

## Perspective Piece

# Remote-Controlled and Pulse Pressure–Guided Fluid Treatment for Adult Patients with Viral Hemorrhagic Fevers

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**Abstract.** Circulatory shock, caused by severe intravascular volume depletion resulting from gastrointestinal losses and profound capillary leak, is a common clinical feature of viral hemorrhagic fevers, including Ebola virus disease, Marburg hemorrhagic fever, and Lassa fever. These conditions are associated with high case fatality rates, and they carry a significant risk of infection for treating personnel. Optimized fluid therapy is the cornerstone of management of these diseases, but there are few data on the extent of fluid losses and the severity of the capillary leak in patients with VHFs, and no specific guidelines for fluid resuscitation and hemodynamic monitoring exist. We propose an innovative approach for monitoring VHF patients, in particular suited for low-resource settings, facilitating optimizing fluid therapy through remote-controlled and pulse pressure–guided fluid resuscitation. This strategy would increase the capacity for adequate supportive care, while decreasing the risk for virus transmission to health personnel.

## INTRODUCTION

Shock is thought to be a common final pathophysiological pathway to death in Ebola virus disease (EVD) and other high-threat viral hemorrhagic fevers (VHFs) such as Marburg hemorrhagic fever and Lassa fever.<sup>1</sup> Although there are limited data on the frequency, timing, and nature of shock, intravascular hypovolemia resulting from gastrointestinal losses and capillary leak are thought to be the important drivers of shock.<sup>2</sup> Intravascular fluid resuscitation presents a clinical management challenge in VHFs due to the need to restore adequate intravascular volume while avoiding excessive organ edema, in particular pulmonary edema resulting in respiratory failure. This challenge is greatest in resource-limited settings where most of these infections are managed. In these settings limited staff, protective clothing, and appropriate intensive care facilities and equipment render the clinical monitoring and support of patients difficult.

The optimal fluid resuscitation strategy for EVD and other VHFs is currently unknown. However, the well-studied fluid management of shock in severe dengue may be used as a guide.<sup>3,4</sup> Severe dengue is associated with a marked increase in capillary permeability, hemoconcentration, and bleeding. A resulting key clinical feature is a reduction in pulse pressure. Fluid resuscitation in severe dengue needs to balance the risk of volume overload with the risk of undertreating intravascular hypovolemia and shock.<sup>5</sup> For this reason, fluid resuscitation strategies in severe dengue are more conservative than in

sepsis and septic shock.<sup>6,7</sup> Dengue shock syndrome (DSS) mortality is less than 1% when fluid management strategies are restricted, but higher with more liberal fluid regimens.<sup>8</sup> The limited data on hypovolemia and hemoconcentration in EVD are reminiscent of severe dengue,<sup>9,10</sup> although there are several important differences between the two diseases. Dehydration from diarrhea and vomiting, electrolyte disturbances, and acute kidney injury are much more prominent in EVD patients, requiring, if available, plasma electrolyte assessments and correction. However, capillary leakage, the pivotal pathophysiological feature of severe dengue,<sup>5</sup> is also a major feature of EVD and other VHFs.<sup>9</sup>

Fluid resuscitation is a central component in the treatment of both diseases. Early and appropriate intravenous fluid administration is likely to reduce mortality in EVD patients.<sup>11</sup> Treating dehydration and shock adequately while minimizing respiratory compromise is even more challenging in EVD and other VHFs, given the need to wear personal protective equipment (PPE) commonly in hot and humid ambient conditions without air-conditioning during patient care. Treatment in a bio-secure emergency care unit, such as the one developed by the Alliance for International Medical Action, allows for patient care without having to wear full PPE suits, but their deployment at sufficient scale during a large outbreak will be challenging. The use of PPE in tropical non-air-conditioned environments severely limits the time healthcare workers can spend at the patient bedside due to heat stress,<sup>12</sup> reducing of frequency and extent of clinical assessments, including hydration and intravascular volume status. The management of dehydration and shock is therefore particularly difficult in EVD. Here, we propose a novel approach for fluid resuscitation and maintenance in EVD and other VHFs that circumvents some of these issues.

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**Proposed approach.** We propose an innovative method in the care of VHF patients applicable in resource-poor settings, albeit also relevant for well-resourced settings, to optimize fluid therapy, while decreasing the risk for virus transmission to health personnel, and increasing the capacity for adequate supportive care. It is based on a remote-controlled and pulse pressure-guided fluid management algorithm. The intervention consists of the use of wireless blood pressure measurement devices, remote-controlled infusion systems, large bags of resuscitation fluids, and an algorithm for fluid resuscitation which is similar to the pulse pressure-guided fluid resuscitation of patients with DSS. Because there are no data on the most appropriate fluid resuscitation strategy in patients with EVD or other VHFs, this algorithm may require modification on the basis of emerging data. Given the pathophysiology of EVD,<sup>1</sup> adequate fluid therapy that restores the circulating volume while avoiding fluid overload and resulting pulmonary edema is likely to be critical.

**Pulse pressure-guided fluid resuscitation.** Fluid therapy in DSS is guided by the systolic blood pressure, the pulse pressure, and changes in hematocrit over time. There are several algorithms available; a guideline primarily directed toward children with DSS has been developed by the WHO and is readily available online.<sup>7</sup> In the absence of hypotension, fluid therapy is adjusted to maintain the pulse pressure above 20 mmHg. Infusion rates are lower than those used in septic shock. If the pulse pressure target is achieved, the infusion rate is reduced under continued monitoring of the pulse pressure and hematocrit. Other parameters of adequate tissue perfusion, such as urine output, are also important in guiding fluid management in DSS. We propose using a similar pulse pressure-guided fluid management algorithm to prevent or reverse shock in patients with EVD and other VHFs with the aid of remote-controlled noninvasive blood pressure monitoring and a remote-controlled volumetric infusion system (Figure 1). The setup also includes a pulse oximeter

wireless peripheral probe to monitor oxygen saturation. Several brands for remotely controlled volumetric infusion pumps are on the market, as well as for wireless blood pressure and oxygen saturation monitoring.

A suggested preliminary algorithm for fluid resuscitation (Table 2), based on the treatment of DSS, can serve as the starting point, but this should be evaluated in a pilot study and adapted as necessary. This algorithm requires at least hourly assessment of the systolic blood pressure and pulse pressure, but more frequently in hemodynamically unstable patients. Estimating fluid losses through vomiting and diarrhea will generally be difficult, unless the patient can stand and be weighed daily, or volumes can be reliably measured (fluids collected in buckets). Estimated fluid losses should be replaced over a 24-hour period. In patients with severe bleeding, blood loss will have to be estimated and transfusion provided when necessary and if feasible. A cumulative fluid balance should be closely monitored to avoid overhydration and pulmonary edema, but again, this is often difficult to achieve in resource-limited settings. Also, additional measures for the assessment of shock in patients with VHFs, such as peripheral perfusion (skin), echocardiographic assessment of vena cava collapsibility, sequential hematocrit measurements, and assessment of urine output, will often be difficult in the treatment of VHFs, for reasons previously described. The results of daily electrolyte assessment ( $\text{Na}^+$ ,  $\text{K}^+$ ,  $\text{Ca}^{2+}$ , and  $\text{Mg}^{2+}$ ) should, if available, inform the composition of the intravenous fluids as adequate. Thus, whereas optimal management of the shocked patient requires detailed clinical and laboratory measures, where resources are limited and patient contact is difficult, the proposed remote blood and pulse pressure-guided approach may be safer and more effective than current management.

**Choice of intravenous resuscitation fluids.** In patients with DSS without severe hypotension, there is no longer an indication for colloids, and isotonic crystalloids are

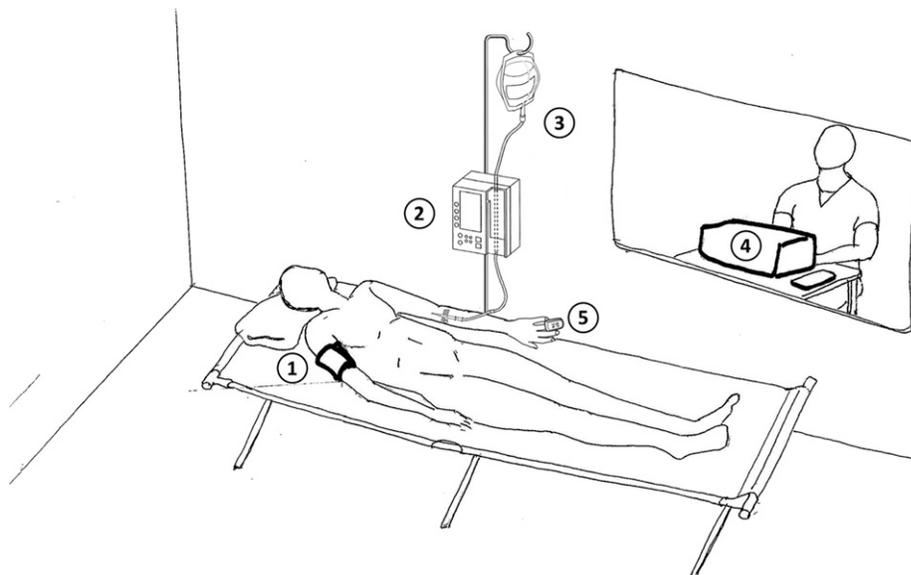


FIGURE 1. A schematic figure of the proposed patient management setup. 1 = automated blood pressure device; 2 = automated volumetric infusion set; 3 = fluid bag, if available with increased volume; 4 = remote readout of blood pressure parameters and infusion rate, and remote control of volumetric infusion set; 5 = pulse oximeter wireless peripheral probe.

TABLE 1  
The composition of commonly available crystalloids for intravenous fluid resuscitation

	Ringer's lactate	Hartman's solution	Ringer's acetate	Balanced solution	Normal Saline
Na <sup>+</sup> (mmol/L)	130	131	130	140	154
K <sup>+</sup> (mmol/L)	4	5	5	5	
Ca <sup>++</sup> (mmol/L)	3	2	1		
Cl <sup>-</sup> (mmol/L)	109	111	112	98	154
Lactate (mmol/L)	28	29			
Acetate (mmol/L)			27	27	
Osmolality (mOsm/L)	273	278	276	295	308

recommended.<sup>4,7,13,14</sup> In patients with DSS and severe hypotension, however, there is still some discussion around the use of colloids. Patients with EVD usually have more severe gastrointestinal symptoms and losses, and therefore electrolyte disturbances such as hypokalemia. The compositions of some of commonly available crystalloids are summarized in Table 1. Ringer's lactate and Hartman's solutions are comparable; however, Ringer's lactate solution has the practical advantage of being packaged in large-volume bags of up to 5 L, although these are not available in all countries. The use of large-volume bags will reduce the frequency of patient contact.

**Safety aspects for healthcare personnel.** The safety of healthcare personnel treating VHF patients is of critical concern. The use of remote-controlled equipment could reduce the risk of nosocomial infection. With the recent availability of a highly effective Ebola vaccine, this risk has been reduced considerably in the care for EBV patients. Vaccines are available for dengue and yellow fever, but not for all other causes of VHFs. Remote-controlled equipment includes automated blood pressure measurements, which can be operated and read out from outside the high-risk area. In addition, the use of volumetric infusion systems is proposed, where the infusion rate can be read-out outside the high-risk area, and changes in the rate can be made remotely. Also, infusion fluid bags of up to 5 L can be used, instead of the usual 0.5 or 1 L. Together, these factors will allow healthcare staff to deliver high-quality care to a larger number of patients. In addition, it will reduce the risk of disease transmission by facilitating less frequent direct patient contact, without jeopardizing frequent patient monitoring.

## SUMMARY

Remote-controlled and pulse pressure-guided fluid resuscitation with a standard fluid algorithm could improve the outcome of VHF, including EBV, while allowing treatment of larger number of patients, freeing up healthcare worker time for other patient interventions, and reducing the frequency of

contacts between patients and healthcare staff. In addition, it could be easily standardized across facilities and thus reduce the inter-facility variability in the supportive care management of patients. This approach should be field-tested to assess its feasibility, acceptability, and safety in a pilot implementation, followed by a definitive trial to assess effectiveness. If beneficial, this intervention could then be rolled out on a large scale in VHF-affected regions.

Received November 27, 2020. Accepted for publication December 17, 2020.

Published online February 16, 2021.

Acknowledgment: We thank Jureeporn Duanguppama for her help in preparing Figure 1.

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TABLE 2

## Suggested infusion rate adjustments

Blood pressure	Infusion rate
BP not measurable	Fluid bolus 20 mL/kg
Systolic BP < 90 mmHg	15 mL/kg/hour
Systolic BP ≥ 90 mmHg but PP < 10 mmHg	12 mL/kg/hour
10 mmHg ≤ PP < 20 mmHg	8 mL/kg/hour
PP ≥ 20 mmHg	2–3 mL/kg/hour

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