CRITICAL CARE IN DENGUE MANAGEMENT

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Abstract. Dengue is one of the re-emerging infections in the Tropics. There is no specific drug to treat this condition. Supportive treatment including hemodynamic optimization, fever control, and prevention end organ injury is the only available treatment. Therefore, every suspected/confirmed dengue patients should be assessed for fluid status. Lactate and bedside ultrasound has been applied to detect plasma leakage early in severe dengue infection. Currently, dynamic parameters (stroke volume variation, pulse pressure variation, inferior vena cava (IVC) collapsibility index, passive leg raising test, and end expiratory occlusion test) predict the fluid responsiveness better than static parameters (central venous pressure, pulmonary capillary wedge pressure). If the patient shows signs of dehydration, the fluid of choice is still crystalloid rather than colloid. Norepinephrine is still the vasopressor of choice. Finally, the target mean arterial pressure (MAP) should be at least 65 mmHg except in chronic hypertension patients who required a MAP of at least 80 mmHg.

Keywords: critical care, dengue, adult

INTRODUCTION

Dengue hemorrhagic fever (DHF) and dengue shock syndrome (DSS) are among the most common causes of hospital admission, death, and disability in children in the Tropics. Recently, the age group of dengue infection has shifted to adolescents and adults. Data from Southeast Asia have shown that the mean age of reported dengue cases has increased from 5-9 years to older children and adults. In Thailand, affected adults over 15 years of age comprise 30-40% of dengue cases (Chareonsook *et al*, 1999; Tantawichien, 2000; Pongsumpan *et al*, 2002; Kularatne *et al*, 2005).

Plasma leakage is the hallmark of severe dengue infection and leads to DSS. Until the present time, there has been no specific treatment for this condition. Hemodynamic optimization is the only mainstay treatment as supportive treatment during this critical period. The aim of this article was to review the most up-to-date knowledge of critical care management focusing on fluid management, choice of vasopressor, and target blood pressure in severe adult dengue infection.

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FLUID ASSESSMENT IN DENGUE PATIENTS

Every patient who is a suspected/confirmed dengue infection should be assessed for volume status as part of hemodynamic optimization. Volume depletion is associated with poor clinical outcome. On the other hand, some suspected/confirmed dengue patients can present with clinical of volume overload. In practice, we define fluid overload condition as a difference between cumulative fluid intake and cumulative fluid output, divided by initial body weight (Bouchard *et al*, 2009). A combination of history taking including medications, physical examination, laboratory testing, and hemodynamic parameters both static and dynamic should still be performed to obtain the best information for fluid assessment.

Clinical variables used for fluid assessment include baseline body weight, history of recent fluid loss, cumulative fluid balance, vital signs, urine

output, capillary refill, and skin turgor. Several trials have shown the limitation of static hemodynamic parameters such as central venous pressure (CVP) and pulmonary capillary wedge pressure in guiding fluid responsiveness (Osman *et al*, 2007). One of the explanations of the limitation of static hemodynamic parameters is heart contractility. At the same CVP, a patient who has normal heart contraction might still be at the steep part of the Frank-Starling curve and still respond to fluid loading. However, a patient who has impaired heart contractility might stay at the plateau phase of Frank-Startling curve and not respond to fluid loading. Therefore, the interpretation of these parameters should be cautious. Dynamic hemodynamic variables including stroke volume or pulse pressure variation, change in vena cava diameter, and passive leg raising test have been introduced as part of clinical decision-making during fluid assessment, and these variables have shown superior results compared with static hemodynamic variables (Feissel *et al,* 2007; Gruenewal *et al,* 2011). However, no study has shown the superiority in major clinical outcome of any particular method. Therefore, a combination of all data of these variables should be used to make a decision on fluid administration.

Recently, blood lactate, which represents global tissue oxygenation, has been introduced into the dengue research field. Thanachartwet *et al* (2016) has studied the role of lactate to predict dengue progression. Plasma lactate was tested on the first day of admission and revealed an area under the curve of 0.84 for identifying severe dengue. At the optimal cutoff value (plasma lactate 2.5 mmol/l), the sensitivity and specificity were 65.0% (95% CI: 40.8-84.6%) and 96.2% (95% CI: 90.5-99.0%), respectively.

Clinical reassessment is one the key concepts of fluid administration. It is becoming apparent that the concept of "one size fits all" cannot apply to fluid therapy in suspected/confirmed dengue patients. The amount of fluid should be based on requirements of the individual.

Careful fluid assessment can be performed many ways depending on the site of care and stage of the disease. We propose the minimum parameters/treatment for fluid administration in Table 1. In the primary care setting, initial fluid management combined with simple bedside physical examination should be applied. In the ICU setting, complex testing such as dynamic hemodynamic parameters should be used. In any setting, we recommend that the clinician/health care personnel should reassess the clinical response as soon as possible (within a few hours) without leaving the bedside. If the patients do not respond within a few hours (possibly within a 6-hour period), we recommend escalate care or transfer out to a tertiary care hospital.

Role of ultrasound for fluid assessment in dengue patients

Ultrasound has recently been introduced into the field of dengue. We can apply ultrasound as a tool for early detection of fluid leakage and for guiding fluid treatment. By lung ultrasound, fluid leakage may be evidenced by the B line sign (sign of interstitial edema) (Fig 1), sign of pleural effusion, or sign of pericardial effusion (Fig 2). By abdominal ultrasound, fluid leakage may be evidenced by gallbladder wall thickness as well as fluid at the hepatorenal or splenorenal pouches. These parameters might be incorporated into WHO warning signs in the future. Parameters obtained from ultrasound such as inferior vena cava (IVC) collapsibility index, IVC distensibility index, IVC variability index, and stroke volume variation can be applied to guide fluid therapy. This avoids unnecessary or overuse of fluid administration.

FLUID OF CHOICE IN DENGUE INFECTION

This section will compare the evidence base of colloid *vs* crystalloid fluid and of balanced crystalloid fluid *vs* non-balanced crystalloid fluid for fluid administration in dengue infection. Unfortunately, there have been few studies that have directly compared fluid type in dengue patients.

Crystalloid *vs* colloid

Colloid has been widely used for fluid therapy in the critical care setting during the past few years

Table 1. Minimum treatment and parameter requirements in dengue patients based on site of care.

Treatments/Parameters	Community setting	Hospital setting	ICU setting
Fluid challenge	✓		
Mental status	✓		
Hemodynamic parameters: HR, BP	✓		
Capillary refill	✓		
Urinalysis	✓		
UOP, fluid balance	✓		
Lactate		✓	✓
Dynamic pressure parameters such as PPV, SVV, IVC collapsibility, PLR testing			✓
Static pressure parameters such as CVP			✓
Echocardiogram			✓
Cardiac output monitoring			✓
ScvO2			✓

BP, blood pressure; CVP, central venous pressure; HR, heart rate; IVC, inferior vena cava; PLR, passive leg raising test; PPV, pulse pressure variation; SVV, stroke volume variation.

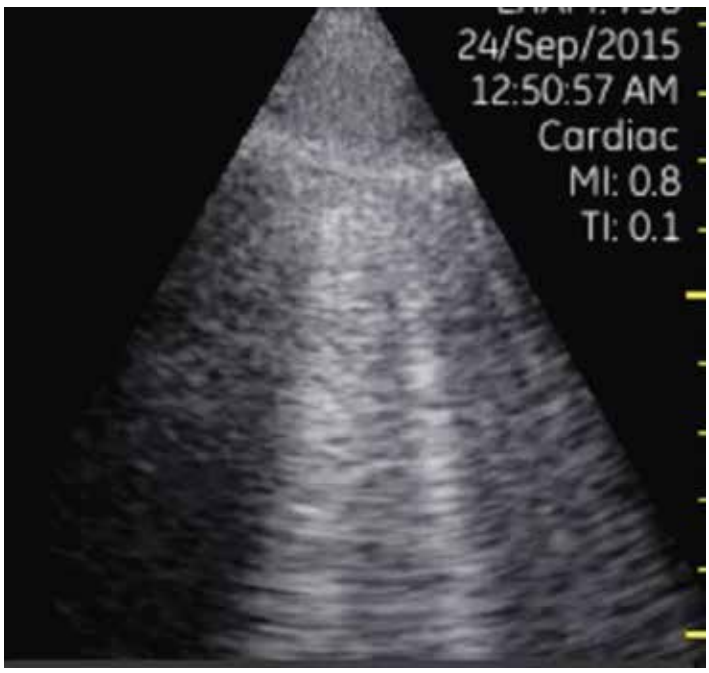

Fig 1–B-line in dengue patients, which is a kind of comet-tailed artifact indicating subpleural interstitial edema.

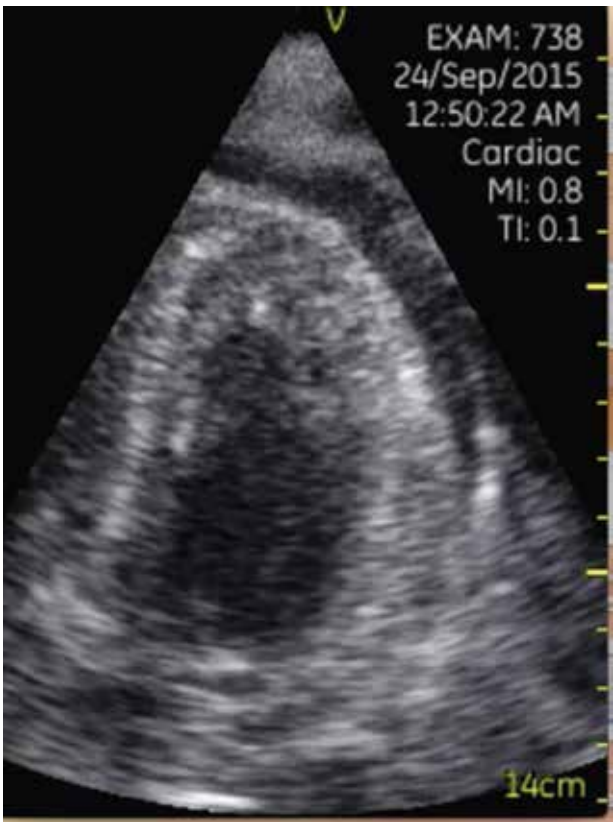

Fig 2–Pericardial effusion due to pericarditis in dengue patients.

(Finfer and Vincent, 2013). One of the main reasons is based on physiologic models. Starling's model assumes colloid can maintain intravascular volume better than crystalloid. The amount of colloid used for fluid resuscitation was expected to be around three times less than the amount of crystalloid (Starling, 1896). However, the assumptions of the Starling's model have been challenged by the endothelial glycocalyx (EG) model. In this model, the vascular integrity is maintained by EG located on the luminal side of vascular endothelium. EG will be directly damaged by process of systemic inflammation and lead to vascular leakage and finally tissue edema. Based on this model, there should be no difference in efficacy among fluid types in holding intravascular fluid when EG has been damaged during process of sepsis. Therefore, the amount of fluid may be more important than the type of fluid to prevent interstitial edema (Varadhan and Lobo, 2010).

Since the publication of two large randomized controlled trials (RCTs), namely, the 6S and CHEST trials 4 years previous, the use of hydroxyethyl starch (HES) has been restricted by regulatory authorities because of its potential for worsening kidney function (Myburgh *et al,* 2012; Perner *et al,* 2012). The 6S trial studied fluid optimization in severe sepsis/septic shock patient. Third generation HES, 6% HES 130/0.4 increased the primary composite end point (dead or dialysis dependent rate on day 90) more than Ringer's acetate (51 *vs* 43%, respectively; p=0.03). Also, the HES group had a higher incidence rate of renal replacement therapy (RRT) than the Ringer's acetate group (22 *vs* 16%, respectively; p=0.04). The CHEST trial studied fluid optimization in ICU patients. There was no difference of mortality rate between HES and saline, but the HES group had a higher incidence rate of RRT than saline group (7 *vs* 5.8%, respectively; p=0.04).

In theory, human albumin is the main protein for maintaining plasma colloid oncotic pressure. It also works as a carrier for several endogenous and exogenous compounds with antioxidant and anti-inflammatory properties. Also, albumin can act as a buffer molecule for controlling acid-base homeostasis (King, 1961; Sudlow *et al,* 1975; Weil *et al,* 1979; Quinlan *et al,* 1998; 2005). The results from large RCTs such as the SAFE study in the ICU setting and the latest ALBIOS study of severe sepsis/septic shock have not shown the benefit of human albumin over crystalloid. In addition, there was no difference of renal outcome between human albumin and crystalloid in both studies (Finfer *et al,* 2004; Caironi *et al,* 2014). It appears to be safe for the kidney to use albumin in the high-risk setting. With high cost and no obvious advantage over crystalloid, human albumin should not be used as the first line therapy.

There are few studies that have compared crystalloids to colloids use in dengue infection. Wills *et al* (2005) conducted a double-blinded RCT of three fluids, Ringer's lactate, 6% dextran 70, and 6% HES, for initial resuscitation in Vietnamese children with DSS. There was no difference in the primary outcome that was rescue colloid administration at any time during the study.

Balanced crystalloid solution *vs* non-balanced crystalloid solution

There are several studies that have addressed the adverse effect of non-balanced crystalloid solution (isotonic saline) on the kidney (Hadimioglu *et al,* 2008; Khajavi *et al,* 2008; Hasman *et al,* 2012). Isotonic saline contains 154 mmol/l of chloride, so its administration with a large volume can result in hyperchloremic metabolic acidosis. This condition can lead to renal vasoconstriction, decreased renal artery flow velocity, decreased renal artery blood flow, afferent arteriole vasoconstriction, and finally decreased glomerular filtration rate (Wilcox *et al,* 1983). Current evidence from three large observational studies has also suggested that the high chloride content of isotonic saline may cause harm, especially to the kidney. A study of 30,994 adult patients undergoing major abdominal surgery found that patients receiving isotonic saline had significantly greater blood transfusion requirements, more infectious complications, and more renal support requirements than those receiving balanced crystalloids (Shaw *et al,* 2012). However, there was no difference in mortality rate between the two groups.

Yunos *et al* (2012) conducted an open-labeled, prospective sequential study comparing between traditional chloride-rich solutions (isotonic sodium chloride, 4% succinylated gelatin solution, or 4% albumin solution) and chloride-restricted fluids (Hartmann's solution, Plasma-Lyte 148 or chloride-poor 20% albumin). After adjusting for confounding variables, the chloride-restricted group had a decreased incidence of acute kidney injury [AKI) [odds ratio (OR)=0.52, $p<0.001$] and reduced use of RRT (OR = 0.52, $p=0.004$). Again, there were no differences in hospital mortality as well as hospital or ICU length of stay. Also, a study by McCluskey *et al* (2013) on postoperative patients showed that the incidence of acute postoperative hyperchloremia was 22%.

Patients with hyperchloremia were found to be at increased risk of 30-day postoperative mortality (3.0 *vs* 1.9%; OR=1.58), have a longer length of hospital stay, and were more likely to have postoperative renal dysfunction (McCluskey *et al*, 2013). These large observational studies suggest that it may be time to consider the use of balanced crystalloid solution as the fluid of choice, especially in metabolic acidosis. However, the SPLIT trial, the largest RCT aiming to compare the effect of balanced crystalloid and non-balanced crystalloid on kidney injury, did not show the difference of AKI incidence within 90 days between Plasma-Lyte 148 solution and isotonic saline (9.6 *vs* 0.2%, $p=0.77$). Moreover, no differences of RRT incidence rate and hospital mortality rate between two groups were found. However, it is noteworthy that the incidence of AKI in this study was quite low, and this low incidence rate might have caused difficulty in demonstrating the effect of isotonic saline on AKI outcome (Young *et al,* 2015). Therefore, it is too early to conclude that isotonic saline has no harmful effect of on kidney function based on only this RCT.

In resource-limited settings such as middle to low income countries, isotonic saline could still be the crystalloid of choice for fluid resuscitation in dengue infection.

Amount of fluid, choice of vasopressor, and target blood pressure in dengue patients

Hemodynamic alteration in severe dengue infection is not the same as in other severe sepsis/septic shock cases. Ranjit *et al* (2007) compared hemodynamic parameters between DSS and severe sepsis/septic shock in 32 patients (16 DSS and 16 severe sepsis patients). The DSS patients presented with narrower pulse pressure (25±8 *vs* 43±8 mmHg; $p<0.01$), less presence of systemic inflammatory response syndrome, (9/16 *vs* 15/16; $p<0.05$), and less requirement of fluid administration (28.5 *vs* 57.5 ml/kg; $p=0.03$).

Since the publication of Early Goal-Directed Therapy (EGDT) study by Rivers *et al* (2001), the concept of protocolized strategy that comprises of fluids, vasopressor, and blood transfusion targeting hemodynamic parameters has been widely adopted (Dellinger *et al,* 2008). The average fluid administration during the first 72 hours in this single-centered study was 13 liters. However, during the past few years, there have been studies that have shown the adverse effect of fluid overload to patient outcome (Bouchard *et al,* 2009). Three large RCTs studies have supported the concept of restricted fluid therapy, namely the PROCESS study (Yealy *et al,* 2014), ARISE study (Peake *et al,* 2014), and ProMISe study (Mouncey *et al,* 2015). These studies compared the mortality between protocolized care and usual care in sepsis patients and showed only 3 to 4 liters of fluid intake during the first 72 hours. All of these three major RCTs also suggested that protocolized therapy and the usual care provided a comparable outcome. This emphasizes the concept that *the amount of fluid to be given should be individualized based on the initial assessment of volume status and clinical background/associated co-morbidities.*

Concerns have been raised about the use of fluid bolus following the Fluid Expansion As Supportive Therapy (FEAST) study by Maitland *et al* (2011). African children who suffered from severe sepsis (mainly malaria) were randomized to receive no fluid bolus, or to receive fluid bolus with either isotonic saline or albumin. At 48 hours, patients who received fluid bolus had higher mortality compared with control patients (relative risk 1.45, $p=0.003$). However, this trial was conducted in resource-limited setting with no access to ventilation to optimize the management of sepsis.

The role of oral fluid administration should be considered in the community setting (Harris *et al,* 2003). This strategy, accompanied by thorough clinical assessment, could decrease the rate of hospitalization. In mild dengue infection, ingestion of fluid in the 24 hours before visiting the clinician was found to be protective against hospitalization after adjusting for distance from health facility, date of symptom onset, and thrombocytopenia (OR=0.74 per each additional glass consumed, $p<0.01$). The most common liquid ingested was water (70%), followed by fruit juice (42%), lemonade (27%), milk (25%), coffee (14%), oral dehydration serum (6%), and tea (2%).

Vasopressor is the essential treatment to achieve the hemodynamic goal after the intravascular volume restoration. Persistent hypotension after initial fluid administration places the patients at risk for organ injuries such as kidney injury, bowel ischemia, and shocked liver. There has been no clinical study to show which vasopressor agents (norepinephrine, dopamine, and vasopressin/terlipressin) is the most effective for prevention or treatment of AKI patients.

A study comparing the efficacy of norepinephrine and dopamine did not show the difference in mortality and AKI incidence between the groups (De Backer *et al,* 2010). However, the use of dopamine in a subgroup of patients with cardiogenic shock from this study was associated with more adverse events such as cardiac arrhythmia.

Vasopressin is another potent vasopressor agent that works at vasopressin receptor of smooth muscle cell. This vasopressor has become more popular in treating shock that is refractory to

norepinephrine (Delmas *et al,* 2005). Compared to norepinephrine, vasopressin increases blood pressure, enhances diuresis, and may lower the rate of AKI progression, but it has neither been proven to enhance survival nor to reduce the need for RRT (Russel *et al,* 2008; Gordon *et al,* 2010).

The Surviving Sepsis Campaign: International Guidelines for Management of Severe Sepsis and Septic Shock: 2012 recommends initial resuscitation with vasopressors to reverse hypotension with a mean arterial pressure (MAP) target of at least 65 mm Hg (Dellinger *et al,* 2013). This recommendation is based on previous studies that have shown no significant difference in lactate level or regional blood flow if the MAP was elevated to more than 65 mmHg in patients with septic shock (LeDoux *et al,* 2000). The kidney is one of the organs prone to compromised blood supply when decreasing MAP. Recently, a large retrospective study shows that a MAP of more than 75 mmHg may be required to maintain kidney function (Dünser *et al,* 2009).

The SEPSISPAM investigator group has conducted a multicentered, open-labeled RCT in patients with septic shock undergoing resuscitation with a MAP of either 80-to-85 mmHg or 65-to-70 mmHg. There was no difference in mortality rate between the two targets MAPs. However, patients in the high-target MAP group with chronic hypertension required less renal-replacement therapy and less doubling of serum creatinine than those in the low-target group (Asfar *et al,* 2014).

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