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REVIEW ARTICLE

Management of Dengue in Children: An Update

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Abstract

Dengue viruses cause symptomatic infections or asymptomatic seroconversion. Symptomatic dengue infection is a systemic and dynamic disease. It has a wide clinical spectrum that includes both severe and non-severe clinical manifestations. Due to its dynamic nature, the severity of the disease will usually only be apparent around defervescence which often coincides with the onset of the critical phase. For a disease that is complex in its manifestations, management is relatively simple, inexpensive and very effective in saving lives, so long as correct and timely interventions are instituted. The main hemodynamic elements of dengue shock is hypovolemia with decreased vascular capacitance resulting from plasma leakage. Thus, the strategy of aggressive fluid resuscitation of septic shock is not applicable to severe dengue with plasma leakage. Volume replacement in children with dengue shock is a challenging management problem. Aggressive fluid resuscitation may indeed be harmful and should be limited to dengue shock with hypotension. There is a "narrow therapeutic index"; therefore, fluids have to be given timely, at the appropriate volume, rate, of the appropriate type (crystalloids, colloid and/or blood) and for the appropriate duration. Therein lies the challenge to physicians who are not familiar with the important practice of fluid titration through frequent and meticulous assessment. Progression of the disease through the critical phase should be tracked in hours of plasma leakage. Recognizing the cues to discontinue intravenous fluid therapy is just as important as knowing when to start it. Given time and hemodynamic stability, other issues such as thrombocytopenia, coagulopathy and raised liver enzymes will recover spontaneously or with supportive care.

Key words: *Dengue; children; shock; intravenous fluid therapy.*

Background

Dengue virus infections affect human populations of all age groups worldwide. In some parts of the world, dengue is mainly a pediatric health problem. The vast majority of dengue cases occur in children <15 years of age and around 5% of all severe dengue cases occur in infants.[1-4] In one dengue-endemic area, the incidence of dengue infection exceeded 10% in infants aged 2-15 months.[5]

Differentiation between dengue and other common infections in infants (such as pneumonia, bacterial sepsis, meningo-encephalitis, measles, rotavirus infections, etc.) is often not possible at the febrile stage. The presence of a febrile seizure, macular

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rash, petechiae and lower platelet counts early in the illness are significantly associated with dengue among infants with acute undifferentiated febrile illness.[5]

Most infants acquire primary dengue virus infections.[1,5,6] As in adults, dengue virus can cause a spectrum of outcomes in children, ranging from asymptomatic infection to mild or clinically significant, severe disease.[5] After the incubation period, the illness begins abruptly and, in patients with moderate to severe disease, is followed by three phases "febrile, critical and recovery. Children with dengue typically have high fever that usually lasts 2-7 days. Upper respiratory tract symptoms (cough, nasal congestion, runny nose, dyspnea), gastrointestinal symptoms (vomiting, diarrhea), and febrile convulsions are more common in infants with dengue compared to older children.[3,5,6] In addition to the somatic symptoms, with the onset of fever patients may suffer an acute and progressive loss in their ability to perform their daily functions such as schooling, work and interpersonal relations.[7] Due to its dynamic nature, the severity of the disease will usually only be apparent around defervescence. During the transition from the febrile to afebrile phase, patients without an increase in capillary permeability will improve without going through the critical phase. Instead of improving with the subsidence of high fever, patients with increased capillary permeability may manifest with the warning signs, mostly as a result of plasma leakage. Progressive leukopenia followed by a rapid decrease in platelet count usually precedes plasma leakage.[3]

The warning signs mark the beginning of the critical phase and usually precede the manifestations of shock and appear towards the end of the febrile phase. These patients become worse around the time of defervescence, when the temperature drops to 37.5-38°C or less and remains below this level, usually on days 3-8 of illness. Persistent vomiting and severe abdominal pain are early indications of plasma leakage and become increasingly worse as the patient progresses to the shock state. The patient becomes increasingly lethargic but usually remains mentally alert. These symptoms may persist into the shock stage. Weakness, dizziness or postural hypotension occur during the shock state. Spontaneous mucosal bleeding or bleeding at previous venipuncture sites are important hemorrhagic manifestations. Increasing liver size and a tender liver is frequently observed along with mean aspartate aminotransferase/alanine aminotransferase (AST/ALT) elevation and prolonged prothrombin time. Clinical fluid accumulation may only be detected if plasma loss is significant or after treatment with intravenous fluids. A rapid and progressive decrease in platelet count and a rising hematocrit above the baseline may be the earliest sign of plasma leakage. This is usually preceded by leukopenia (≤5000 cells/ mm3).[8,9] Splenomegaly is seen in almost 10% of dengue infants, seven times more frequently than in older children.[2,6] As the patient survives the 24-48-hour critical phase, a gradual reabsorption of extravascular compartment fluid takes place in the following 48-72 hours. General wellbeing improves, appetite returns, gastrointestinal symptoms abate, hemodynamic status stabilizes, and diuresis ensues. Some patients have a confluent erythematous or petechial rash with small areas of normal skin, described as "islets of white in the sea of red". Some may experience generalized pruritus.The hematocrit stabilizes or may be lower due to the dilutional effect of reabsorbed fluid. The white blood cell count usually starts to rise soon after defervescence but the recovery of the platelet count is typically later than that of the white blood cell count. Respiratory distress from massive pleural effusion and ascites, pulmonary edema or congestive heart failure will occur during the critical and/or recovery phases if excessive intravenous fluids have been administered. Cases of dengue with warning signs will usually recover with intravenous rehydration. Some cases will deteriorate to severe dengue.[10]

The burden of severe dengue lies predominantly in infants 4-9 months of age.[1,4,6] A case of severe dengue[11] is defined as a suspected dengue patient with one or more of the following:(i) severe plasma leakage that leads to shock (dengue shock) and/or fluid accumulation with respiratory distress; (ii) severe bleeding; (iii) severe organ impairment. Patients with severe plasma leakage may not have

shock if prompt fluid replacement has been carried out. Instead, they manifest with respiratory distress due to massive pleural effusion and ascites, which can also be exacerbated by unguided intravenous fluid therapy.[11] Shock occurs when a critical volume of plasma is lost through leakage and it often preceded by warning signs. The body temperature may be subnormal when shock occurs. However, some infants may still have fever at the onset of shock; in these patients a differential diagnosis of septic shock should be kept in mind.[6] With prolonged shock, the consequent organ hypoperfusion results in multiple organ dysfunction, metabolic acidosis and disseminated intravascular coagulation. The degree of increase above the baseline hematocrit often reflects the severity of plasma leakage. Hemoconcentration, manifested by an increase in hematocrit of ≥20% above the baseline hematocrit may be seen.[6,12]

Dengue shock syndrome (DSS) is a form of hypovolemic shock and results from continued vascular permeability and plasma leakage. This usually takes place around defervescence, i.e., on days 4-5 of illness (range of days 3-8), and is often preceded by warning signs. From this point onwards, patients who do not receive prompt intravenous fluid therapy progress rapidly to a state of shock. Dengue shock presents as a physiologic continuum, progressing from asymptomatic capillary leakage to compensated shock to hypotensive shock and ultimately to cardiac arrest. Tachycardia (without fever during defervescence), is an early cardiac response to hypovolemia. During the initial stage of shock, the compensatory mechanism that maintains a normal systolic BP produces tachycardia, quiet tachypnoea (tachypnoea without increased effort), and peripheral vasoconstriction with reduced skin perfusion (manifested as cold extremities and delayed capillary refill time of > 2 seconds and weak volume peripheral pulses).[13] As peripheral vascular resistance increases, the diastolic pressure rises towards the systolic pressure and the pulse pressure (the difference between the systolic and diastolic pressures) narrows. The patient is considered to have compensated shock if the systolic pressure is maintained at the normal or slightly above normal range but the pulse pressure is ≤20 mmHg in children (e.g., 100/85 mmHg) or if they have signs of poor capillary perfusion (cold extremities, delayed capillary refill, or tachycardia). Patients who have dengue and are in compensated shock often remain conscious and lucid. The inexperienced physician may measure a normal systolic pressure and a normal pulse oximetry (SpO_2 95-100%) in a conscious patient and underestimate the critical state of the patient. Worsening hypovolemic shock manifests as increasing tachycardia and peripheral vasoconstriction. Not only are the extremities cold and cyanosed but the limbs become mottled, cold and clammy. By this stage the breathing becomes more rapid and increases in depth " a compensation for the metabolic acidosis (Kussmaul's breathing). Finally, there is decompensation, both systolic and diastolic BPs disappear suddenly and dramatically, and the patient is said to have hypotensive or decompensated shock. At this time the peripheral pulses disappear while the central pulse (femoral) will be weak. Hypotension develops when physiologic attempts to maintain systolic BP and perfusion are no longer effective. One key clinical sign of this deterioration is a change in mental state as brain perfusion declines. The patient becomes restless, confused and extremely lethargic. Seizures may occur and agitation may alternate with lethargy. On the other hand, children and young adults have been known to have a clear mental status even in profound shock. The failure of infants and children to recognize, focus or make eye contact with parents may be an early ominous sign of cortical hypoperfusion, as is the failure to respond to painful stimuli such as venipuncture. Parents may be the first to recognize these signs but they may be unable to describe them, other than to say something is wrong. Hypotension is a late finding and signals an imminent total cardiorespiratory collapse. Prolonged hypotensive shock and hypoxia lead to severe metabolic acidosis, multiple organ failure and an extremely difficult clinical course. It may take a few hours for patients to progress from warning signs to compensated shock and another few hours for compensated shock to progress to hypotensive shock, but only minutes for hypotensive shock to progress to cardio-respiratory collapse and cardiac arrest. Hypotension is associated with prolonged shock which is often complicated by major bleeding.[14]

With profound and/or prolonged shock, hypoperfusion results in metabolic acidosis, progressive organ impairment, and disseminated intravascular coagulation. This in turn can lead to severe hemorrhage causing the hematocrit to decrease in severe shock. Instead of the leukopenia usually seen during this phase of dengue, the total white cell count may increase as a stress response in patients with severe bleeding. In addition, severe organ involvement may develop such as severe hepatitis, encephalitis, myocarditis, and/or severe bleeding, without obvious plasma leakage or shock**.** Patients with severe dengue have varying degrees of coagulation abnormalities, but these are usually not sufficient to cause major bleeding. When major bleeding does occur, it is almost always associated with profound shock since this, in combination with thrombocytopenia, hypoxia and acidosis, can lead to multiple organ failure and advanced disseminated intravascular coagulation. Massive bleeding may occur without prolonged shock in instances when acetylsalicylic acid (aspirin), ibuprofen, or corticosteroids have been taken. Bleeding may occur in patients with previous peptic or duodenal ulcers.[15,16]

Most deaths from dengue occur in patients with profound and prolonged shock resulting from plasma leakage and complicated by bleeding and/or fluid overload.[17] Acute liver and renal failure and encephalopathy may be present in severe shock; these have been described even in the absence of severe plasma leakage or shock.[18-20] Cardiomyopathy and encephalitis have also been reported in a few dengue case series.[21,22]

Vertical transmission and neonatal dengue

Pregnant women with dengue virus infection can transmit the virus to their fetus and vertical dengue transmission has been described. In the vertical transmission cases, some newborns may be asymptomatic. Clinical manifestations of vertically infected neonates vary from mild illness such as fever with petechial rash, thrombocytopenia and hepatomegaly, to severe illness with clinical sepsis, pleural effusion, gastric bleeding, circulatory failure, massive intracerebral hemorrhage and death.[23-28] Clinical presentation in the newborn infant does not appear to be associated with maternal disease severity or dengue immune status, or mode of delivery.[29] However, timing of maternal infection may be important; peripartum maternal infection may increase the likelihood of symptomatic disease in the newborn. A review of 17 mother-infant pairs with dengue infection found that the time intervals between the mothers' onset of fever and that of their neonates, were 5-13 days (median, 7 days); fever in neonates occurred at 1-11 days of life (median, 4 days), and the duration of fever in neonates was 1-5 days (median, 3 days)**.** Antibodies to the dengue virus in the dengue infected mother can cross the placenta and can cause severe dengue in newborn infants.[30]

Diagnostics issues of dengue

The objectives of dengue laboratory diagnosis are (i) to confirm the clinical diagnosis and (ii) to provide information for epidemiological surveillance. Laboratory diagnosis is not necessary for clinical management except in atypical cases or when carrying out differential diagnosis with other infectious diseases. Laboratory diagnosis of dengue is made by detecting the virus and/or any of its components (infective virus, virus genome, dengue NS1 Ag) or by investigating the serological responses present after infection (seroconversion of IgM or IgG from negative to positive IgM/IgG or four-fold increase in the specific antibody titre) in paired sera. Additional tests should be considered in patients with co-morbidities and severe disease as indicated. These may include tests of liver function, glucose, serum electrolytes, urea and creatinine, bicarbonate or lactate, cardiac enzymes, electrocardiogram (ECG) and urine specific gravity.[31-36]

A full blood count should be done at the first visit (it may be normal); and this should be repeated daily until the critical phase is over. The earliest abnormality in the full blood count is a progressive decrease in total white cell count, which should alert the physician to a high probability of dengue. 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 has been associated with severe disease. A rapid decrease in platelet count, concomitant with a rising hematocrit compared to

the baseline, is suggestive of progress to the plasma leakage/critical phase of the disease. These changes are usually preceded by leukopenia (<5000 cells/ mm3). In the absence of the patient's baseline, age-specific population hematocrit levels could be used as a surrogate during the critical phase. A rising hematocrit precedes changes in blood pressure (BP) and pulse volume.[37-39]

Management of Dengue

On the basis of evaluations of the history, physical examination and/or full blood count and hematocrit, clinicians should determine whether the disease is dengue, which phase it is in (febrile, critical or recovery), whether there are warning signs, the hydration and hemodynamic state of the patient, and whether the patient requires admission. Depending on the clinical manifestations and other circumstances, patients may either be sent home (Group A); be referred for in-hospital management (Group B); or require emergency treatment (Group C).[31, 34]

Management of Group A patients[33, 41]

Group A patients who may be sent home as they are able to tolerate adequate volumes of oral fluids, pass urine at least once every six hours and do not have any of the warning signs (particularly when fever subsides). The key to the success of ambulatory (out patient) management is to give clear, definitive advice on the care that the patient needs to receive at home: i.e. bed rest and frequent oral fluids. Patients with ≥3 days of illness should be reviewed daily for disease progression (indicated by decreasing white blood cell and platelet counts and increasing hematocrit, defervescence and warning signs) until they are out of the critical period. They should be advised to return to the nearest hospital immediately if they develop any of the warning signs.

Encourage oral intake to replace fluid loss from fever and vomiting. Small amounts of oral fluids should be given frequently for those with nausea and anorexia. Oral rehydration solution or soup and fruit juices may be given to prevent electrolyte imbalance. Commercial carbonated drinks that exceed the isotonic level (5% sugar) should be avoided. They may exacerbate hyperglycemia related to physiological stress from dengue and diabetes mellitus. Sufficient oral fluid intake should result in a urinary frequency of at least 4 to 6 times per day. Paracetamol for high fever@10 mg/kg/dose, not more than 3-4 times in 24 hours. Sponge with tepid water if the patient still has a high fever. Do not give acetylsalicylic acid (aspirin), ibuprofen or other non-steroidal anti-inflammatory agents (NSAIDs) or intramuscular injections, as these aggravate gastritis or bleeding. Patient should be brought to hospital immediately if any of the following occur: no clinical improvement, deterioration around the time of defervescence, severe abdominal pain, persistent vomiting, cold and clammy extremities, lethargy or irritability/restlessness, bleeding (e.g. black stools or coffeeground vomiting), shortness of breath, not passing urine for more than 4-6 hours. Admission during the febrile period should be reserved for those who are unable to manage adequate oral hydration at home, infants, and those with co-existing conditions. Ambulatory patients should be monitored daily for temperature pattern, volume of fluid intake and losses, urine output (volume and frequency), warning signs, signs of plasma leakage and bleeding and complete blood counts.

Management of Group B patients[42-44]

Group B patients are those who should be admitted for in-hospital management for close observation as they approach the critical phase. These include patients with warning signs, those with co-existing conditions that may make dengue or its management more complicated (such as, extreme age, obesity, diabetes mellitus, hypertension, heart failure, renal failure, chronic hemolytic diseases such as sickle-cell disease and autoimmune diseases), and those with certain social circumstances (such as living alone, or living far from a health facility without reliable means of transport). Rapid fluid replacement in patients with warning signs is the key to prevent progression to the shock state. If the patient has dengue with warning signs or signs of dehydration, judicious volume replacement by intravenous fluid therapy from this early stage may modify the course and the severity of disease.

The action plan should be as follows:

Intravenous fluids are usually needed for only 24-48 hours.

Use the ideal body weight for calculation of fluid infusion for obese and overweight patients.

Obtain a reference hematocrit before intravenous fluid therapy begins.

Give only isotonic solutions such as 0.9% saline, Ringer's lactate or Hartmann's solution.

Start with 5-7 ml/kg/hour for 1-2 hours, then reduce to 3-5 ml/kg/hour for 2-4 hours, and then reduce to 2-3 ml/kg/hour or less according to the clinical response

Reassess the clinical status and repeat the hematocrit. If the hematocrit remains the same or rises only minimally, continue at the same rate (2-3 ml/kg/hour) for another 2-4 hours.

If the vital signs are worsening and the hematocrit is rising rapidly, increase the rate to 5-10 ml/kg/hour for 1-2 hours.

Reassess the clinical status, repeat the hematocrit and review fluid infusion rates accordingly.

Give the minimum intravenous fluid volume required to maintain good perfusion and a urine output of about 0.5 ml/kg/hour. Patients may be able to take oral fluids after a few hours of intravenous fluid therapy.

Reduce intravenous fluids gradually when the rate of plasma leakage decreases towards the end of the critical phase which is indicated by urine output and/or oral fluid intake improving, or the hematocrit decreasing below the baseline value in a stable patient.

Patients with warning signs should be monitored until the period of risk is over.

A detailed fluid balance should be maintained.

Parameters that should be monitored include

vital signs and peripheral perfusion (1-4 hourly until the patient is out of the critical phase),

urine output (4-6 hourly),

hematocrit (before and after fluid replacement, then 6-12 hourly), blood glucose and

other organ functions (such as renal profile, liver profile, coagulation profile).

If the patient has dengue with co-existing conditions but without warning signs, the action plan should be as follows:

Encourage oral fluids.

If not tolerated, start intravenous fluid therapy of 0.9% saline or Ringer's lactate with or without glucose at the appropriate maintenance rate.

Management of Group C patients[45-53]

Group C patients are those with severe dengue who require emergency treatment because they are in the critical phase of the disease and have:

Severe plasma leakage leading to dengue shock and/or fluid accumulation with, respiratory distress

Severe hemorrhages.

Severe organ impairment (hepatic damage, renal impairment, cardiomyopathy, encephalopathy or encephalitis).

Judicious intravenous fluid resuscitation is the essential and usually sole intervention required. The crystalloid solution should be isotonic and the volume just sufficient to maintain an effective circulation during the period of plasma leakage. Plasma losses should be replaced immediately and rapidly with isotonic crystalloid solution: in the case of hypotensive shock, colloid solution is preferred. If possible, obtain hematocrit levels before and after fluid resuscitation. Continue replacement of further plasma losses to maintain effective circulation for 24-48 hours. For overweight or obese patients, the ideal body weight should be used for calculating fluid infusion rates. Blood transfusion should be given only in cases with established severe bleeding, or suspected severe bleeding in combination with otherwise unexplained hypotension. Fluid resuscitation must be clearly separated from simple fluid administration. This is a strategy in which larger volumes of fluids (e.g., 10-20 ml/kg boluses) are administered for a limited period of time under close supervision, to evaluate the patient's response and to avoid the development of pulmonary edema. These fluids should not contain glucose. The degree of intravascular volume deficit in dengue shock varies. Input is typically much greater than output, and the input/output ratio is of no help in judging fluid resuscitation needs during this period.

The goals of fluid resuscitation include

Improving central and peripheral circulation - i.e. decreasing tachycardia, improving BP and pulse volume, warm and pink extremities, a capillary refill time <2 seconds.

Improving end-organ perfusion - i.e. achieving a stable conscious level (more alert or less restless), and urine output ≥0.5 ml/kg/hour or decreasing metabolic acidosis.

The action plan for treating patients with compensated shock is as follows:

Obtain a reference hematocrit before starting intravenous fluid therapy.

Start intravenous fluid resuscitation with isotonic crystalloid solutions at 10-20 ml/kg/hour over one hour.

Then reassess the patient's condition (vital signs, capillary refill time, hematocrit, urine output).

If the patient's condition improves, intravenous fluids should be gradually reduced to 5-7 ml/kg/hour for 1-2 hours; then 3-5 ml/kg/hour for 2-4 hours and finally 2-3 ml/kg/hour which can be maintained up to 24-48 hours.

Consider reducing intravenous fluid earlier if oral fluid intake improves.

The total duration of intravenous fluid therapy should not exceed 48 hours.

If vital signs are still unstable (i.e. shock persists), check the hematocrit after the first bolus:

If the hematocrit increases or is still high, change to colloid solution at 10-20 ml/kg/hour.

After the initial dose, reduce the rate to 10 ml/kg/hour for 1 hour, then reduce to 7 ml/kg/hour.

Change to crystalloid when the patient's condition improves.

If the hematocrit decreases compared to the initial reference hematocrit, and the patient still has unstable vital signs, this may indicate bleeding and following steps to be taken:

Look for severe bleeding.

Cross-match fresh whole blood or fresh packed red cells and transfuse if there is severe overt bleeding.

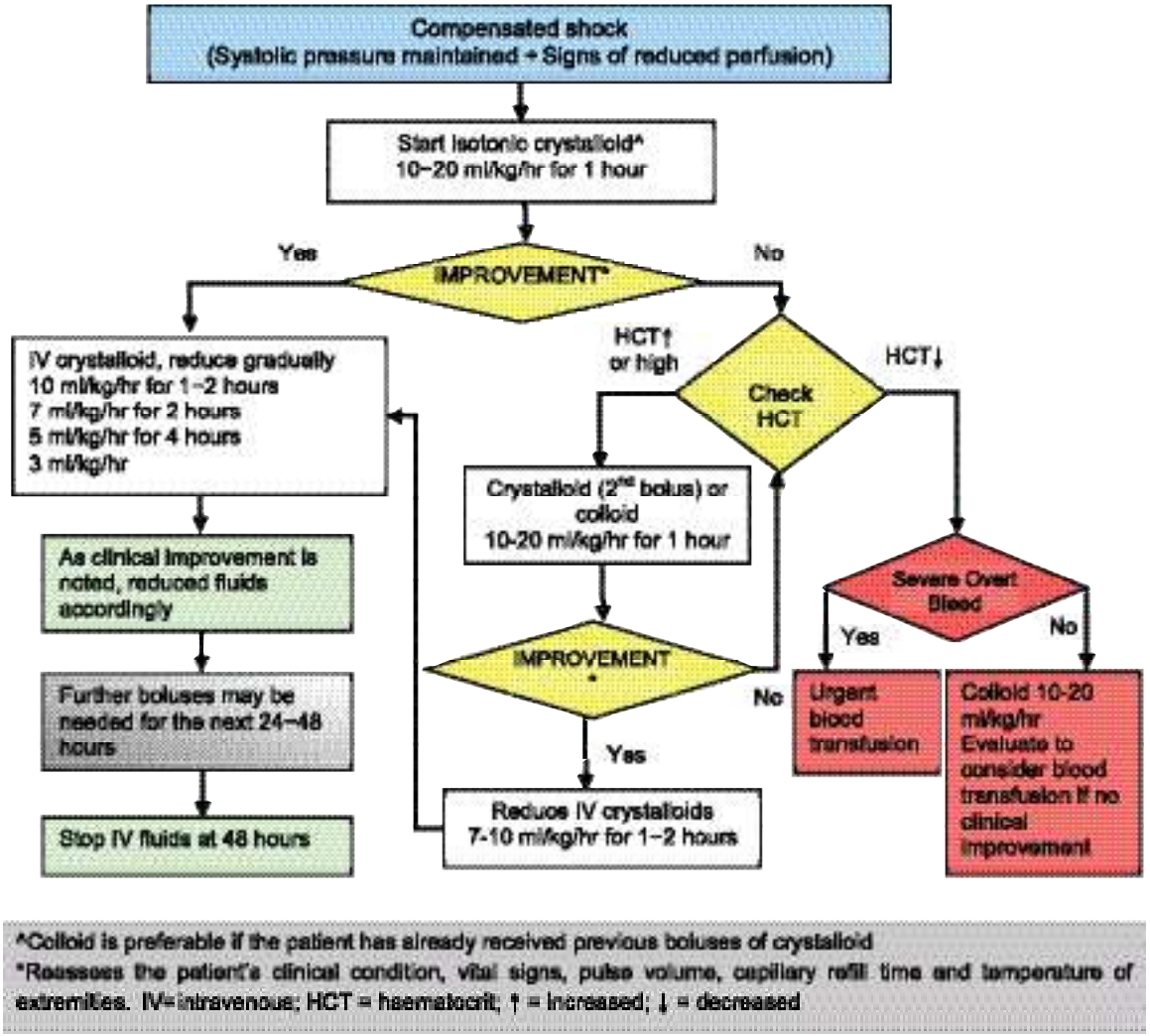

Fig 1 *Algorithm for fluid management of compensated shock in infants and children*[54]

If there is no bleeding, give a bolus of 10-20 ml/kg of colloid over 1 hour, repeat Mclinical assessment and determine the hematocrit level.

Further boluses of crystalloid or colloidal solutions may need to be given during the next 24-48 hours.

Clinicians should remember that a child with a low baseline hematocrit of 30%, presenting with dengue shock and a hematocrit of 40%, is relatively more hemo-concentrated than another child with a baseline value of 42% and a hematocrit of 50% at the time of shock. In patients with profound, recurrent or prolonged shock, a central venous catheter may be inserted through the antecubital basilic vein or internal jugular vein to guide intravenous fluid therapy. Intravenous fluids must be administered with special care to avoid fluid overload. Fluids account for a greater proportion of body weight in infants than children and minimum daily requirements are correspondingly higher. Infants have less intracellular fluid reserve than older children and adults. Moreover, capillary beds are intrinsically more permeable than those of older children or adults. Both early cardiovascular compromise and significant fluid overload are more likely if capillary leaks occur in these circumstances.[53]

Treatment of profound shock (hypotensive; undetectable pulse and BP)[45-47]

All patients with hypotensive shock should be managed more vigorously. The action plan for treating patients with hypotensive shock is outlined below:

Initiate intravenous fluid resuscitation with crystalloid or colloid solution at 20 ml/kg as a bolus given over 15-30 minutes to bring the patient out of shock as quickly as possible.

Colloids may be the preferred choice if the BP has to be restored urgently, i.e. in those with pulse pressure less than 10 mmHg.

Colloids have been shown to restore the cardiac index and reduce the level of hematocrit faster than crystalloids in patients with intractable shock.

Intra-osseous route should be attempted if peripheral venous access cannot be obtained.

If the patient's condition improves:

Give colloid infusion of 10 ml/kg/hour for 1 hour.

Then continue with crystalloid 10 ml/kg/hour for 1 hour, then to 7 ml/kg/hour for 2 hours, to 5 ml/kg/hour for 4 hours and to 3 ml/kg/hour, which can be maintained for up to 24-48 hours.

Consider reducing intravenous fluid earlier if oral fluid intake and urine output improve.

The total duration of intravenous fluid therapy should not exceed 48 hours. If vital signs are still unstable (i.e. shock persists), review the hematocrit obtained before the first bolus.

If the hematocrit is normal or low (<30-35% in infants, <35-40% in children), this may indicate bleeding.

Look for severe bleeding.

Cross-match fresh whole blood or fresh packed red cells and transfuse if there is severe overt bleeding.

If there is no bleeding, give a second bolus of 10-20 ml/kg of colloid over 30 minutes to 1 hour, repeat clinical assessment and hematocrit level to consider blood transfusion.

If the hematocrit is high compared to the baseline value (if not available, use population baseline), change intravenous fluids to colloid solutions at 10-20 ml/kg as a second bolus over 30 minutes to 1 hour.

After the second bolus, reassess the patient.

If the condition improves, reduce the rate to 7-10 ml/kg/hour for 1-2 hours,then change back to crystalloid solution and reduce the rate of infusion as mentioned above.

If the condition is still unstable, repeat the hematocrit after the second bolus:

If the hematocrit decreases compared to the previous value (<35% in infants, <40% in children), this indicates bleeding and the need to cross-match and transfuse blood as soon as possible.

If the hematocrit increases compared to the previous value or remains very high (>50%), continue colloid solutions at 10-20 ml/kg as a third bolus over 1 hour.

After this dose, reduce the rate to 7-10 ml/kg/hour for 1-2 hours, then change back to crystalloid solution and reduce the rate of infusion as mentioned above when the patient's condition improves.

If the condition is still unstable, repeat the hematocrit after the third bolus:

Further boluses of fluids may need to be given during the next 24 hours.

The rate and volume of each bolus infusion should be titrated to the clinical response.

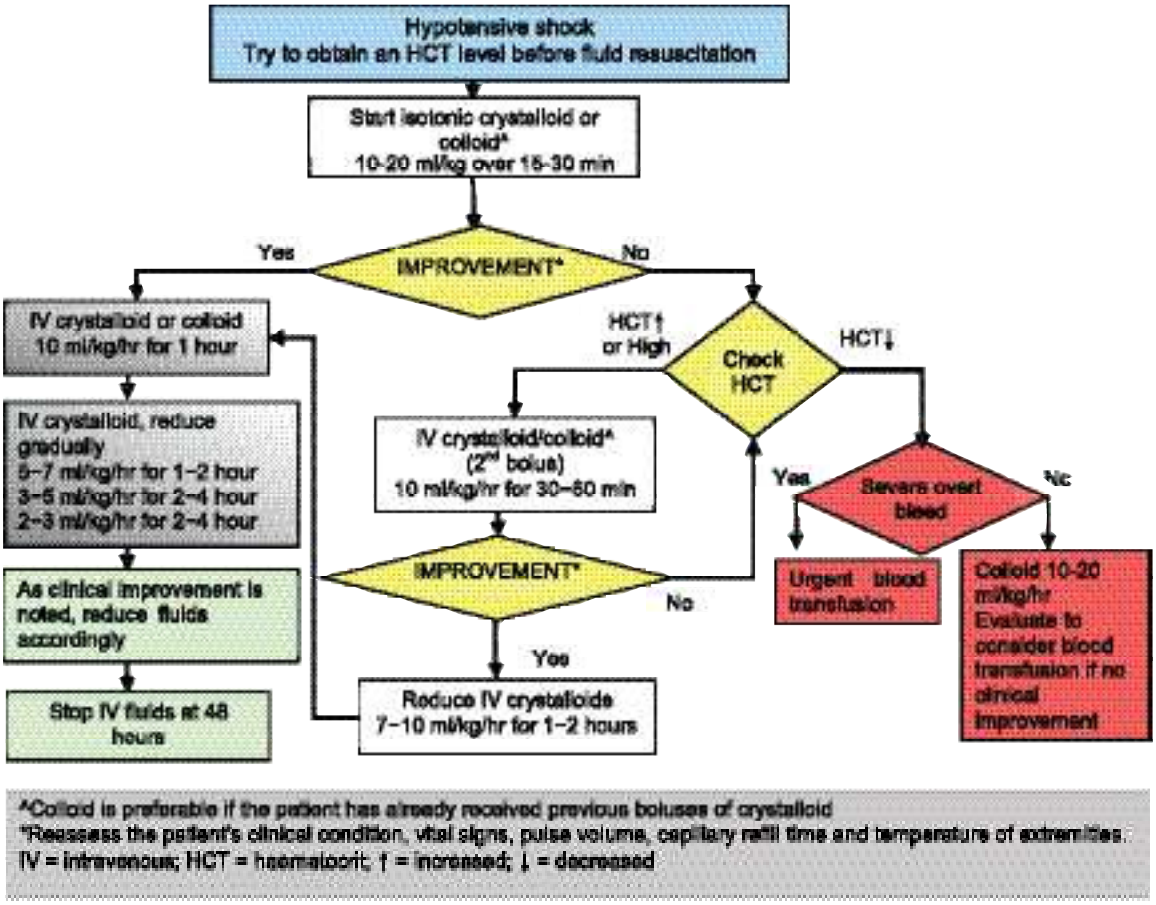

Fig 2 *Algorithm for fluid management in hypotensive shock-infants, children.*[54]

Monitoring patients with dengue shock[6,31,39]

Patients with dengue shock should be monitored frequently until the danger period is over. A detailed fluid balance of all inputs and outputs should be maintained. Parameters to be monitored include: alertness and comfort levels, vital signs and peripheral perfusion (every 15-30 minutes until the patient is out of shock then 1-2 hourly). In general, the higher the fluid infusion rate, the more frequently the patient should be monitored and reviewed in order to avoid fluid overload while ensuring adequate volume replacement. If previously not detectable, pleural effusion and ascites should be detectable after fluid boluses. Monitor their effects on breathing. Blood gas and/ or lactate analysis to be done to monitor changes in the circulation during fluid replacement. The advantage of an arterial line is that in shock states, estimation of BP using a cuff is commonly inaccurate. The use of an indwelling arterial catheter allows for continuous and reproducible BP measurements and frequent blood sampling to base decisions regarding therapy. Monitoring of ECG and pulse oximetry should be available. Urine output should be checked regularly (each hour until the patient is out of shock, then every 1-2 hours). A continuous bladder catheter enables close monitoring of urine output. The first urine volume after bladder catheterization should be discarded because the duration in the bladder is unknown. Thereafter, an acceptable urine output would be about 0.5 ml/kg/hour. Hematocrit should be monitored (before and after fluid boluses until stable then 4-6 hourly). In addition, there should be monitoring of: blood glucose (before fluid resuscitation and repeat as indicated); arterial or venous or capillary blood gases; lactate; and other organ functions (such as renal profile, liver profile, coagulation profile) before resuscitation and as indicated.

Recognizing when to decrease or stop intravenous fluids as part of the treatment of severe dengue is crucial to prevent fluid overload. When any of the

following signs are present, intravenous fluids should be reduced or discontinued:

- signs of cessation of plasma leakage
- stable BP, pulse and peripheral perfusion
- hematocrit decreases in the presence of a good pulse volume
- a pyrexia (without the use of antipyretics) for more than 24–48 hours
- resolving bowel/abdominal symptoms
- improving urine output.

Continuing intravenous fluid therapy beyond the 48 hours of the critical phase will put the patient at risk of pulmonary edema and other complications such as thrombophlebitis.

Hemorrhagic complications [49-51]

Mucosal bleeding may occur in any patient with dengue but if the patient remains stable with fluid resuscitation/replacement, this should be considered as a minor issue. The bleeding usually improves rapidly during the recovery phase. In patients with profound thrombocytopenia, ensure strict bed rest and protection from trauma. Do not give intramuscular injections. No evidence exists that prophylactic platelet transfusions are beneficial in hemodynamically stable patients. If major bleeding occurs it is usually from the gastrointestinal tract, and/or hypermenorrhea. Internal bleeding may not become apparent for many hours until the first black stool is passed.

Patients at risk of severe bleeding are those who:

- have profound/prolonged/refractory shock;
- have hypotensive shock and multi-organ failure or severe and persistent metabolic acidosis;
- are given non-steroidal anti-inflammatory agents;
- have pre-existing peptic ulcer disease;
- are on anticoagulant therapy;
- have any form of trauma, including intramuscular injection.

Patients with hemolytic conditions are at risk of acute hemolysis with hemoglobinuria and may require blood transfusion. Severe and occult bleeding is the most common cause of profound/refractory/ prolonged shock, but can be difficult to recognize. This is because bleeding usually occurs after a period of prolonged shock in dengue.

The preceding plasma leakage causes the hematocrit to rise to very high levels. When bleeding occurs, the hematocrit will then drop from this high level and as a result hematocrit levels may not be as low as in the absence of plasma leakage. Even in severe bleeding, the hematocrit remains above the baseline and only drops to normal or low levels after several fluid boluses.

Severe bleeding should be recognized in the following situations:

- persistent and/or severe overt bleeding in the presence of unstable hemodynamic status, regardless of the hematocrit level;
- a decrease in hematocrit after boluses of fluid resuscitation together with unstable hemodynamic status;
- refractory shock that fails to respond to consecutive fluid resuscitation of 40-60 ml/kg;
- hypotensive shock with inappropriately low/ normal hematocrit;
- persistent or worsening metabolic acidosis in patients with a well-maintained systolic BP, 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. Do not wait for the hematocrit to drop too low before deciding on blood transfusion.

The action plan for the treatment of hemorrhagic complications is as follows:

- If possible, attempts should be made to stop bleeding if the source of bleeding is identified e.g., severe epistaxis may be controlled by nasal adrenaline packing.
- If blood loss can be quantified, this should be replaced. If not, give aliquots of 5-10 ml/kg of fresh packed red cells or 10-20 ml/kg of fresh or fairly fresh whole blood (FWB) at an appropriate rate and observe the clinical response.

It is important that fresh whole blood or fresh red cells are given. Oxygen delivery at tissue level is

optimal with high levels of 2,3 diphosphoglycerate (2,3 DPG). Stored erythrocytes lose 2,3 DPG, low levels of which impede the oxygen-releasing capacity of hemoglobin, resulting in functional tissue hypoxia. A good clinical response includes improving hemodynamic status and acid-base balance. Consider repeating the blood transfusion if there is further overt blood loss or no appropriate rise in hematocrit after blood transfusion in an unstable patient. There is no evidence that supports the practice of transfusing platelet concentrates and/or fresh-frozen plasma for severe bleeding in dengue.

Observational studies show that transfusions of platelet concentrate and fresh frozen plasma in dengue were not able to sustain the platelet counts and coagulation profile. However, in the case of massive bleeding, they often exacerbate the fluid overload. Nevertheless, in certain situations such as obstetrical deliveries or other surgeries, transfusions of platelet concentrate with or without fresh frozen plasma should be considered in anticipation of severe bleeding. In gastrointestinal bleeding, H-2 antagonist and proton pump inhibitors have been used. Great care should be taken when inserting a nasogastric tube or bladder catheters which may cause severe hemorrhage. It is essential to remember that blood transfusion is only indicated in dengue patients with severe bleeding. Unnecessary blood transfusions cause the hematocrit to rise sharply, thus giving a false impression of hemoconcentration and severe plasma leakage leading to unwarranted fluid therapy.

Glucose control[53]

Hyperglycemia and hypoglycemia may occur in the same patient at different times during the critical phase through the following mechanisms.

Hyperglycemia is the result of a neuroendocrine stress response, occurs in diabetes mellitus and results from large quantities of glucose-fluids administered in resuscitation.

Starvation in young children, diabetic patients on oral hypoglycemic agents and severe liver involvement can cause hypoglycemia.

Hyperglycemia causes osmotic diuresis which worsens the hypovolemic shock. Osmotic diuresis also gives a false impression of a "good urine output". Hyperglycemia is associated with increased morbidity and mortality in critically ill patients. Hypoglycemia may cause seizures, mental confusion and unexplained tachycardia. Most cases of hyperglycemia will resolve with appropriate (isotonic, non-glucose) and adequate fluid resuscitation. When the hemodynamic state improves, normal blood glucose levels should be maintained with a glucose-isotonic fluid, such as dextrose 5%-0.9% sodium chloride, at 1-3 ml/kg/hour. In infants and children, blood glucose should be monitored frequently during the critical phase and into the recovery phase if the oral intake is still reduced. However, if hyperglycemia is persistent, undiagnosed diabetes mellitus or impaired glucose tolerance should be considered and intravenous insulin therapy initiated. Subcutaneous insulin should be avoided as absorption is unreliable in the shock state. Hypoglycemia should be treated as an emergency with 0.1-0.5 g/kg of glucose, rather than with a glucose-containing resuscitation fluid. Frequent glucose monitoring should be carried out and euglycemia should then be maintained with a fixed rate of glucose-isotonic solution and enteral feeding if possible.

Electrolyte and acid-base imbalances and Metabolic acidosis[6,33,52,53,55]

Hyponatremia is a common observation in severe dengue; the underlying mechanism is not fully understood. It could be related to gastrointestinal losses through vomiting and diarrhea or the use of hypotonic solutions for resuscitation and correction of dehydration. The use of isotonic solutions for resuscitation will prevent and correct this condition. Hyperkaliemia is observed in association with severe metabolic acidosis or acute renal injury. Appropriate volume resuscitation will reverse the metabolic acidosis and the associated hyperkaliemia. Life-threatening hyperkaliemia, in the setting of acute renal failure should be managed with Resonium A and infusions of calcium gluconate and/or insulin-dextrose. Renal support therapy may have to be considered. Hypokalemia is often associated with gastrointestinal fluid losses and the stress-induced hypercortisol state; it is usually encountered towards the later part of the critical phase. It should be corrected with potassium supplements in the parenteral fluids. Serum calcium levels should be monitored and corrected when large quantities of blood have been transfused or if sodium bicarbonate has been used. Compensated metabolic acidosis is an early sign of hypovolemia and shock. Lactic

acidosis due to tissue hypoxia and hypoperfusion is the most common cause of metabolic acidosis in dengue shock. Correction of shock and adequate fluid replacement will correct the metabolic acidosis. If metabolic acidosis remains uncorrected by this strategy, one should suspect severe bleeding and check the hematocrit. Transfuse fresh whole blood or fresh packed red cells urgently. Sodium bicarbonate for metabolic acidosis caused by tissue hypoxia is not recommended for pH ≥7.10. Bicarbonate therapy is associated with sodium and fluid overload, an increase in lactate and pCO_2 and a decrease in serum ionized calcium.

Complications and management [56,57,58]

Many of the complications seen in dengue are preventable if clinicians are alert to the physiological problems of the three different phases. When hypovolemic shock is adequately managed, patients appear to "sail out" of the critical phase with mere parenteral fluids. But that belies the effort that has been invested in the monitoring and careful titration of intravenous fluid therapy, guided by frequent clinical and hematocrit evaluation.

Causes of complications in dengue include:

missed diagnosis at the frontline;

inadequate monitoring and misinterpretation of vital signs;

inadequate monitoring of fluid intake and urine output;

late recognition of shock leading to profound and/or prolonged shock;

late recognition of severe bleeding;

too much or too little intravenous fluids i.e. not following/understanding the treatment guidelines;

careless attitude towards aseptic techniques.

Outcome of complications in dengue lead to a life-threatening situation characterized by one or a combination of the following:

prolonged and/or profound shock;

severe bleeding with severe disseminated intravascular coagulopathy;

fluid overload;

respiratory distress and failure;

multi-organ dysfunction of liver, kidneys and neurological system;

irreversible shock and death.

Prolonged/profound shock [45, 48]

Prolonged/profound shock is characterized by severe metabolic acidosis ± multi-organ failure. An urgent hematocrit will guide further fluid therapy. If the analysis indicates severe bleeding and matched fresh whole blood (FWB) is available, blood transfusion should be started as soon as possible. However, the following applies if blood is not available:

If the patient has received <2 boluses of resuscitation fluid, a colloid solution of 10-20 ml/kg over 15-30 minutes should be used.

If the patient has received more than 2 boluses of resuscitation fluid, fluids should be switched to a colloid solution of 10-20 ml/kg over 30 minutes for hypotensive shock, and over 1-2 hours for compensated shock.

If severe overt bleeding is apparent (hematemesis, melaena or hypermenorrhea), the colloid bolus should be followed urgently by transfusion of 10-20 ml/kg fresh whole blood (FWB), regardless of the hematocrit level. After transfusion of FWB, some degree of hemodynamic stability is usually achieved together with improvement of metabolic acidosis. Further colloid infusions may be necessary if the hematocrit rises again. A repeat transfusion of FWB will be required if bleeding continues. Bleeding will usually slow down towards the end of the critical phase. There is no evidence that transfusion of platelet concentrates or the disseminated intravascular coagulopathy (DIVC) regime is effective. This practice will contribute to third space losses and expose the patient to multiple blood donors. Prolonged stay in the intensive care unit (ICU) is also expected. If no overt bleeding is seen after the colloid bolus, a repeat clinical evaluation and hematocrit level should be performed. A decrease in hematocrit together with clinical improvement means there is restoration of circulatory volume with colloids. However, a decrease in hematocrit, not accompanied by clinical improvement should prompt the suspicion of severe internal/occult bleeding.

Acute respiratory distress and failure [59]

Causes of acute respiratory distress and failure are:

severe metabolic acidosis from severe shock;

fluid overload - large pleural effusions and ascites

acute pulmonary edema;

acute respiratory distress syndrome (ARDS);

Severe metabolic acidosis from severe shock[56]
Kussmaul's breathing will be observed in addition to tachycardia and other signs of shock. Tracheal intubation should not be the first treatment. Instead, these patients should be given treatment as for hypotension shock i.e., prompt resuscitation with fluid boluses after sampling blood for hematocrit determination. After fluid resuscitation, evaluate to ensure that the respiratory effort has subsided and that other parameters of adequate circulation are present. Otherwise the hematocrit needs repeating and the question of severe bleeding needs to be considered.

Fluid overload[15]
Some degree of fluid overload is inevitable in patients with severe plasma leakage. The skill is in giving them just enough intravenous fluid to maintain adequate perfusion to keep them alive, while waiting it out until the plasma leakage process spontaneously reverses, and at the same time avoiding excessive fluid overload. Recognizing when to decrease or stop intravenous fluids is crucial to preventing fluid overload.

Causes of excessive fluid overload are:

excessive and/or too rapid intravenous fluids during the critical phase;

incorrect use of hypotonic crystalloid solutions e.g. 0.45% sodium chloride solutions;

inappropriate use of large volumes of intravenous fluids in patients with unrecognized severe bleeding;

inappropriate transfusion of fresh-frozen plasma, platelet concentrates and cryoprecipitates;

prolonged intravenous fluid therapy, i.e., continuation of intravenous fluids after plasma leakage has resolved (>48 hours from the start of plasma leakage);

co-morbid conditions such as congenital or ischemic heart disease, heart failure, chronic lung and renal diseases.

Early clinical features of fluid overload are:

rapid breathing;

suprasternal in-drawing and intercostal recession;

respiratory distress, difficulty in breathing;

wheezing, crepitations;

large pleural effusions;

tense ascites, persistent abdominal discomfort/ pain/tenderness (this should not be interpreted as warning signs of shock);

increased jugular venous pressure (JVP).

Late clinical features are:

pulmonary edema (cough with pink or frothy sputum, wheezing and crepitations, cyanosis) - this may be mistaken as pulmonary hemorrhage;

irreversible shock (heart failure, often in combination with ongoing hypovolemia).

Investigations to be done:

blood gas and lactate analysis;

the chest X-ray which shows cardiomegaly, pleural effusion, upward displacement of the diaphragm by the ascites and varying degrees of "bat's wings" appearance ± Kerley B lines, suggestive of fluid overload and pulmonary edema;

ECG to exclude ischemic changes and arrhythmia;

echocardiogram;

cardiac enzymes.

Action plan:

Oxygen therapy should be given immediately

The further action plan for the treatment of fluid overload is dependent on the patient's hemodynamic stability, intravascular volume status and the timing of this event with respect to the timeline of the critical phase.

Strong pulses with warm extremities are positive indications to stop (≤48 hours of plasma leakage) or reduce (if ≤48 hours of plasma leakage) intravenous fluids.

If the patient has difficulty in breathing because of excessive third space fluid accumulation, it is all the more imperative to stop fluid therapy.

Small doses of furosemide 0.1-0.5 mg/kg/dose twice or thrice daily or a continuous infusion of furosemide 0.1 mg/kg/hour may be indicated for patients who are out of the critical phase.

Monitor serum potassium and correct the ensuing hypokalemia.

Watch out for hypertension and treat during the recovery phase otherwise hypertensive encephalopathy may occur.

Respiratory support may be indicated depending on the severity of respiratory distress.

Pulmonary edema and acute respiratory distress syndrome (ARDS)[45,47,48]

These two conditions will cause life-threatening hypoxemia. Pulmonary edema is more common than ARDS. Both are aggravated by rapid infusion of large volumes of fluid during the critical phase. The goals of therapy are to optimize oxygenation and ventilation with respiratory support and stabilize the hemodynamic situation.

Apart from increasing the fractional inspired oxygen, positive end-expiratory pressure (PEEP) is essential to maintain adequate oxygenation and reduce the work of breathing.

If the patient is out of the plasma leakage phase and has stable hemodynamics, intravenous fluid therapy should be discontinued and diuretic therapy can be commenced cautiously.

Indications for mechanical ventilation include:

patients who have shock and are restless, combative or confused;

respiratory failure from acute pulmonary edema/ARDS ± shock;

patients who fail to respond to non-invasive ventilation.

Co-infections and nosocomial infections[14, 35]

Co-infections with gram-negative bacteria have been reported in patients with diabetes mellitus and renal failure. Other tropical diseases such as leptospirosis, typhus, malaria, chikungunya and enteric fever may occur concomitantly. A high index of suspicion is necessary to recognize this, especially in those with atypical presentations such as prolonged fever, pulmonary hemorrhage, unexplained renal failure or liver failure in the absence of shock. It is not uncommon for patients to acquire a nosocomial infection, especially those with severe dengue and when intravenous therapy has been prolonged. Careful attention to aseptic techniques is necessary in procuring and accessing intravascular devices. Prompt and appropriate antibiotic therapy will be crucial to prevent morbidity and mortality.

Hemophagocytic syndrome[60-63]

Evidence of hemophagocytes in dengue was alluded to by the presence of numerous macrophages that have phagocytosed erythrocytes and lymphocyte phagocytosis in the spleen. The unusual incidence of phagocytic reticulum cells which phagocytosed all blood elements has been reported. Case reports of prolonged fever in dengue patients have been attributed to this phenomenon. The clinical picture is characterized by persistent high fever, variable cytopenia and multi-organ failure associated with macrophage activation, hemophagocytes and hypertyrosinemia. Serum ferritin levels are markedly elevated. Definitive diagnosis is made by bone marrow biopsy which demonstrates hemophagocytic activity. Response to methyl-prednisolone and immunoglobulin has been reported to be dramatic. However, supportive treatment leading to spontaneous recovery has also been reported.

Supportive care and adjuvant therapy[13,31,34]

Supportive care and adjuvant therapy may be necessary in severe dengue and includes vasopressor and inotropic therapy.

The use of vasopressor and inotropic therapy should be limited to the following clinical situations:

As a temporary measure to prevent life-threatening hypotension in dengue shock and during induction for intubation, while correction of intravascular volume is being vigorously carried out. Vasopressor therapy should be weaned off as intravascular volume is restored and end-organ perfusion re-established.

Evidence of cardiogenic shock due to myocarditis or ischemic heart disease. Dobutamine is the recommended choice. In concomitant septic shock, dopamine or norepinephrine are the vasopressors of choice. Vasopressor therapy should be carefully monitored since dengue shock is primarily a hypovolemic shock caused by plasma leakage ± hemorrhage. The most essential and effective strategy is the correction of intravascular volume with the appropriate types of fluids. Vasopressors, by further increasing the peripheral vascular resistance, may be able to maintain the central BP but

without improving end-organ perfusion. Paradoxically, vasopressors exacerbate tissue hypoxia and lactic acidosis when the intravascular volume has not been restored. The correct use of vasopressor therapy is reflected in an increased BP concomitant with a decreased tachycardia. If both the BP and tachycardia increase, then repletion of intravascular volume should be considered as the urgent alternative strategy.

Renal replacement therapy may be indicated in acute kidney injury. It should be commenced after hemodynamic stability has been achieved and maintained without further fluid resuscitation, usually after the critical period of plasma leakage. The preferred choice of renal replacement therapy is continuous veno-venous hemodialysis (CVVH). Peritoneal dialysis may be considered if CVVH is not available, but there is a risk of bleeding. When renal replacement therapy is not available or cannot be performed yet, the ensuing hyperuricemia, hyperkaliemia and hyperphosphatasemia should be managed with allopurinol, Resonium A and calcium carbonate respectively.

Other organ impairment[64]

Drug toxicity resulting from the use of paracetamol or acetaminophen should be suspected if liver enzymes have increased disproportionate to the severity of shock. Paracetamol should be discontinued in patients with liver enlargement or raised liver enzymes. Further treatment of organ impairment, such as severe hepatic involvement, encephalopathy or encephalitis may be needed otherwise cardiac abnormalities, such as conduction abnormalities, may occur (the latter usually not requiring interventions). The most critical issue for recovery is stabilization of the hemodynamic state; without this there can be no recovery of any organ. Once the critical period is over and stability of the hemodynamic state attained, it is essential to stop or reduce intravenous fluids to the minimum and to maintain euglycemia. The body will heal itself remarkably over the next few days to weeks. Excessive fluid is cleared by the kidneys and normal liver function returns gradually, coagulation abnormalities and platelet counts return to normal. During this period any suspected nosocomial sepsis should be treated vigorously, but without adding further insults to the kidneys or liver. Supportive treatment (for the liver and kidneys) and enteral nutrition is all that is required in most cases.

Management of neonatal dengue[67, 68, 69]

When a pregnant or parturient woman develops signs consistent with dengue, the diagnosis of dengue should be considered in her neonate even if the neonate appears well in the first several days of life. Remember that some neonates have become ill as long as 11 days after birth**.** The diagnosis of neonatal dengue could eventually be suspected on clinical grounds and then confirmed in the laboratory, but initial presentation may be confused with bacterial sepsis, birth trauma and other causes of neonatal illness. Symptomatic and supportive treatment under close observation is the mainstay of treatment**.**

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