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REVIEW

Treatment of adults with severe dengue in Thailand

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ABSTRACT:

Key measures for improving the survival rate in dengue shock patients are an early and appropriate diagnosis and treatment together with close monitoring by early provision of appropriate types, rates, objectives, and limits (TROLs) of fluid therapies, especially in the critical phase of the disease. The hemodynamic assessments to guide fluid resuscitation should mainly rely on clinical signs, hematocrit along with non-invasive monitoring tools. These concepts aim to maintain adequate oxygen delivery to the vital organs, to prevent a prolonged shock stage and subsequent organ failures. Diagnosis and treatment for poor tissue perfusion should be initiated as early as possible from the onset of the cytokine cascade-induced plasma leakage and disruption of the glycocalyx layer of the vascular endothelial cells.

Keywords: Treatment, Adult, Severe dengue, Dengue shock, Thailand

INTRODUCTION

Mortality rate of dengue

Dengue cause by Dengue virus which is a mosquito-borne, positive-sense single-stranded RNA virus of the genus Flavivirus in the family Flaviviridae. Currently, the mortality rate among dengue cases worldwide is 0.5 - 5% [1]. In Thailand, the mortality rate of dengue cases is around 0.1% [2], which is less than the reported rate worldwide [3].

Key concepts in improving survival rates of dengue shock patients

Key measures for improving the survival rate in dengue shock patients are an early and appropriate diagnosis and treatment in conjunction with close monitoring of patients with severe dengue, that have plasma leakage e.g., pleural effusion, ascites and pericardial fluid, shock, or bleeding, by early provision of appropriate types, rates, objectives, and limits (TROLs) of fluid therapies, especially in the critical phase of the disease (Table 1). These concepts aim to maintain adequate oxygen delivery to the vital organs, to prevent a prolonged shock stage and subsequent organ failures. Diagnosis and treatment for poor tissue perfusion should be initiated as early as possible from the onset of the cytokine cascade-induced plasma leakage [4] and disruption of the glycocalyx layer of the vascular endothelial cells [5].

Presentation of dengue shock and discriminating between dengue shock syndrome and septic shock

Severe plasma leakage in dengue may lead to hypovolemic shock (i.e., dengue shock syndrome, DSS). This is different from septic shock, which is mainly due to vasodilation. Clinical characteristics that discriminate between DSS and septic shock are shown in Table 2. The best treatment for DSS is to prevent development of prolonged shock. Dengue patients with prolonged shock, due to inadequate resuscitation, develop multi-organ failure, and have a very poor outcomes, with mortality rates over 90% [6]. The dengue patients with shock may present with a systolic blood pressure > 90 mmHg. Impaired consciousness is often seen, like a decreased responsiveness to painful stimuli such as blood drawings. Mottled, cold and clammy skin may be detected on the hands and/or feet with or without decreased central pulse intensity. Patients may develop rapid and deep breathing (i.e., Kussmaul's breathing) due to a lactic acidosis or bleeding disorders, which may be difficult to estimate due to concealed internal hemorrhage that is enhanced by thrombocytopenia and disseminated intravascular coagulation (DIC).

Clinical course of the dengue

The course of dengue follows three phases: febrile, critical, and recovery (or convalescent) as shown in more detail in Table 1 [7].

Causes of death in dengue shock patients

The most common cause of death in dengue shock patients is hypovolemic state caused by plasma leakage and/or bleeding with inadequate or delayed fluid and/or blood resuscitation [4]. Mortality in the dengue shock patient in the intensive care unit (ICU) is significantly associated with a decreased level of consciousness, the lowest platelet count, and the number of organs that have failed [6].

Causes of shock in dengue patients who have received initial fluid resuscitation and/or blood components

In the dengue patient who is still shock despite initial fluid resuscitation and/or blood components transfusion, the following reasons may be the cause [11,12] :

1. Prolonged hypovolemic state due to severe plasma leakage and/or uncontrolled bleeding, with inadequate resuscitation leading to DIC, acute liver failure, acute renal failure, acute respiratory failure, mental status change or encephalopathy.
2. Concomitant septic shock
3. Worsening of myocardial function, possibly due to prolonged hypovolemic shock and/or myocarditis

MONITORING DENGUE PATIENTS IN THE INTENSIVE CARE UNIT [11]

General recommendations

On the basis of evaluation including history, physical examination, and/or complete blood count and hematocrit, the clinician should confirm if the patient has dengue, if yes, the phase of dengue (table 1), check for presence of warning signs, hydration and hemodynamic status, and if the patient requires ICU admission.

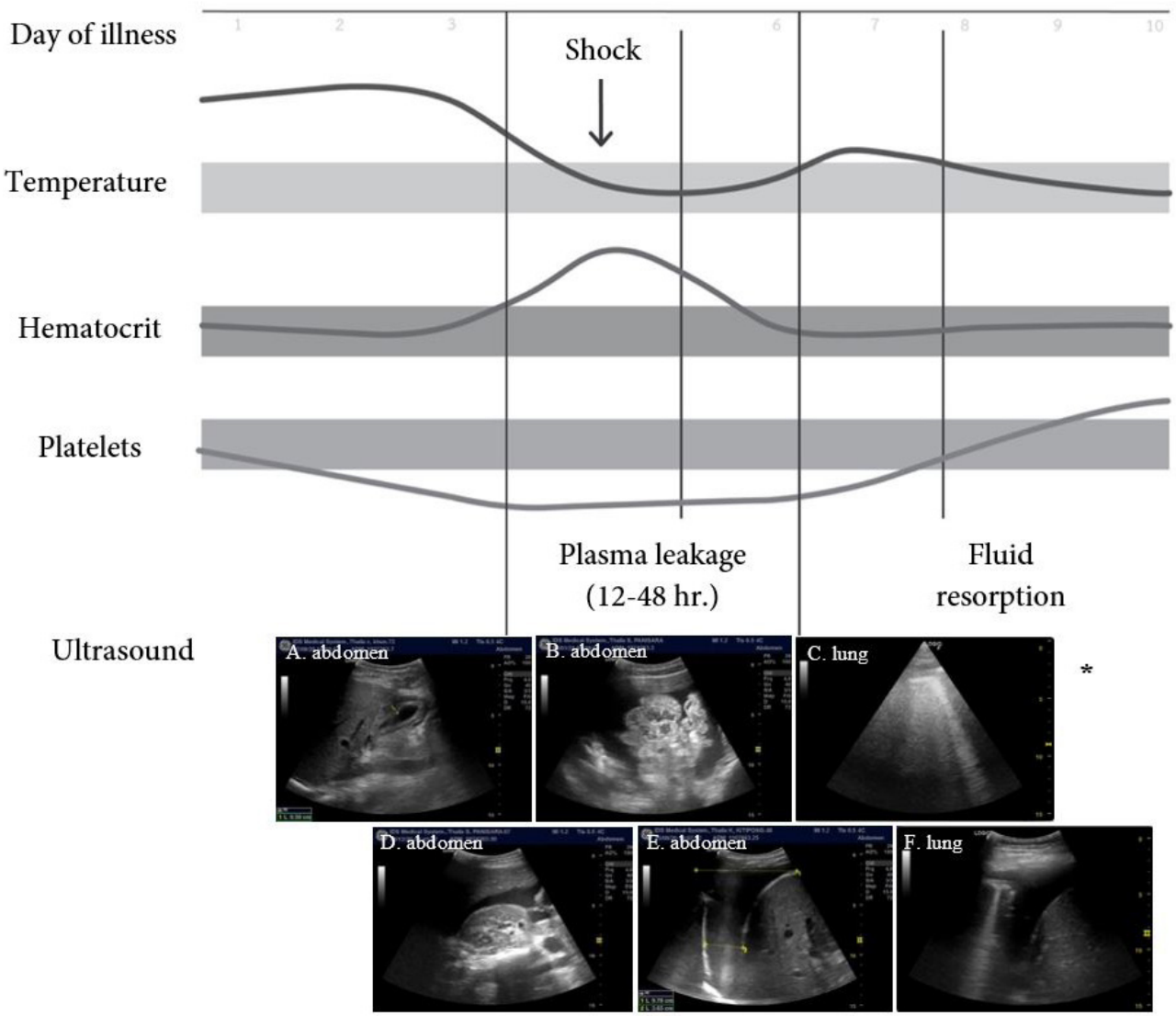
The hematocrit in the early febrile phase could be used as the patient's own baseline. Decreasing white blood cell and platelet counts make the diagnosis of dengue very likely. Leukopenia usually precedes the onset of the critical phase and indicates disease severity. A rapid decrease in the platelet count that is concomitant with a rising hematocrit compared to the baseline is suggestive of progression to the plasma leakage/critical phase of dengue [11]. If the patient survives the 24–48 hours of critical phase, a gradual reabsorption of extravascular compartment fluid takes place during the recovery phase in the following 48–72 hours [7].

A dengue patient, in the plasma leakage/critical phase that does not improve despite initial fluid resuscitation, should be monitored in the ICU. The ICU admission for the dengue patients are shown in Table 3. Blood pressure should be monitored frequently, i.e. every 5 to 30 minutes as per the disease severity. Urinary catheterization is necessary in the patient with shock, targeting a urine output of at least 0.5 mL/kg/hour. Intraabdominal pressure measurement (indirectly by measurement of the bladder pressure) could be useful in the dengue patient with suspected intra-abdominal hypertension. The hemodynamic assessment to assess the severity of plasma leakage for guiding fluid resuscitation should mainly rely on non-invasive methods [13,14], depending on the available tools and expertise of the physician. Temperature gradients between core to ambient temperature and extremities, skin mottling score and capillary refill time have been validated and shown to be reproducible signs for monitoring tissue perfusion. [15,16]. Great care should be taken when inserting a nasogastric tube because it may cause severe hemorrhage and may obstruct the airway. A lubricated orogastric tube will avoid this trauma. If the patient's condition worsens or if they have cardiac arrest, invasive monitoring using central venous /or arterial cannulation may be required. To reduce the risks of bleeding and complication, ultrasound should be used to guide catheter placement, and thrombocytopenia along with coagulopathy should be corrected before the procedure.

KEY MESSAGES:

- Early and appropriate diagnosis and treatment together with close monitoring are key measures for improving the survival rate in dengue shock patients to prevent a prolonged shock stage and subsequent organ failures.
- The hemodynamic assessments to guide fluid resuscitation in dengue shock patients should mainly rely on clinical signs, hematocrit along with non-invasive monitoring tools.

Table 1. Febrile, critical and recovery phases in dengue [7]



Ultrasound check points:
Abdomen: gall bladder wall thickening, free fluid in right and left lateral paracolic gutter, ascites
Lung: pleural effusion, increase of positive B-lines (3 or more) in a longitudinal plane between two ribs in 12-field approach

Phase of disease	Febrile phase 2-7 days	Critical phase 24-48 hours	Recovery phase 2-4 days
Symptoms and potential complications	Dehydration, high grade fever, anorexia, nausea, vomiting, facial flushing, skin erythema, generalized body ache, myalgia, arthralgia, headache, neurological disturbances, and positive tourniquet test	Shock from plasma leakage, severe hemorrhage, and organ impairment Presence around the time of defervescence usually lasting 24-48 hours on the 4th to 7th day of illness	Usually, the presence of the 'ABCD' (i.e., Appetite, Bradycardia, Convalescence rash, and Diuresis) Hypervolemia (only if intravenous fluid therapy has been used excessively and/or has been extended into this period) due to the gradual reabsorption of the extravascular compartment fluid, which takes place in the following 48-72 hours. Respiratory distress from massive pleural effusion and ascites will occur if excessive intravenous fluids have been administered.

*Ultrasound findings in dengue: A, gall bladder wall thickening; B, free fluid in right lateral paracolic gutter; C, B-lines from lung ultrasound; D, free fluid in hepatorenal fossa; E and F, pleural effusion from lung ultrasound.

Table 2. Discriminating clinical presentations, laboratories, hemodynamic and physiologic responses, and managements between dengue shock syndrome and septic shock [8]

Concept	Dengue shock syndrome	Septic shock
	Clinical presentations	
SIRS	Less	More
Mental status	Better	Worse
Temperature	Normothermic	Usually has fever
Tachycardic response	Sub-optimal until circulatory decompensation is advanced	Usually seen early, reflects degree of circulatory problem
Spontaneous bleeding	More	Less
	Laboratories	
Platelet count	Less	More
	Hemodynamic and physiologic responses	
Endothelial permeability	- Increased vascular permeability without morphological damage to the capillary endothelium due to a cytokine cascade - Possible role for disruption of the surface glycocalyx	- Disruption of the glycocalyx
Type of shock	- Hypovolemic shock - Vasoconstrictor state with a narrow pulse pressure (i.e., cold shock)	- Vasodilatory shock, relative hypovolemia - Wide pulse pressure (early stage) (i.e., warm shock)
Rate of fluid leakage	- Slow with intermittent periods of increased microvascular dysfunction [9] - Very rapid fluid replacement may result in pulmonary edema and cardiac instability	- Faster fluid loss
	Managements	
Fluid volumes at initial resuscitation	Less initial fluid resuscitation and minimizing complications (10 – 20 mL/kg), ideal to individualise	More initial fluid resuscitation (20 – 30 mL/kg)
Transfusion decision	In the critical phase of dengue when the Hct. level is "normal" or lower than expected for the degree of shock or the hemodynamics fail to normalize despite the initial use of crystalloids/colloids in resuscitation	Hb. < 7 mg/dL (i.e., restrictive transfusion strategy) [10]
Steroid	Less benefit	More benefit shock not responsive to fluid therapy
Cardiac involvement	- Functional myocardial impairment - Myocardial dysfunction (systolic and diastolic) due to prolonged uncorrected hypovolemic shock - Myocarditis - Electrical abnormalities: bradyarrhythmia, ST segment changes, T- wave abnormalities	- Myocardial depression (i.e., decreased ejection fraction) - Modulated by ventricular dilation to maintain stroke volume - Sepsis-induced cardiomyopathy

Abbreviations: SIRS, systemic inflammatory response syndrome; Hct., hematocrit; Hb., hemoglobin

Table 3. Criteria for considering admission to the intensive care unit for the dengue patient

Detection of signs of severe plasma leakage or shock such as:
- Cold, clammy, pale skin, or a capillary refill time over 2 seconds
- Weak or absence of the peripheral or central pulse even though blood pressure is normal
- Systolic blood pressure below 90 mmHg or mean arterial pressure values below 70 mmHg (systolic pressure drop below 40 mmHg from baseline in patients underling with hypertension [17])
- Urine output less than 0.5 mL/kg/hour
- A patient with signs of dyspnea or gasping or a patient using a mechanical ventilator
- Bleeding affecting blood pressure or inability to control bleeding by applying pressure or using hemostatic agents
- A pregnant woman or a patient with a body mass index greater than 35, both of which make it difficult to assess the volume status and may make it difficult to gain vascular access during shock.
- An elderly patient over 60 years of age or a patient who has comorbidities including heart disease, liver disease, or chronic renal failure, or who is taking anticoagulants. (N.B. This is at the physician's discretion).

Additional laboratory tests that may be considered in the intensive care unit

In the intensive care setting, additional laboratory tests for consideration are shown in Table 4.

Table 4. Additional laboratory tests to be considered in the intensive care setting

Laboratory test	Purpose
Hematocrit	- To guide fluid resuscitation - To guide sufficient provisioning of blood components - Serial monitoring • A hematocrit value is 50% or higher than patient's baseline hematocrit that was greater than or equal to 20% indicates plasma leakage • A hematocrit that is lower than patient's baseline hematocrit or a normal hematocrit in the patient with shock indicates bleeding
Complete blood count and coagulation profile	- To diagnose DIC and effects of dengue virus on the fibrinolytic system e.g., prolonged PTT, PT; decreases of platelet counts, fibrinogen level, antithrombin III; increases of D-dimer, fibrin degradation products. - To monitor DIC
Liver function tests and INR	- To diagnose liver failure - To monitor liver failure
Blood urea nitrogen and creatinine	- To diagnose acute kidney injury - To monitor renal function
Electrolytes and calcium	- To diagnose electrolyte imbalance (e.g. hyponatremia or hypocalcemia) - To monitor electrolyte imbalance
Blood glucose	- To diagnose hypo/hyperglycemia - To monitor hypo/hyperglycemia
Chest radiography	- To diagnose fluid overload and pulmonary edema (i.e., cardiothoracic ratio > 0.55, increased pulmonary vascular markings, a bat's wings appearance, Kerley B lines, or small lung volume due to pleural fluid and/or ascites)
Venous blood gas with base excess	- To assess metabolic acidosis - A decrease in base excess was associated with increased mortality in dengue shock patients [18].
Blood lactate	- To aim for a lactate clearance [($lactate_{initial}$ - $lactate_{delay}$) / $lactate_{initial}$] x 100% by 10% over 1 to 2 hours [19,20].
Hemoculture	- To aid diagnosis of suspected septic shock

Abbreviations: PT, prothrombin time; PTT, partial thromboplastin time; DIC, disseminated intravascular coagulation; INR, international normalized ratio

RESUSCITATION FLUID IN THE INTENSIVE CARE UNIT [21-24]

Type of resuscitation fluid are shown in Table 5.

Table 5. Type of resuscitation fluid in dengue shock patients

0.9% sodium chloride	0.9% sodium chloride is a resuscitation fluid with a concentration of 308 mOsm/L. It contains 154 mmol/L of sodium (Na) and chloride (Cl) each while the serum chloride level is approximately 95-105 mmol/L. Compared to human serum, 0.9% sodium chloride has a nearly 10% higher Na concentration and 50% higher Cl concentration. 0.9% sodium chloride can be used in the initial resuscitation for dengue shock. However, 0.9% sodium chloride in large quantities causes hyperchloremic metabolic acidosis and increase major adverse kidney events compared to the balanced-crystalloid group in an ICU setting [25].
Ringer's lactate / Ringer's acetate	Ringer's lactate has a sodium content of 130 mmol/L, a chloride content of 109 mmol/L, and a lactate content of 28 mmol/L with an osmolarity of 273 mOsm/L. Ringer's acetate has a sodium content of 131 mmol/L, a chloride content of 110 mmol/L, and an acetate content of 30 mmol/L with an osmolarity of 270 mOsm/L. Both types of fluid should be used carefully in dengue patients because the incidence of hyponatremia is 9.7 times higher in dengue patients compared with non-dengue patients and more prevalent in dengue shock patients [26,27]. Ringer's acetate can be converted to bicarbonate even in liver failure [28]. This might be helpful in patients with metabolic acidosis.
Albumin	In a dengue shock patient who has received crystalloid resuscitation and shows no improvement in hemodynamics, iso-oncotic albumin may be considered for use because the pathology of the vascular endothelium in this stage is similar to that of a septic shock patient [4,5]. Iso-oncotic albumin maintains a microvascular fluid dynamic [29], which is obtained by maintaining plasma oncotic pressure [30], endothelial glycocalyx integrity, and vascular permeability via sphingosine-1-phosphate-dependent pathways [31]. Hyper-oncotic albumin has not been studied for its benefits or its adverse effects in dengue shock patients. However, hyper-oncotic albumin has the same renal protection effect as iso-oncotic albumin [32] and is might be considered using in dengue shock patients with interstitial edema.
Fresh frozen plasma	Fresh frozen plasma is used as an alternative colloid in a dengue patient with circulatory failure who does not respond to the initial crystalloid resuscitation [33], especially in a dengue shock patient with prolonged prothrombin time or activated thromboplastin partial time. However, administration of fresh frozen plasma as a plasma expander might cause serious respiratory complications including transfusion-related acute lung injury or transfusion-associated circulatory overload [34].
Other synthetic colloids	In a dengue patient who has about a 20-30% increase in hematocrit from the baseline despite having received a large amount of isotonic crystalloid: for instance a dengue patient who has received isotonic crystalloid at the rate of 200-500 mL/hour during the first 6 hours after the onset of shock or a dengue patient who has received isotonic crystalloid with the total amount of more than 1.5 - 2 liters, the physician may consider administering 500 mL/hour of 10% dextran 40 in 0.9% sodium chloride with maximum total dosage of 1000 mL in first 24 hours as a plasma expander, which usually brings the hematocrit down by 10 percentage points. [35-37]. The hematocrit should be obtained before and 1 hour after resuscitating dengue patient with 10% dextran 40 in 0.9% sodium chloride of 500 mL in 1 hour. In a patient with a decrease in hematocrit of no more than 10 percentage points and not below the patient's baseline hematocrit, we suggest changing the type of resuscitation fluid to isotonic crystalloid. In a patient with a decrease in hematocrit greater than 10 percentage points or below the patient's baseline hematocrit, the physician should consider the possibility of bleeding. Packed red cells should be used. Another indication for 10% dextran 40 in 0.9% sodium chloride is a rise in hematocrit in a dengue patient with ongoing plasma leakage with complications of fluid overload, such as pleural effusion or ascites [35-37]. Consider avoiding synthetic colloids such as dextran, hydroxyethyl starch, and gelatin-based solution in a dengue patient with prolonged shock because the patient will suffer from various adverse effects. Theoretically, dextran binds to von Willebrand factor/Factor VIII complex and impairs coagulation [38]. However, this has not been observed to be of clinical significance in fluid resuscitation of dengue shock patients [23,24]. Gelatin has a lesser effect on coagulation but has the highest risk of allergic reaction, which has also been observed in patients treated with dextran [22]. Dextran and hydroxyethyl starch adversely affect the kidneys through osmotic renal injury mechanisms [39,40], which adversely affect dengue shock patients with DIC, renal failure from DIC, or prolonged shock.

Rate and objective of resuscitation fluid

Fluid infusion in the critical phase in a dengue patient with plasma leakage should be given with caution and sparingly to obtain an adequate amount to maintain blood flow to vital organs. This does not usually exceed 5-6 liters during the critical period. In addition, an assessment should be made for vital signs, and other signs of adequacy of circulation for adjusting the rate of the resuscitation fluid. The urine volume should be monitored and maintained at 0.5-1 mL/kg/hour, and the hematocrit should be checked every 1-2 hours during the critical period [37]. If the serum albumin continues

to decline, there is still leakage of the plasma. Conversely, increase in serum albumin represents the onset of plasma reabsorption. Elevation of aspartate transaminase/alanine transaminase ratio indicates poor blood supply to the liver. If the blood lactate value continues to rise, this represents poor blood supply to the organs, resulting in insufficient oxygen delivery. The patient should be re-evaluated for hematocrit, fluid responsiveness, and complications of plasma leakage to adjust the resuscitation fluid or blood component with the goal of achieving lactate clearance by 10% over 1 to 2 hours [19,20].

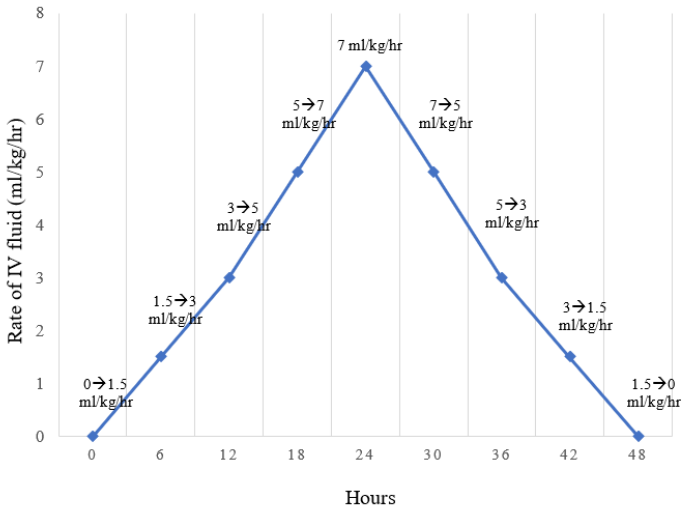
Dengue patients with severe plasma leakage subsequently develop DSS due to an increased rate of the plasma leakage which reaches a maximum rate within 24 hours. Fluid titration in this phase aims to overcome the rate of plasma leakage to maintain the effective circulatory volume. After the onset of shock, the rate of plasma leakage rapidly decreases within 6 hours and continues to decrease for approximately 24 hrs. Therefore, the rate of IV fluid replacement has characteristic inverted 'V' appearance (Figure 1A). A decrease in hematocrit with unstable vital signs (in particular, a narrowing of the pulse pressure, tachycardia, metabolic acidosis, and poor urine output) indicates major hemorrhage and the need for urgent transfusion. However, a decrease in hematocrit together with stable hemodynamic status and adequate urine output indicates hemodilution and/or reabsorption of extravasated fluids. In this case, intravenous fluids must be discontinued immediately.

The total duration of intravenous fluid resuscitation should not exceed 24-36 hours in a patient with shock patient and 48-60 hours in a patient without shock or from the onset of a decrease in platelet count that is < 100,000 cells/mm3 to prevent fluid overload (Figure 1). The key to resuscitate a dengue patient with shock is to reduce the fluid rate as quickly as 15-30 minutes as the patient improves. Adjustment of the resuscitation fluid and adjunctive monitoring are presented in Table 6.

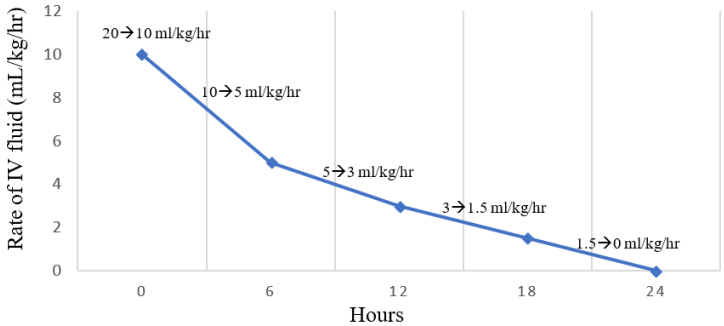
Pausing or stopping of resuscitation fluid

Consider stopping fluid resuscitation in severe dengue patients when the following conditions are present [41] :

1. cessation of plasma leakage demonstrated by stable hematocrit and no bleeding
2. SBP > 90 mmHg or equal to the patient's baseline systolic pressure with MAP > 70 mmHg and PP > 20 mmHg
3. Urine output more than 0.5 mL/kg/hr
4. Improved organ perfusion i.e. stable level of consciousness, a CRT < 2 seconds, and warm extremities



A: Rate of IV fluid in dengue patients with plasma leakage (ml/kg/hr)



B: Rate of IV fluid in dengue patients with shock (mL/kg/hr)

Figure 1. Rate of intravenous infusion (IV) in dengue patients with plasma leakage (A) and in dengue patients with shock (B)

Table 6. Rate of intravenous fluids at the initial stage for dengue patients [35,41]

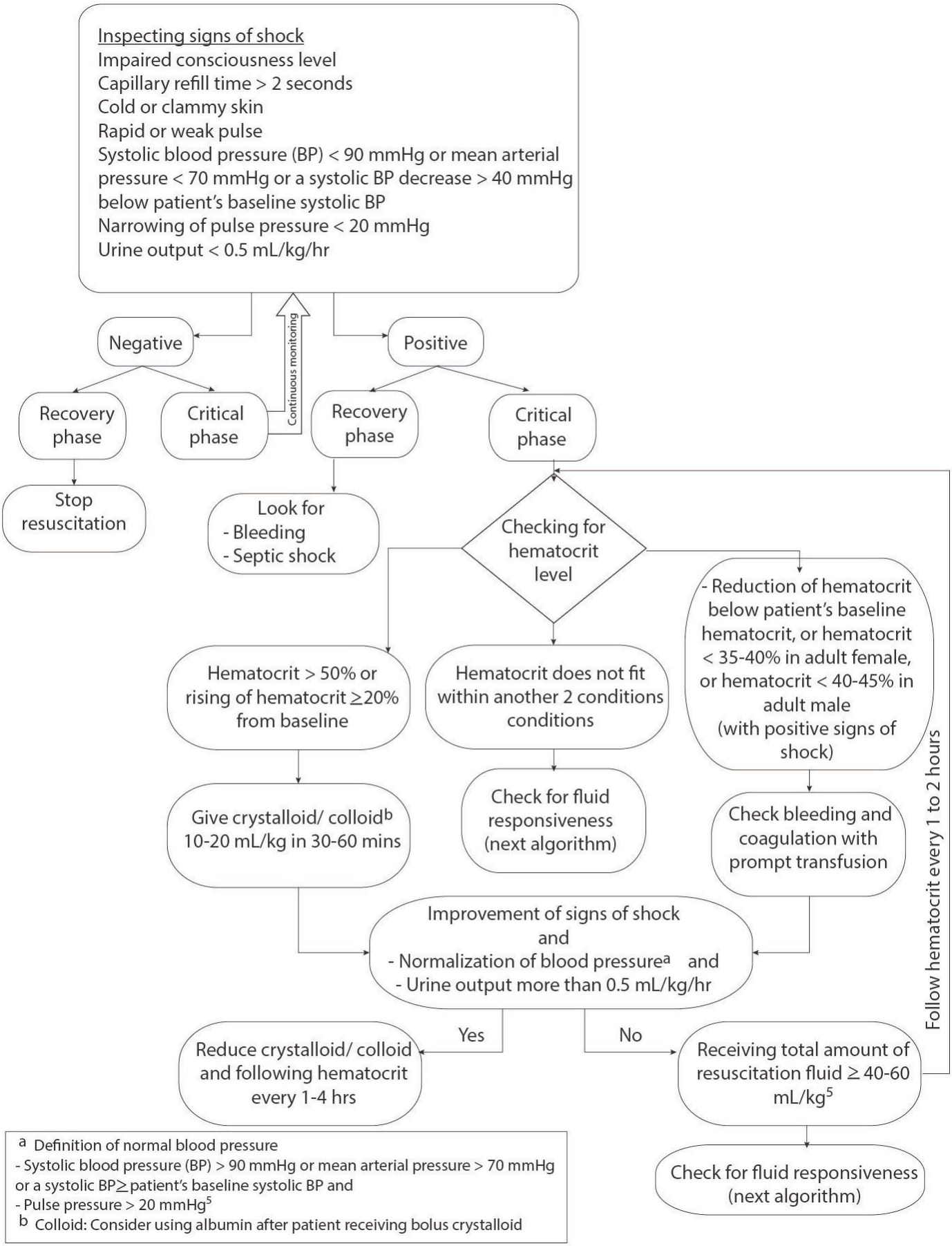
1997 WHO classification [42]	2009 WHO classification [7]	Suggested fluid strategies	Monitoring
DF Clinical manifestation: acute febrile illness plus two or more of the following: - Headache - Retro-orbital pain - Myalgia - Arthralgia/bone pain - Rash - Hemorrhagic manifestations - Leukopenia; and supportive serology*	**Probable and/or laboratory confirmed dengue* and dengue with warning signs** Presumptive diagnosis - Anorexia and nausea - Rash - Aches and pain - Warning signs - Leukopenia - Positive tourniquet test Warning signs - Abdominal pain or tenderness - Persistent vomiting - Clinical fluid accumulation - Mucosal bleed - Lethargy; restlessness - Liver enlargement > 2cm - Laboratory: Increase in Hct. concurrent with rapid decrease in platelet count	- Oral fluid intake in most of case - IV fluid (5%D/NSS, crystalloid) in patients who are unable to have adequate oral intake - Amount of fluid: 40-80 mL/hr and adjust according to vital signs, urine parameter, and Hct. - If the Hct. is increased by 5-10%, consider the rate of the fluid at 40-60 mL/hr. - If the Hct. is increased by > 10 - < 20 %, consider the rate of the fluid at 60-80 mL/hr. - If the Hct. is increased by > 20 %, consider the rate of the fluid at 80-100 mL/hr.	- Daily review for disease progression: warning signs, defervescence, decrease in WBC or platelet numbers. - Admit to hospital if close observations are needed. - Monitor Hct. or CBC every 4-6 hrs post-defervescence for early detection of hemoconcentration representing plasma leakage.
DHF grades I - II Grade I: DF + positive tourniquet test + platelet < 100000 cells/mm3 and Hct. rise > 20% of patient baseline Grade II: DF + spontaneous bleeding + platelet < 100000 cells/mm3 and Hct. rise > 20% of patient baseline		- Start with IV crystalloid e.g., NSS or RLS/RAS of 5-7 mL/kg/hr over 1-2 hrs. - If the clinical status and target parameters are improved, decrease the rate to 3-5 mL/kg/hr for 2-4 hrs, and then 2-3 mL/kg/hr until vital signs are stable and repeated Hct.'s remain the same or rise only minimally with good perfusion and a urine output of about 0.5 mL/kg/hr. - If the clinical status and target parameters are worsened or not improved, review the Hct. obtained before the first bolus. If the Hct. was high compared to the initial Hct. before fluid therapy (if not available, use Hct. > 20% of patient baseline or Hct. > 50%), increase the rate to 7-10 mL/kg/hr for 1-2 hrs and re-evaluate. - If the clinical status and target parameters are worsened or not improved, review the Hct. obtained before the first bolus. If the Hct. was low (< 40% in adult females, < 45% in adult males), this indicates bleeding and the need to cross-match and transfuse blood as soon as possible. - If not improved, the patient should be managed as "dengue shock syndrome".	- Admit to a hospital with access to intensive care facilities and blood transfusion. - Perform daily physical examination to assess clinical signs including general symptoms, appetite, warning signs, and bleeding. - Obtain a reference Hct. before fluid therapy and monitor the rising or falling of the Hct. every 1-2 hrs until clinically stable, and then monitor the Hct. every 4–6 hrs. - A decrease in Hct. together with unstable vital signs (particularly narrowing of the pulse pressure, tachycardia, metabolic acidosis, and poor urine output) indicates major hemorrhage and the need for urgent blood transfusion. - A decrease in Hct. together with stable hemodynamic status and adequate urine output indicates hemodilution and/or reabsorption of extravasated fluids, so in this case, intravenous fluids must be discontinued immediately to avoid pulmonary edema. Target parameters (reassess every 15-30 minutes) - Normal blood pressure and pulse pressure > 20 mmHg - Improving of pulse volume - Warm extremities - Capillary refill < 2 seconds - Improved organ perfusion and plasma leakage, e.g., stable conscious level, urine output > 0.5 - 1.0 mL/kg/hr, decrease in blood lactate, and increase in serum albumin. (To be continued)

Table 6. (Continued) Rate of intravenous fluids at the initial stage for dengue patients [35,41]

1997 WHO classification [42]	2009 WHO classification [7]	Suggested fluid strategies	Monitoring
DHF grades III - IV /DSS (Grade III: DF + circulatory failure (rapid or weak pulse and narrowing of pulse pressure, hypotension, restlessness, cold or clammy skin) + platelet < 100000 cells/mm3 and Hct. rise>20%) (Grade IV: DF + profound shock with undetectable blood pressure and pulse + platelet < 100000 cells/mm3 and Hct. rise>20%)	**Severe Dengue** 1. Severe plasma leakage leading to: • Shock (DSS) • Fluid accumulation with respiratory distress 2. Severe bleeding as evaluated by clinician 3. Severe organ involvement • Liver: AST or ALT>=1000 • CNS: Impaired consciousness • Heart and other organs	- Start with IV crystalloid e.g., NSS or RLS/RAS of 10-20 mL/kg/hr (500-1,000 mL) over 15 minutes then 10-20 mL/kg/hr over 30 minutes to 1 hr. - If clinical status and target parameters are improved, decrease the rate to 5-7 mL/kg/hr for 1-2 hr and then gradually decrease the rate to 2-3 mL/kg/hr or less, which can be maintained for up to 24–48 hrs. - If clinical status and target parameters are worsened or not improved, review the Hct. obtained before the first bolus. If the Hct. was high compared to the initial Hct. before fluid therapy (if not available, use Hct. > 20% of patient baseline or Hct. > 50%) change to colloid solution: 5% albumin, dextran, FFP 10 mL/kg/hr over 1 hr. - If clinical status and target parameters are worsened or not improved, review the Hct. obtained before the first bolus. If the Hct. was low (< 40% in adult females, < 45% in adult males), this indicates bleeding and the need to cross-match and transfuse blood as soon as possible. - If not improved, the patient should be managed as "persistent shock despite adequate crystalloid replacement".	(continued) - Frequently reassess for complication of fluid resuscitation, which can increase the amount of plasma leakage including pleural effusion, pulmonary edema, and ascites
DHF grade IV / DSS with persistent shock		- Manage as 'Figure 1B and Figure 2' - Evaluate for other comorbidities, e.g., conditions: severe plasma leakage, severe bleeding, poor cardiac function, severe sepsis, metabolic acidosis, and pneumothorax. - Start vasopressor, e.g., norepinephrine 0.1-0.2 μg/kg/min. Adjusted dosage every 10-15 min (max. dose 1-2 μg/kg/min). Decrease the dose when clinical status and parameters are improved. - In the 24 hours after the onset of shock, the velocity of the fluid is adjusted according to the variation of Hct. as well as the following indicators: improvement of vital signs, stronger pulse volume, better capillary refill time, warmer hands and feet, and a urine volume of 0.5-1 mL/kg/hr. Further boluses of crystalloid/colloid may need to be given during the next 24 hours. The rate and volume of each bolus infusion should be titrated to fluid responsiveness, plasma leakage complication, and clinical response.	- Admit to an intensive care unit - Adjunctive monitoring (if resources are available) • Continuous monitoring of vital signs and other parameters closely until resolution of shock. • Invasive monitoring such as central line and/or arterial line insertion may be required. • Fluid balance of all input and output by bladder catheter: check urine output every 1–2 hours till the patient is no longer shock. • Follow up the rising and falling of Hct. every 1-2 hrs until clinically stable, and then monitor every 4–6 hours. (N.B. interpret in parallel with the hemodynamic status, the clinical response to fluid therapy, and any plasma leakage complication). • Arterial or venous blood gases, blood lactate, serum albumin, and blood glucose (repeat as clinical indicated). • Other organ functions and plasma leakage complications such as renal profile, liver profile, coagulation profile, ECG, pulse oximetry, intra-abdominal pressure (before and after resuscitation and as indicated).

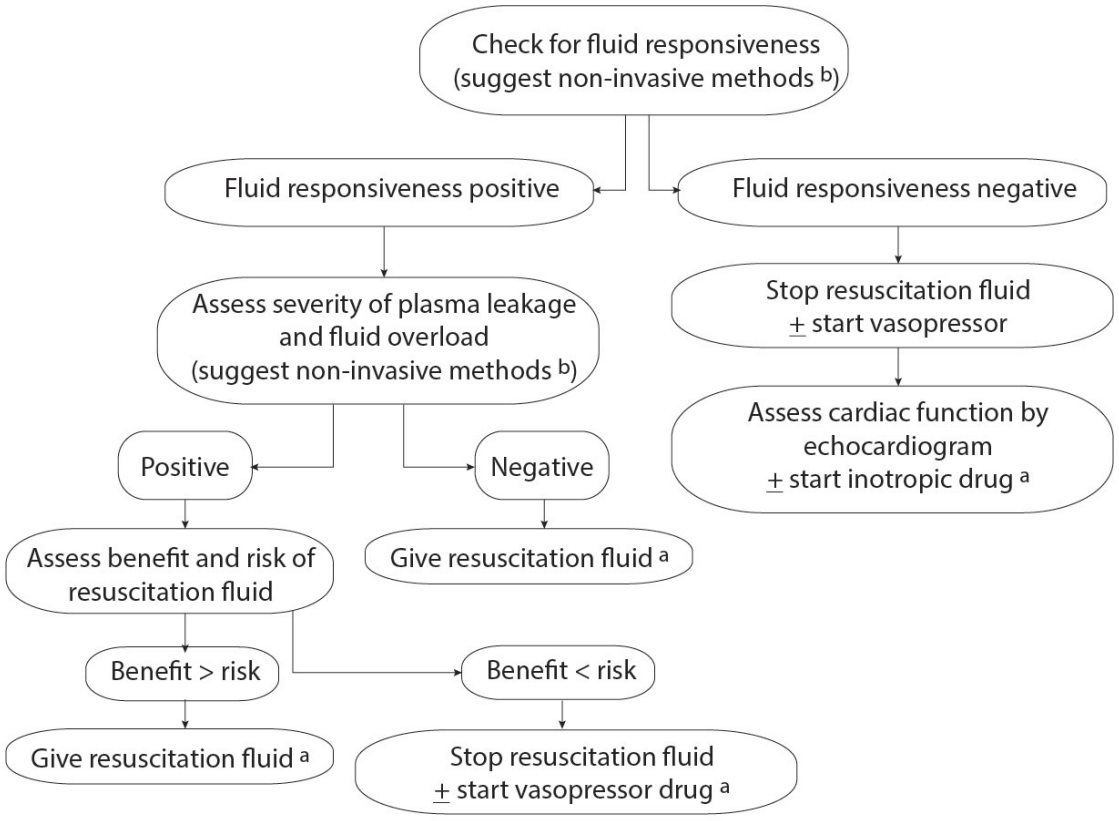
*Serum specimen positive for (i) reverse transcription polymerase chain reaction assay for detection of dengue virus or (ii) nonstructural protein 1 antigen test or (iii) dengue viral culture (iv) immunoglobulin M (IgM) seroconversion in paired serum or (iv) immunoglobulin G (IgG) seroconversion in paired serum or IgG titer increase with a fourfold or greater change in paired serum.

Abbreviations: CBC, complete blood count; DF, dengue fever; DHF, dengue hemorrhagic fever; D, dextrose; ECG, electrocardiogram; FFP, fresh frozen plasma; Hct, hematocrit; IV, intravenous; NSS, normal saline solution; RLS, ringer's lactate solution; RAS, Ringer's acetate solution; WBC, white blood cell; WHO, World Health Organization



[a] Definition of normal blood pressure
- Systolic blood pressure (BP) > 90 mmHg or mean arterial pressure > 70 mmHg or a systolic BP≥ patient's baseline systolic BP and
- Pulse pressure > 20 mmHg[5]

[b] Colloid: Consider using albumin after patient receiving bolus crystalloid



[a] Always monitor abnormal conditions

[b] Non-invasive methods

1. Dynamic indices may be used to guide fluid resuscitation as shown e.g., heart-lung interaction indices (pulse pressure variation, systolic volume variation, tidal volume challenge), inferior vena cava collapsibility/ distensibility index, mini-fluid challenge, passive leg raising test, end-expiratory occlusion test
2. Other ultrasound features to assess fluid responsiveness and cardiac function [43-45]
   - Collapsing of left ventricular walls at end-systolic (kissing LV wall) could be combined with other assessments to denote hypovolemic state. Echocardiograms can be used to evaluate cardiac function and pericardial effusion. Side effects from fluid resuscitation, such as pleural effusion or B-lines detected by lung ultrasound or ascites detected by abdominal ultrasound, can be evaluated.
   - Changes of cardiac output before and after fluid resuscitation to assess fluid responsiveness by non-invasive instruments, such as transthoracic echocardiogram, suprasternal doppler, bioimpedance and bioreactance, and etc, can be measured.

Figure 2. Algorithm for fluid resuscitation in dengue shock patients that do not improve after preliminary fluid exposure.

VASOPRESSOR AND INOTROPE USE

Using vasopressor drug too early in dengue patients with shock is harmful because it elevates blood pressure while the blood supply is inadequate, possibly causing prolonged hypovolemic shock. Consider using vasopressor drug in dengue patients only when mean arterial pressure is < 70 mmHg, or whose systolic blood pressure is < 90 mmHg, or whose systolic blood pressure is decreased by > 40 mmHg below patient's baseline [11], or who has already received sufficient fluid resuscitation, or who has concurrent with septic shock, or who is having side effects from the plasma leakage or resuscitation fluid.

An initial vasopressor for dengue shock patients is norepinephrine starting at a rate of 0.05-0.1 µg/kg/min. The dose could be adjusted every 10-15 minutes until the resumption of organ perfusion pressure demonstrated by the improvement of vital signs, pulse volume, level of consciousness, a capillary refill time less than 2 seconds, warm hands and feet, and a urine volume of 0.5-1 mL/kg/hr [41]. If the dose of norepinephrine is up to 1-2 µg/kg/min, consider adrenaline as a second vasopressor drug. Dopamine is not recommended due to increased risk of cardiac arrhythmias [46].

TREATMENT OF COMPLICATIONS

Bleeding complications

Mucosal bleeding may occur in any patient with dengue. However, if the patient's condition is stable with fluid treatment, it is considered as 'minor bleeding'. The bleeding usually improves automatically during the recovery phase. In a patient with profound thrombocytopenia, strict bed rest should be adhered to in order to reduce the risk of trauma. Intramuscular injections should be avoided to prevent hematoma. It should be noted that prophylactic platelet transfusions for mild to moderate thrombocytopenia in otherwise hemodynamically stable dengue patients have not been shown to have a benefit for bleeding reduction [33].

Major bleeding is usually from the gastrointestinal or genitourinary tract. Internal organ bleeding may not be apparent. Patients at risk of major bleeding are those who have 1) prolonged/refractory shock; 2) hypotensive shock with renal or liver failure and/or severe persistent metabolic acidosis; (3) been given non-steroidal anti-inflammatory agents; 4) pre-existing peptic ulcer disease; 5) been on anticoagulant therapy; and 4) any form of trauma, including intramuscular injection [7].

Patients with hemolytic conditions are at risk of acute hemolysis with hemoglobinuria and will require blood transfusion.

Severe bleeding can be recognized by [7] :

1. persistent and/or severe overt bleeding in the presence of unstable hemodynamic status, regardless of the hematocrit level;
2. a decrease in hematocrit after fluid resuscitation together with unstable hemodynamic status;
3. refractory shock that fails to respond to consecutive fluid resuscitation of 40-60 mL/kg;
4. hypotensive shock with low/normal hematocrit before fluid resuscitation;
5. persistent or worsening metabolic acidosis ± a well-maintained systolic blood pressure, especially in those with severe abdominal tenderness and distension.

Blood transfusion is life-saving and should be given as soon as severe bleeding is suspected or recognized. However, blood transfusion must be given with care because of the risk of fluid overload. Consider packed red cells transfusion if there is further blood loss or no appropriate rise in hematocrit after blood transfusion. There is little evidence to support the practice of transfusing platelet concentrates and/or fresh-frozen plasma for severe bleeding. It is being practiced when massive bleeding cannot be managed with just packed red cells [37]. Prophylactic platelet transfusion should not be routinely prescribed in patients with dengue with no bleeding based on thrombocytopenia. There is a need for further, well-designed RCTs to evaluate the role of tranexamic acid, recombinant activated factor VII (rFVIIa) in both the prevention of bleeding and in the setting of clinically significant bleeding in dengue infection [47].

Do not wait for the hematocrit to drop too low before deciding on blood transfusion. Note that the hemoglobin concentration of < 70 g/L that is a trigger for blood transfusion as recommended in the Surviving Sepsis Campaign Guideline [10] is not applicable to severe dengue. The reason for this is that bleeding in dengue usually occurs after a period of prolonged shock that is preceded by plasma leakage. During the plasma leakage, the hematocrit increases to relatively high values before the onset of severe bleeding. When bleeding occurs, the hematocrit then drops from this high level. As a result, hematocrit levels may not be as low as in the absence of plasma leakage.

Secondary infection

Concurrent bacterial infections were found in 0.18% to 7% of dengue infections, and as high as 14.3% to 44% in patients that die, and these seem to be associated bacterial coinfections [48]. Amongst dengue shock patients, 55.9 percent who were admitted to the critical ward had accompanying concurrent bacterial infections [6].

Timely diagnosis and proper antibiotic treatment are important. Factors associated with secondary bacterial infection in dengue are elderly age group, multiple comorbidities, severe symptoms since hospitalization, and a history of prolonged fever more than 7 days [49].

Laboratory tests that may help recognizing patients who may have concomitant bacterial infection are procalcitonin, leukocyte count, and band form [48]. Pathogens depend on site of infection, local epidemiological data, and the patient's baseline immunity. Both gram-positive bacteria such as methicillin-susceptible *Staphylococcus aureus, Streptococcus agalactiae, Group A Streptococcus, Enterococcus faecalis,* and Enterococcus faecium and gram-negative bacteria such as *Salmonella spp., Orientia tsutsugamushi, Burkholderia pseudomallei, Klebsiella pneumoniae, Escherichia coli, Pseudomonas aeruginosa, Stenotrophomonas maltophilia,* and *Leptospira spp.* have been found [48,49]. Drug-resistant strains occur in the hospital or in the intensive care unit setting [6]. Early appropriate empirical antibiotics can reduce mortality in dengue shock patients with bloodstream infections [50].

In the intensive care unit setting, if a dengue patient has worsening clinical condition, antibiotic should be empirical covering the drug-resistant bacteria according to the local epidemiological data, and if the patients is hospitalized for more than 5 to 7 days, Candida spp. infection should be empirically suspected, especially in patients who are elderly, immunocompromised, dialytic patients, or receiving broad-spectrum antibiotics during the first week of hospitalization [50]. An infectious specialist should be consulted to provide appropriate treatments.

MECHANICAL VENTILATION AND OTHER TREATMENTS

Mechanical ventilation

Respiratory failure in dengue patients can be caused by four conditions: 1) Kussmaul's breathing from lactic acidosis, 2) interstitial edema and pleural effusion due to plasma leakage, 3) reduction of chest wall compliance and compressive atelectasis from ascites [51], or 4) hypoxemic respiratory failure or acute respiratory distress syndrome.

Non-invasive ventilation and oxygen supplementation through high flow oxygen symptoms, may be considered in a dengue shock patient with respiratory failure [52]. However, in patients with contraindications to non-invasive ventilation, such as patients with cardiac arrest, hypotension which cannot be rapidly resolved, or patients who are at risk of aspiration, intubation should be performed immediately [53]. Initial ventilator settings are shown in table 7. and a pulmonary or critical care specialist should be consulted for proper treatment.

Table 7. Basic mechanical ventilation in dengue shock patients [53,54]

Mode	Assist-control ventilation
Rate	14-20/min or allow higher RR to maintain pH above 7.20
Volume/pressure control	Pressure or volume
Tidal volume	6-8 mL/kg to maintain pH above 7.20 and provide plateau pressure < 30 cmH_2O
PEEP	3-10 cmH_2O; to achieve SpO_2 target
FiO_2	Lowest level to achieve SpO_2 target
Non-ventilator strategies	Use 7.5% $NaHCO_3$ to maintain pH above 7.20

Abbreviations: FiO_2, fraction of inspired oxygen; PEEP, positive end-expiratory pressure; RR, respiratory rate; SpO_2, peripheral capillary oxygen saturation

Diagnosis and monitoring of intra-abdominal hypertension [55,56]

Patients with dengue who are suffering from a tight abdomen should be assessed for intra-abdominal pressure with a urinary catheter to measure the transmitted pressure inside the bladder. Intra-abdominal pressure is indirectly measured via a Foley catheter by connecting the pressure tubing from the urine sampling with the other end of the pressure tubing connected to a 3-way, of which one side is connected to the disposable pressure transducer and sterile saline infusion set, and one side is connected to syringe for saline infusion into the bladder as shown in figure 3. The procedure for measuring intra-abdominal pressure by measuring the pressure inside the bladder is shown in Table 8.

Table 8. Procedure for intra-abdominal pressure measurement by measuring the pressure inside the bladder

Procedure
Measure the pressure in the horizontal position
Measure the position relative to iliac crest at mid-axillary line
25 mL of saline is inserted into the bladder.
Begin to measure the pressure in the abdomen after 30-60 seconds of saline installation to allow the release of the detrusor muscle.
Measure the pressure while there is no contraction of the abdominal muscles and while the patient is fully exhaled

If the intra-abdominal pressure is greater than or equal to 12 mmHg, this indicates intra-abdominal hypertension (IAH) and if an intra-abdominal pressure is greater than 20 mmHg that is associated with new organ failure such as respiratory failure, renal failure, hemodynamic instability, metabolic failure, gastrointestinal failure, and even intracranial hypertension, which indicates abdominal compartment syndrome. IAH may require immediate aggressive treatment before reaching the value of 20 mmHg of intra-abdominal pressure.

In the dengue patient with IAH, the physician should identify the causes of IAH and try to correct them by non-invasive method with an aim to decrease intra-abdominal pressure to preserve intra-abdominal organ perfusion and venous return from lower part of the body. The non-invasive measures for lowering abdominal pressure in a dengue shock patient include (i) improve abdominal wall compliance by placing the patient in a reverse Trendelenburg position, sedating the patient with or without neuromuscular blockage and avoid elevating a head of the bed more than 30 degrees, (ii) avoid excessive fluid and keep negative balance by diuretics, hemodialysis, or ultrafiltration and (iii) reduce intra-luminal gut content by non- or less-invasive methods such as reducing the amount of food given to the patient, using prokinetic agents, performing rectal decompression, and nasogastric decompression by an experienced operator. The goal of reduction of pressure in the abdomen is to improve the patient's hemodynamics, which are demonstrated by a slower heart rate, a higher cardiac output, an increased urine output, and improved gas exchange. However, the intra-abdominal pressure should not be rapidly reduced to normal to prevent increased leakage of plasma into the abdominal cavity.

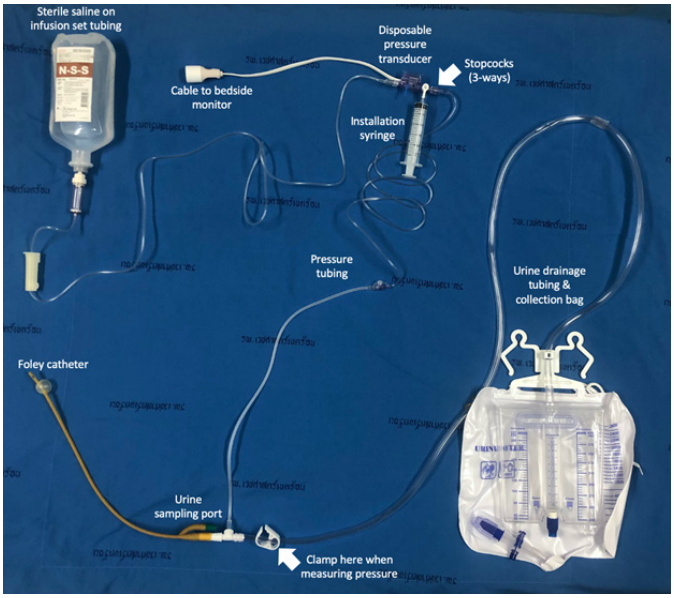


Figure 3. Connected devices used to measure an abdominal pressure in dengue patients.

In the case that the patient still has intra-abdominal pressure higher than 20 mmH_2O and unimproved or worsened organ failure despite performing the previous supportive measures, the physician should find the other causes of refractory abdominal compartment syndrome, which is mostly caused by ascites, which requires careful abdominal paracentesis such as guidance by ultrasound to find the right puncture site, or by intra-abdominal bleeding, which requires surgery. In addition, prior to these procedures, thrombocytopenia and coagulation disorders must be corrected to avoid bleeding complication. The inserted catheter can be connected to a 3-way so that the physician can periodically open the 3-way to drain the ascites to reduce abdominal pressure, and if draining the ascites for more than 5 liters, 6 to 8 grams of albumin per liter of released water should be given to prevent paracentesis-induced circulatory dysfunction. On the other hand, it can be used to measure and monitor abdominal pressure by connecting it to the same device used to measure central venous pressure, which can be an extension cable or a pressure transducer.

Corticosteroid use

In dengue shock patients, corticosteroid does not reduce mortality [57,58], improve shock, or increase platelet numbers without any other significant adverse effects or complications [59]. Corticosteroid may be considered in a dengue patient with concomitant bacterial infection as indicated in a septic shock guideline.

CONCLUSION

Only symptomatic treatments are available for dengue. A key measure for improving survival rate in dengue shock patients is early and appropriate diagnosis and treatment in conjunction with close monitoring in the dengue patient with warning signs and symptoms, especially in the dengue patient who is in the critical phase. Treatments of dengue in the ICU include hemodynamic optimization, early provision of appropriate types, rates, objectives, and limits (TROLs) of fluid therapies. This concept aims to

keep adequate oxygen delivery towards the vital organs with an aim to prevent prolonged shock stage and subsequent organ failure.

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AUTHORS' CONTRIBUTIONS

CS, MS, DM, SC, AW and NS drafted the manuscript. All authors contributed to revise the manuscript. All authors approved the final version.

SUPPLEMENTARY MATERIALS

none

ABBREVIATIONS

SIRS, systemic inflammatory response syndrome; Hct., hematocrit; Hb., hemoglobin; ICU, intensive care unit; DIC, disseminated intravascular coagulation; INR, international normalized ratio; CBC, complete blood count; DF, dengue fever; DHF, dengue hemorrhagic fever; D, dextrose; ECG, electrocardiogram; FFP, fresh frozen plasma; Hct, hematocrit; IV, intravenous; NSS, normal saline solution; RLS, ringer's lactate solution; RAS, Ringer's acetate solution; WBC, white blood cell; WHO, World Health Organization; FiO_2, fraction of inspired oxygen; PEEP, positive end-expiratory pressure; RR, respiratory rate; SpO_2, peripheral capillary oxygen saturation

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