Editorial Response: Resuscitation of Patients with Dengue Hemorrhagic Fever/Dengue Shock Syndrome

Dung and colleagues [1] have provided a valuable impetus to generate new evidence-based studies that might improve methods of resuscitating patients with dengue hemorrhagic fever/ dengue shock syndrome (DHF/DSS). Among infectious diseases, the viral hemorrhagic fevers, particularly DHF/DSS, present the physician with unique pathophysiological disturbances that require customized yet potentially successful resuscitation methods.

Patients with DHF/DSS, who usually are children, predominantly present with fever of several days’ duration and the suddenly occurring signs of blood-volume loss; tachycardia; weak, thready pulse; skin that is cool to the touch; slow venous filling; and decreased urine output. This state may progress to cyanosis, confusion, lethargy, and frank hypotension. The underlying mechanism is rapid appearance of putative “capillary pores” that leak fluid (and, in more severe cases, smaller proteins such as albumin) into interstitial spaces.

Although most patients with DHF/DSS are resuscitated as if they have diarrhea, a more apt therapeutic analogy may be a burn injury or hypovolemia from “third space” loss in surgery. To add to resuscitative problems in DHF/DSS, virtually all patients have ill-defined platelet abnormalities that contribute to altered hemostasis. After a period of sustained hypotension, bleeding—sometimes severe—may develop, particularly in the gastrointestinal tract. The period of increased vascular permeability is characterized by rapid onset and termination. A major complication is fluid overload, leading to pulmonary edema and heart failure.

See article by Dung et al. on pages 787–94.

Following the widespread adoption of resuscitation methods pioneered in Bangkok [2, 3], DHF/DSS case-fatality rates have fallen dramatically in many hospitals in dengue-endemic areas [4]. The strategy in wide use has been to rapidly administer crystalloids while actively monitoring the hematocrit level at the bedside and adding a colloid to the regimen when there is evidence of continuing hypovolemia. Although no surveys of treatment regimens have been published, it is supposed that dextran 70 is the colloid most widely used in DHF/DSS.

The Vietnam study has attempted to answer the age-old question of crystalloid vs. colloid. First, it must be acknowledged in agreement with the authors that the study is under-powered. Even if a slight benefit was demonstrated following initial fluid resuscitation with colloid, what might be the benefit in lives saved when the baseline mortality (on the basis of current World Health Organization [WHO] guidelines) is only 2%? With assumption of an optimistic figure of 5% less mortality, one would need to treat a thousand patients with colloid to have one extra patient survive. If each patient uses only 2 L, this would translate to an extra $15,000 cost per death averted.

When colloids were given immediately in the Vietnam study, as compared with crystalloids, children showed significantly faster improvements in hematocrit, blood pressure, and cardiac index values. However, the difference in cardiac indexes associated with colloids and crystalloids, while statistically significant, is not impressive clinically. Differences in cardiac indexes over a range of 2.8 to 3.2 are clinically unimportant.

Although this study was too small to reliably detect even moderate differences in outcome, even a larger study with the same study design might miss an early clinically important effect of fluid resuscitation. Because outcomes were measured at specified times such as 1 or 2 hours post-infusion, an early effect within the first hour might have been missed. Regardless of whether colloid or crystalloid is superior, if equal volumes are infused, then there is no advantage with regard to fluid overload.

The Vietnam study looked at changes in physiological or laboratory parameters after infusion of a given volume of fluid: 20 mL/kg in the first hour and 10 mL/kg in the second. A preferable design might be to measure the volume of fluid infusion necessary to achieve an endpoint such as a target pulmonary wedge pressure. Such a study would determine the volume of study fluids necessary to reach equal effects and would be best done by emplacing a pulmonary artery catheter and titrating different fluids or different infusion rates to achieve a desired wedge pressure. The time necessary to achieve a satisfactory filling pressure is presumably an important clinical parameter when a patient is anoxic due to hypovolemic shock. In addition, if a euvoletic state can be restored with a minimal replacement volume, this diminishes the risk of fluid overload.

Before recommending invasive procedures, a word of caution. Reports from Southeast Asia of biphasic distribution of deaths due to DHF/DSS may in some instances be explained by nosocomial infections that complicate the use of indwelling intravascular catheters, such as the Swan-Ganz thermodilution catheters that might be used for pulmonary wedge-pressure determination or urinary catheters for monitoring urine output. Sustained, meticulous infection control is an absolute prerequisite to any invasive physiological study. Invasive monitoring studies should be done only to more precisely evaluate treat-
ment protocols that, in turn, lead to resuscitation that can be carried out in real-world conditions.

A future trial might be improved by using more sensitive methods to detect the rate of improvement in physiological parameters such as wedge pressure. If a clear benefit was shown, then a protocol that involved rapid infusion of a colloid very early in the resuscitation might be an interesting strategy. The study could look at different infusion rates within the first hour. This may prove to be more important than what type of fluid is used. The 20-mL/(kg·h) infusion recommended by the WHO Technical Guide is a good bolus of fluid for the first hour, but for a patient with shock there would appear to be no reason why fluid boluses of 2–4 mL/(kg·min) should not be used until blood pressure has stabilized.

The Vietnamese study used isotonic saline with 6% dextran. Of more interest would be small-volume hypertonic saline with or without colloid. There are limited human data (virtually no pediatric trials have been done) on the use of this strategy in traumatic hemorrhagic shock [4–8]. Especially since the patients with DHF have not actually lost body fluid, it would be interesting to evaluate hypertonic-hyperoncotic solutions as plasma-volume expanders to avoid fluid overload. The reviewers know of no pediatric trials of this strategy.

In their admittedly small study, Dung et al. [1] provide evidence that the widely used and relatively more expensive Ringer’s lactate provides no greater benefit than 0.9% saline. As noted by the authors, there are important unanswered questions about the safety of lactate. It has been known for >30 years that D-lactate induces cardiac arrhythmias of neurological origin in experimental animals [9]. It appears that racemic lactate, in wide use, may be better tolerated than D-lactate [10].

There may be significant additional costs associated with the use of dextran 70 rather than crystalloids. A problem is the possibility that dextran contributes to altered hemostasis. The dextrans are known to affect platelet coagulability [11]. Could dextran, particularly if given for more than an initial bolus, cause unrecognized gastrointestinal bleeding and thus contribute to the use of questionable safe blood products such as platelet packs? In the Vietnam study, might a drop in hematocrit associated with dextran have been due to occult gastrointestinal bleeding? Gastrointestinal bleeding in the different groups was not compared.

Intravenous resuscitation fluids were introduced in the 1930s, in the era before modern molecular biology. Their composition has not changed much over the past 40 years. Their use in medical practice reflects more fade than hard data. None of the generally available fluids support functions of normal, much less hypoxic cells. The discovery of blood-borne diseases has made formerly less expensive colloids such as serum albumin generally unavailable. The wide use of blood and platelet transfusions in DHF/DSS in the era of lethal blood-borne agents demands that careful studies be done on the efficacy of use of biologicals and the indications for their use, defined in view of safety concerns.

The study reported by Dung et al. in this issue addresses the need to reevaluate traditional fluid-resuscitation protocols for DHF in light of improved understanding of shock management. The venerable WHO resuscitation protocols have been a tremendous success, saving tens of thousands of lives over the past 30 years. This study allows us to consider the application of modern study design and methods to develop and test even more efficient and effective protocols for the future.

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References