Perspectives

Revisiting the fluid requirement during the critical phase of dengue: Does it actually follow a bell-shaped curve?

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Abstract

Plasma leakage due to a transient increase in capillary permeability is the hallmark of dengue haemorrhagic fever. There is no specific antiviral agent for dengue. Therefore, the mainstay of management during the plasma leakage phase is the judicious use of intravenous fluid to ensure adequate organ perfusion and to prevent fluid overload. The current practice guidelines for dengue are empirical. They are mostly based on expert opinions. The rates and amounts of fluid to be administered during the critical phase of the disease have not been studied in randomised controlled trials. It is hypothesised that the rate of fluid leakage during the critical phase follows a bell-shaped curve. Based on this concept, both World Health Organisation and Sri Lankan guidelines recommend starting fluid at a lower rate, increasing the rate until the midpoint of the critical phase, and gradually reducing the infusion rate thereafter. However, the authors believe that the more fluid you give during the critical phase, the more will leak out into the third space. Thus, increasing the complications of fluid overload without improving the effective plasma volume. Therefore, administering fluids at an escalating rate may be superfluous and could result in fluid overload.

Keywords: Dengue, critical phase, plasma leakage

Dengue is a mosquito-borne viral infection transmitted mainly by Aedes aegypti and, to a lesser extent, by Aedes albopictus [1]. Dengue virus belongs to the genus flavivirus, and there are four distinct serotypes, DEN-1 to DEN-4 [2]. Dengue is the most important mosquito-borne viral infection globally due to its high morbidity and mortality. It is estimated that 390 million dengue infections occur annually, resulting in 96 million symptomatic cases [3]. Currently, dengue is endemic in tropical and subtropical areas of the globe, spanning over 100 countries [4]. The majority of dengue infections are asymptomatic [5]. The clinical spectrum of dengue ranges from mild self-limiting undifferentiated fever to life-threatening dengue haemorrhagic fever (DHF) and dengue shock syndrome (DSS). Transient increase in vascular permeability and resultant plasma leakage is the
hallmark of DHF [1]. The plasma leakage phase or critical phase (CP) usually lasts 24 to 48 hours [1,6]. There is no specific antiviral agent for dengue. Therefore, the mainstay of management during the CP is to identify the leaking of plasma early and the judicious use of intravenous fluid to ensure adequate organ perfusion and to prevent fluid overload [1]. The current practice guidelines for dengue are empirical due to the lack of research in this field. They are mostly based on expert opinions. According to the World Health Organization (WHO) and Sri Lankan national dengue guidelines, the amount of fluid required for 48-hour CP is the sum of maintenance fluid for 24 hours and a 5% deficit [1,6]. Maintenance fluid for a day is calculated using the Holliday-Seger formula [7]. A fluid deficit of 5% is equal to 50 mL/kg. Therefore, for example, the fluid quota for a 50 kg adult person for the 48-hour CP is 4600 mL. Sri Lankan guidelines recommend the use of a maximum of 50 kg body weight to calculate the fluid quota for adults [6]. However, a similar ceiling for body weight is not placed by the WHO guidelines when calculating the fluid quota [1]. This fluid quota is administered over the 48-hour CP in non-shock patients [1]. Although this fluid quota is widely used in managing patients with DHF, it is seemingly arbitrary. The rates and amounts of fluid to be administered during the critical phase of the disease have not been studied in randomized controlled trials [8].

It is hypothesized that the rate of fluid leakage is slower in the early part of CP and rises until it peaks at around the midpoint, at approximately 24 hours of CP, and then reduces and resolves within about 48 hours from its onset. Kalayanarooj et al. first proposed in 2003 that fluids should be started at a lower rate, continued at an increasing rate up to the mid-time point of CP, and then given at a decreasing rate until CP is over [9]. Since then, this has been adopted by some practice guidelines [1,6]. One review article suggested that the rate of fluid replacement during CP has an inverted “V” shape, which is illustrated in Figure 1 [10]. Based on this concept, both WHO and Sri Lankan guidelines recommend starting fluid at a low rate, increasing the rate until the midpoint of the CP, and gradually reducing the infusion rate (a bell-shaped curve). Nevertheless, whether this concept is empirical or based on scientific work is unclear. Overenthusiastic fluid management will lead to fluid overload, respiratory distress, secondary infections, prolonged hospital stay, and, in some cases, fatalities [11]. Fluid overload has been recognised as an independent risk factor for mortality in children with dengue infection [12]. On the other hand, undertreatment with fluids can result in mortality due to DSS. One observational study done in Sri Lanka reports fluid overload in 12.1% of patients with DHF, and 5.2% had moderate to severe fluid overload when managed according to the Sri Lankan guidelines [13]. The authors have observed that giving fluid at an increasing rate during the initial half of CP in DHF results in complications of fluid overload without an increase in effective intravascular volume. Therefore, considering these observations, we managed patients with DHF, giving fluid that was just sufficient to maintain organ perfusion. We maintained a pulse pressure of more than 30 mmHg and the minimum obligatory urine output of (0.5 mL/kg/hour). Further, fluids were infused at a more or less consistent rate during the CP. With the onset of CP, fluids were started at 100 mL/hour for adults weighing 50 kg or more. However, the fluid infusion rate was increased if the urine output dropped below 0.5mL/Kg/hour, and the rate was decreased when patients were haemodynamically stable with a urine output of more than 0.5 mL/kg/hour.

**Figure 1:** Rate of intravenous fluid in dengue patients with plasma leakage (ml/kg/hour) [Source: Sivakom C et al. Treatment of adults with severe dengue in Thailand. Clin Crit Care 2022; 30: e0005.]
It was not needed to infuse fluids at an incremental pattern during the first 24 hours of CP to maintain haemodynamic stability and adequate urine output. In this cohort, only 3 out of 60 (5%) developed compensated shock (narrow pulse pressure of 30mmHg or less with normal systolic pressure), and none developed DSS (hypotension) with this approach. Compared to the aforementioned observational study, in that study, out of a total of 115 patients with DHF, 25 (21.7%) developed compensated shock. In contrast, 2 (1.7%) developed DSS when managed according to the Sri Lankan guidelines [13].

The person who received 6,300 mL of fluid developed moderately severe fluid overload, but none of the other patients developed any degree of fluid overload. Therefore, we were able to discharge our patients quickly. The median duration of hospital stay after completion of the CP was 20.5 hours, and 34 out of 60 (56.6%) were discharged within 24 hours. Most patients were kept in the ward, after completion of CP, to meet the criteria of platelet rise. Some delays were still due to administrative procedures.

In conclusion, the authors believe that the more fluid you give during CP, the more will leak into the third space, increasing the complications of fluid overload. The administration of fluids at an escalating rate during the initial phase of CP in DHF may, therefore, be superfluous and could result in fluid overload. A more conservative approach where fluid is given at a flat rate starting at 2 mL/kg/hour for an adult weighing 50 kg or more and judiciously adjusting the rate, only when necessary, according to urine output and other vital parameters would be more appropriate to manage CP in DHF. However, further research is required before generalizing this idea.

**Ethical statement**

We used data from an observational study conducted at the University Medical Unit of Teaching Hospital Anuradhapura. Ethical approval was obtained from the ethics review committee of the Faculty of Medicine and Allied Sciences of Rajarata University, Sri Lanka. Informed written consent was taken from all participants.

**References**


