dextran group. However, the significant advantage was minor because of the small proportion of the results. This may be attributed to insufficient sample size. Larger trials are required for further conclusion.

**Severe group.** Ngo et al. [22] found that the median PPRT of the colloid group was significantly less than the crystalloid group. However, the study did not stratify each type of colloid and crystalloid. In the study by Wills et al. [23], the patients did not receive crystalloid for resuscitation, as they concerned about the development of fluid overload without proper advanced respiratory support. Hence, using
crystalloids in this group of patients was considered unethical. The results comparing between HES and dextran was insignificant in respect to the number of patients needed rescue colloid and PPRT.

There were few studies in fluid therapy in DSS and there was no absolute conclusion about definite treatment in initial fluid resuscitation. Therefore, we had to further search for other studies that would help consider the most appropriate solution. Moreover, the adverse reactions, cost and local availability would also be considered.

The international guidelines for management of severe sepsis and septic shock 2008 stated that there was no difference between resuscitating with crystalloid and colloid because of insignificant difference in mortality rate. However, crystalloid resuscitation required larger volume and resulted in more frequent fluid overload to achieve the equivalent outcome to colloid [25]. In addition, the SAFE study, conducted in intensive care unit, found similar mortality rate at 28 days from using 4% albumin and NSS for resuscitation [26]. Though Wills et al. [23] and Ngo et al. [22] showed that initial resuscitation with colloid was better than crystalloid in severe DSS, American Heart Association [27] recommended that all children who are in shock state should receive isotonic crystalloid first. Administration of colloid solution was recommended in case of no clinical improvement after 20–60 mL/kg of crystalloid administration had been completed. Total volume of colloid should be limited to less than 20–40 mL/kg [27].

There is no strong evidence that supports the difference in clinical response among types of colloid. However, all types have risk of inducing anaphylactoid reaction especially for dextran and gelatin [28]. Paul et al. [29] also reported other complications of dextran such as ascites, oliguria, transient prolonged bleeding time and hemodilution. Because of reports about side effect of dextran in aspect of coagulopathy, the clinician should keep careful using dextran in DSS patient. Ellingson et al. [30] found that infusing dextran greater than 1.5 g/kg could prolong bleeding time, impair platelet aggregation and disrupt platelet procoagulant activity. It could also lead to reduction in plasma von Willebrand factor concentration.

In clinical settings, NSS is still widely used. The main advantage of NSS is lowest cost compared to other types of fluid as shown in Table 6, but incidence of hyperchloremic metabolic acidosis is increased. Skellett S et al. [31] found that there were relation between administrating large volume of NSS (infusion rate >40 mL/hr) and the incidence of hyperchloremic metabolic acidosis. In studying about fluid administration in meningococcal septic shock patient, O'Dell et al. [32] found that NSS might not be the cause of hyperchloremic metabolic acidosis and discussed that there were many confounding factors causing acidosis. However, According to the result by Wills et al. [23], RLS is recommended as the initial fluid resuscitation for moderate DSS patients.

**Conclusion**

DSS patients should be separately grouped into moderate and severe groups based on initial pulse pressure due to different severity that may differ in management strategies. In moderate DSS, there is no significant difference between crystalloids (RLS/normal saline solution) and colloids (dextran/HES/gelatin) in the aspect of initial fluid resuscitation. The decision in choosing the type of fluid depends on the physician’s judgment. In severe DSS, although some data suggests colloids as the fluid of choice for initial

<table>
<thead>
<tr>
<th>Fluid product (mL)</th>
<th>Cost per unit (Baht)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal saline (1,000)</td>
<td>33</td>
</tr>
<tr>
<td>5% D/N/2 (1,000)</td>
<td>33</td>
</tr>
<tr>
<td>Ringer lactate (1,000)</td>
<td>57</td>
</tr>
<tr>
<td>Acetar (1,000)</td>
<td>53</td>
</tr>
<tr>
<td>20% Albumin (50)</td>
<td>1,262</td>
</tr>
<tr>
<td>25% Albumin (50)</td>
<td>1,519</td>
</tr>
<tr>
<td>3.5% Haemaccel solution (500)</td>
<td>315</td>
</tr>
<tr>
<td>6% HemoHES (500)</td>
<td>245</td>
</tr>
<tr>
<td>6% Voluven (500)</td>
<td>490</td>
</tr>
</tbody>
</table>
resuscitation, there is no significant evidence strong enough to support this. Moreover, any type of colloid is also not significantly different from one another.

The decision in choosing the type of fluid depends on the physician’s judgment as well.

From current available data, we cannot conclude the best choice of fluid for resuscitating DSS, so further well-designed RCTs are much needed. We suggest stratifying participants’ severity by using pulse pressure, rather than classify them into WHO grades due to high clinical diversity of DHF grade III. We also recommend study of the effect of plasma which is one alternative fluid used to resuscitate crystalloid-unresponsive DSS.

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