Current Management of Dengue in Adults: a Review

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ABSTRACT

Dengue infection ranks highly among new and newly emerging arthropod-borne viral diseases affecting humans. It affects a large proportionof the population, mainly in tropical and sub-tropical countries, causing a high morbidity and mortality due to rising incidence of dengue haemorrhagic fever. The rapidly expanding global footprint of dengue is a public health challenge with a high economic burden.Appropriate management of the burden of dengue is hindered by several issues,including lack of understanding of the exact pathophysiology of the disease, failure to control the vector population effectively,lack of specific treatment for the disease, and technical obstacles in developing a vaccine. This review provides an overview on the epidemiology, natural history and management strategies of adult dengue patients.

KEYWORDS: Dengue,management, fluid resuscitation

INTRODUCTION

Dengue is a self-limiting, systemic viral infection transmitted by mosquitoes of genus aedis.[1] It affects a large proportion of the population in tropical and sub-tropical countries, causing high morbidity and mortality.[2,3,4] The rapidly expanding global footprint of dengue is a public health challenge with a high economic burden, that currently remains unchecked due to lack of licensed vaccines,specific therapeutic agents, or effective vector control strategies.[1] However, improved care in hospitals has led to a significant drop of mortality. As such, furthers effort should be taken optimized the treatment strategies based on proper understanding of the pathophysiology of the disease. In this review we intend to discuss the current practice of management of adult dengue patients in hospitals.

MATERIALS AND METHODS

A PubMed search was performed on all articles with the key word “dengue” in the title and “management” in the abstract.The initial search yielded 458 articles based on these criteria.The search was then restricted to articles published in the English language within the last decades. Endnote X3 software was used to filter articles.All abstracts were read independently by the two authors, and key articles were identified based on a consensus among the authors.The search was then confined to last decade to select more recent evidence. However,related or cited papers of importance before this period were also included. The epidemiological data and guidelines of management were downloaded from the websites of local and international agencies, including the World Health Organization guidelines.

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RESULTS

Case classification

According to the WHO 1997 guideline of Dengue Haemorrhagic Fever Diagnosis,Treatment, Prevention and Control,[2nd] edition a proportion of patients develops dengue fever(DF) in the initial stages and recovers, while other patients may progress on to develop dengue haemorrhagic fever(DHF).[5,6,7] The clinical diagnosis and severity of DHF was graded from grade I to IV.The WHO guidelines define Grade I as fever accompanied by non specific constitutional symptoms with the only haemorrhagic manifestation being a petechial rash.Grade II is defined as cases with spontaneous bleeding from any site.Grade III and Grade IV are together defined as dengue shock syndrome(DSS).Grade III cases have circulatory failure manifested by rapid and weak pulse, narrowing of pulse pressure (20 mmHg or less) or hypotension,with presence of cold clammy skin and restlessness.Grade IV (DSS) is defined as patients having profound shock.[6,7] According to the new WHO 2009 guideline book, dengue cases are no longer classified as DF and DHF, instead patients are divided in to two simplified groups.

They are either sever or non -sever dengue patients (Fig.1). The non-severedengue patients are further divided into two subgroups:patients with warning signs and those without warning signs.[7,8] The classification criteria for non-severe dengue without warning signs are fever and any two of either nausea/vomiting, rash, aches and pain, a positive tourniquet test, and leucopenia. There may even be a combination of these warning signs. The warning signs are: abdominal pain or tenderness, persisting vomiting, clinical fluid accumulation (pleural effusion/ ascites), mucosal bleeding, lethargy, restlessness, liver enlargement (>2cm), and an increase in haematocrit(HCT) concurrent with a rapid decrease in platelet count. Severe dengue infections are characterized by significant plasma leakage, severe bleeding, and severe organ dysfunction such as of the liver.[6,8]

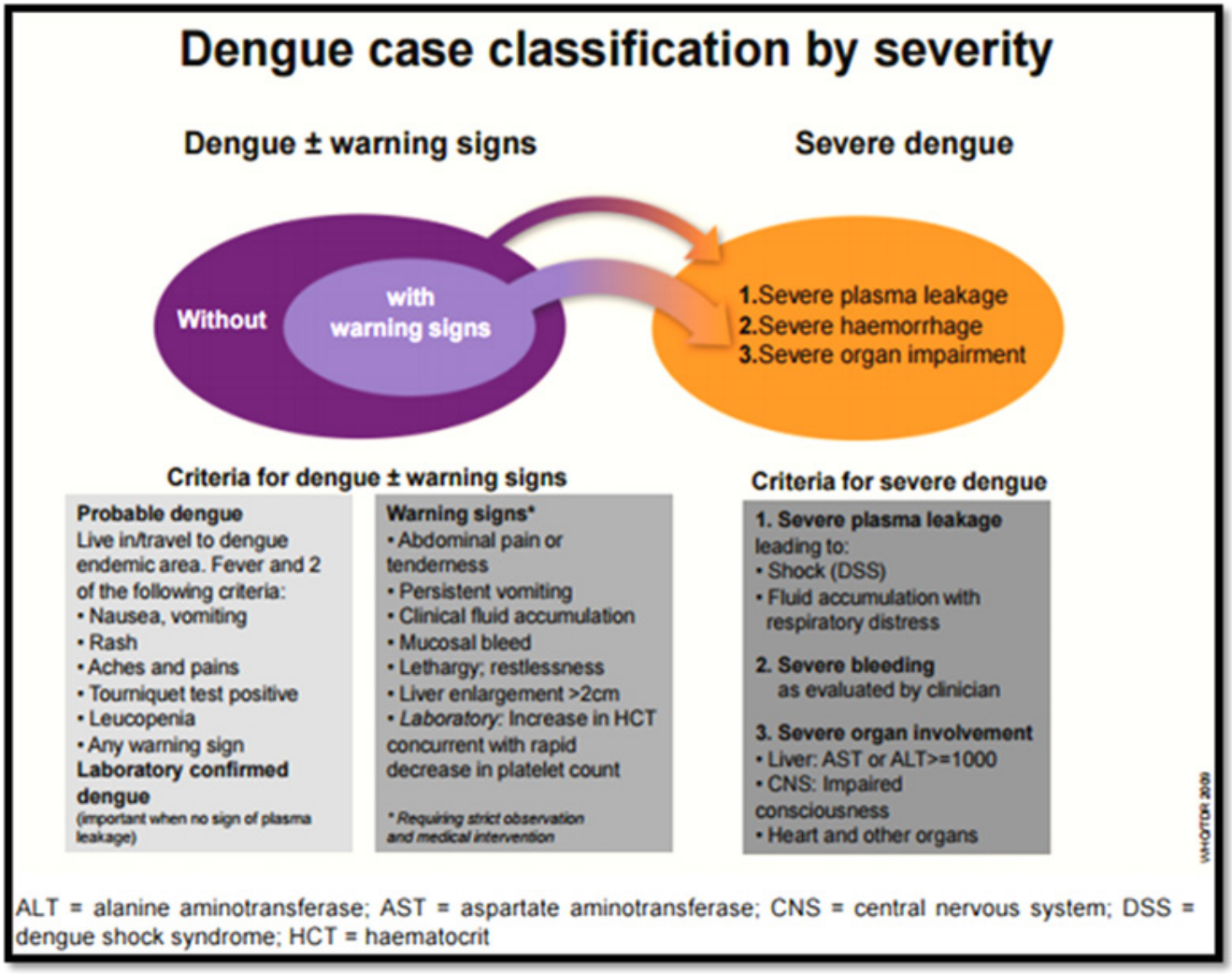

Fig.1. WHO 2009 Dengue case classification by severity. Source: Handbook for clinical management of dengue.WHO 2012)

Expanded dengue syndrome(unusual or atypical manifestations)

Unusual manifestations of dengue are rare. In recent years with the increased spread of dengue infection and with increased involvement of adults,there has been an increase in reported cases of DF and DHF with unusual manifestations, which include: neurological, hepatic, renal and isolated organ involvement.[3,5,9] Table 1 demonstrates the unusual/ atypical manifestations of dengue. These unusual manifestations may be underreported, unrecognized or not related to dengue infection. However, it is essential that proper clinical assessment is carried out for appropriate management and causal studies should be done.[3]

Table 1. Expanded dengue syndrome (Unusual or atypical manifestations of dengue)

System	Unusual or atypical manifestations
Neurological	Febrile seizures in young children Myoclonus Encephalopathy Encephalitis/ Aseptic meningitis Intracranial haemorrhages/ Thrombosis Subdural effusions Mononeuropathies/ Polyneuropathies/ Guillane-Barre syndrome Transverse myelitis
Gastrointestinal/ Hepatic	Hepatic/ Fulminant hepatic failure Acalculous cholecystitis Bilateral parotitis Acute pancreatitis
Renal	Acute renal failure Haemolytic uraemic syndrome
Cardiac	Conduction abnormalities Myocarditis Pericarditis
Respiratory	Acute respiratory distress syndrome Pulmonary haemorrhage
Musculoskeletal	Polyartritis Rhabdomyolysis Myositis with raised creatine phosphokinase
Lymphoreticular/ Bone marrow	Infection associated haemophgocytic syndrome/ IAHS or Haemophagocytic lymhohistiocytosis, Idiopathic thrombocytopenic Purpura Spontaneous splenic rupture Lymph node infarction
Eye	Macular haemorrhages/ impaired visual acuity/ optic neuritis
others	Post infectious fatigue syndrome/ depression/ hallucinations/ psychosis/ alopecia

Source: Gulati S, Maheshwari A.[9]

DISCUSSION

The clinical diagnosis and management of dengue

Overview

There are currently no available antiviral agents to treat dengue infection, and treatment remains supportive, with particular emphasis on careful fluid management. Patients who have no complications and who can tolerate oral fluids may remain at home with instructions to return to the hospital immediately in case of development of bleeding or warning signs suggestive of vascular leakage.[1] Development of any warning signs and any other criteria listed on text box 1 indicates the need for hospitalization and close observation.[1,10]

Text box 1. Admission criteria

Warning signs	**Any of the warning signs**
Signs and symptoms related to hypotension (possible plasma leakage)	Dehydrated patient, unable to tolerate oral fluid Dizziness or postural hypotension Profuse perspiration, fainting, prostration during defervescence Hypotension or cold extremities Difficulty in breathing/ shortness of breath
Bleeding	Spontaneous bleeding, independent of the platelet counts
Organ impairment	Renal, hepatic, neurological or cardiac -Enlarged, tender liver although not yet in shock -Chest pain, respiratory distress or cyanosis
Findings through further investigations	Rising haemoatocrit Pleural effusions, ascites or asymptomatic gall-bladder thickening
Co-existing conditions	Pregnancy Co-morbid conditions, such as diabetes, hypertension, peptic ulcer, haemolytic anaemias and others Overweight or obese Infancy or old age
Social circumstances	Living alone Living far from health facility Without reliable means of transport

Source: Hand book for clinical management of dengue. WHO 2012.

Management of febrile phase

The febrile phase of dengue illness, which usually lasts 5-7 days in most cases, may be biphasic, with the temperature ranging between 390C and 400C.[3,10] During this phase of illness, liberal administration of oral fluid and treatment with antipyretics like paracetamol as required is recommended.Other non-steroidal anti-inflammatory drugs should be avoided.[5] Patients in the febrile phase with no warning signs can be managed at home.The key to successful ambulatory(outpatient) management is to give clear,definitive advice on the care the patient should adhere to at home, such as bed rest and frequent oral fluids. Adequate urine output should be maintained at least once every six hours.[10,11]Patients with illness lasting ≥ 3 days should be reviewed daily for disease progression(indicated by decreasing white blood cell and platelet counts and increasing haemotocrit(HCT), defervescence and warning signs) until they are out of the critical period. Those with stable haematocrit can be sent home but should be advised to return to the nearest hospital immediately if they develop any of the warning signs and to adhere to the following action plan:[4,12,13,14]

- Adequate oral fluid intake to replace fluid loss from fever and vomiting should be encouraged.Those with nausea and anorexia should receive small amounts of oral fluids frequently.[4,10] The choice of fluids, such as coconut water in some countries, in others rice water or barley water may be based on the local culture.Oral rehydration solution or soup and fruit juices may be given to prevent electrolyte imbalance.[10] Commercial carbonated drinks that exceed the isotonic level(5% sugar) should be avoided, as they may exacerbate hyperglycaemia related to physiological stress from dengue and diabetes mellitus.Sufficient oral fluid intake should result in a urinary frequency of at least 4-6 times per day.A record of oral fluid and urine output could be maintained and reviewed daily in the ambulatory setting.[4,10,11,14]

- Fever should be treated with paracetamol, with the recommended dose being 10mg/kg, not exceeding 3-4 times in 24 hours in children and not exceeding 3g/ day in adults. Acetylsalicylic acid(Asprin),ibuprofen

or other non-steroidal anti-inflammatory agents or intramuscular injections should be avoided as they aggravate gastritis and bleeding.[4,10,11,12]

• Caregivers should be instructed to bring the patient to hospital in case of either failed 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 coffee ground vomiting), shortness of breath,or anuria for more than 4-6 hours.[3,4,10,11,14]

Management of the critical phase without shock

Patients who have approached the critical phase should be admitted for in-ward management. These include patients with warning signs, those with co-existing conditions that may make dengue or its management more complicated(such as pregnancy, infancy, old age, obesity, diabetes mellitus, hypertension, heart failure, renal failure, chronic haemolytic 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).[15,16,17,18] Rapid fluid replacement in patients with warning signs is the key to prevent progression to shock state.[3,4]

The critical phase of DHF which is the period of plasma leakage,begins around the transition from the febrile to the afebrile phase.[1,3,19,20] The key issue here is the prediction and identification of the onset of the critical phase. When an effusion or ascites becomes clinically detectable,it indicates that the commencement of the critical phase had occurred several hours ago.[5] Generally, the onset of the critical phase can be predicted when the haematocrit starts rising about 10%-15% above base line.[3,5,10] A drop in platelet count to less than 100,000µL is also an indicator that the patient is at risk of entering the critical phase in the next 24 hours.[5] Other supporting evidence of plasma leakage are a decrease in serum albumin (<3.5g/dL) and non fasting serum cholesterol(<100mg/dL).[10,11] The degree and the rate of plasma leakage in DHF can vary, being minimal in some patients while being very significant in others.The leak usually starts slowly, increases gradually, slows down and then ceases altogether at the end of the critical phase(usually within 48 hours from the onset)(Fig. 2).[4,5,10]

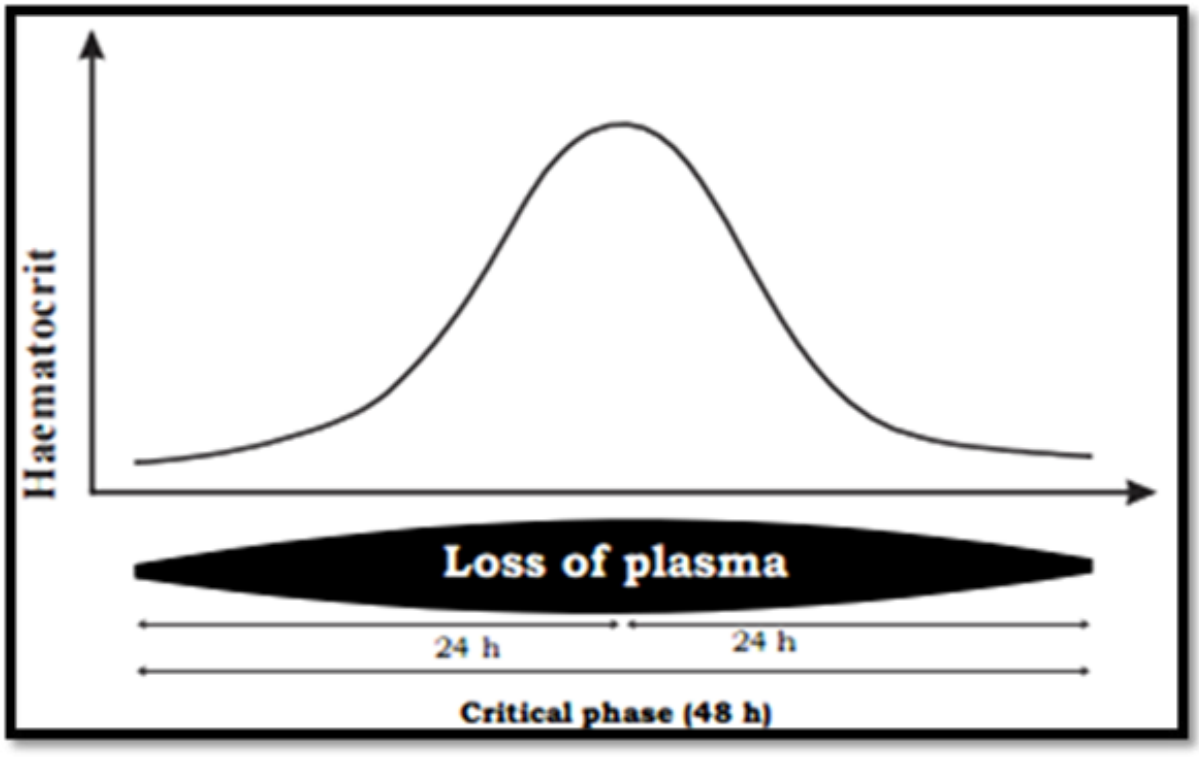

Figure 2.Fluid leakage in the critical phase.Source: www.epid.gov.lk/.../guidelines_for_the_management_of_df_and_dhf_in.Sri.

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 the disease.[4,5,10,11]The action plan should be as follows:

- Obtain a reference haematocrit before commencement of intravenous fluid therapy.Give only isotonic solutions such as 0.9% saline,Ringer's lactate or Hartmann's solution.Start with 5-7ml/kg/hour for 1-2 hours,then reduce to 3-5ml/kg/hour for 2-4 hours,and then reduce to 2-3ml/kg/hour or less depending on the clinical response.[4,10,11]
- Reassess the clinical status and repeat the haematocrit. If the haematocrit remains the same or rises only minimally,fluids should be continued at the same rate(2-3 mL/kg/hour) for another 2-4 hours.If the vital signs are worsening and the haematocrit is rising rapidly, the rate should be increased to 5-10ml/kg/hour for 1-2 hours and reassess the patient.[4,10,21,22]
- The aim is to give the minimum intravenous fluid volume required to maintain good perfusion and urine output of about of about 0.5ml/kg/hour. Intravenous fluids are usually needed for only 24-48 hours. Intravenous fluid should be gradually reduced when the rate of plasma leakage decreases towards the end of the critical phase.This is indicated by increased urine output and/or improvement of oral fluid intake, or decrease in the haematocrit below the baseline value in a stable patient.[4,10,11,23,24]
- Patients with warning signs,should be monitored until the period of risk is over. Parameters that should be monitored include vital signs and peripheral perfusion(1-4 hourly until the patient is out of the critical phase), haematocrit (before and after fluid replacement,then 6-12 hourly),blood glucose and other organ functions(such as renal profile,liver profile,coagulation profile, as indicated)[4,10,11,25,26]

Calculation of fluid quota for adults

Fluid quota in adults is based on the maximum lean mass of 50kg.Irrespective of the actual weight of the adult(even if he weighs more than 50kg)he still would have the same amount of circulatory volume as that in a 50kg adult.For adults weighing less than 50kgs,the actual weight may be used for calculating fluid quota. The fluid quota calculating formula is referred to as M+5%.This refers to a sum of maintenance fluid plus 5% losses.The entire fluid quota is given over 48hours(the duration of the critical phase). For patients presenting in shock the quota may be given over 24 hours.Such a patient may have been leaking for a considerable length of time and may well be in the latter half of the critical phase.[10,11,25]

Calculation of total fluids during critical phase in adult (50 kg)

M (Maintenance)	100ml/kg for 1st 10kg	=1,000mL
	+50ml/kg for next 10kg	= 500 mL
	+20ml/kg for balance weight	= 600 mL
	Total maintenance	= 2,100 mL
5% deficit		= 50mL × body wt (kg)
		=50mL × 50kg
		=2,500 mL
Total fluid quota (oral + iv) for 50kg adult		= M+5%
		= 2,100 mL + 2,500 mL
		= 4,600 mL

Therefore, the maximum fluid requirement for an average adult for the entire phase of critical phase of 48 hours is 4,600mL.10It is important to note that if the patient is taking oral fluids, this oral intake should also be included in the total fluid quota which also would include any fluid given in the form of boluses.Fluid quota is aimed at giving just adequate amount of fluid to maintain perfusion to vital organs without causing fluid overload.[10,11]Once the fluid quota is exceeded, chance of fluid overload is high.All patients will not need the full fluid quota of M+5% and some may need less than this. The recommended intravenous fluid is normal saline or Hartmann's solution.Oral fluid should consist of electrolyte solutions such as king coconut water,other fruit juices,oral rehydration fluid and kanji.Drinking plain water should be minimized.[10,11,27,28] How this volume should be infused during this the critical period depends on the haemodynamic status of the patient.If the patient is haemodynamically stable, and not in shock,but in the critical(leaking) phase this volume(M+5%) could be spread over 48 hours.[10,11,29] However this volume should be not given at a uniform rate.Considering the dynamic nature of the leakage(Fig. 2),fluid should be started at a

slower rate.The rate of fluid should be increased in a stepwise pattern,guided by haematocrit and other parameters.Since plasma leakage does not persist at a higher rate for more than a few hours, the rate of fluid intake should be reduced in a stepwise pattern again. Urine output should be maintained at 0.5-1ml/kg/hour(Calculate the urine output in ml/kg/hour,using the same weight used for fluid calculation) and pulse pressure around 30mmHg during the entire critical period.[5,10]

Management of shock

Those who have severe leakage may develop shock when a critical volume of plasma is lost. Dengue shock syndrome is a medical emergency. The initial rate of fluid replacement depends on whether the patient is in shock with narrow pulse pressure(Fig. 3) or in hypotensive/profound shock (Fig. 4).[5,10,30,31] Recognition of shock on its early(compensated)stage and prompt fluid resuscitation will ensure a good clinical outcome(Fig.5).[10,11,32,33] Consequences of failure to recognize the compensated shock phase may be drastic. As the compensated phase leads to the decompensated phase, the disease outcome becomes less certain with increasing chance of a more complicated course.The volume of initial and subsequent fluid resuscitation depends on the degree of shock.Initial fluid bolus can be 10 or 20 ml/kg ideal body weight in compensated and decompensate shock respectively.[10,11,34,35,36]

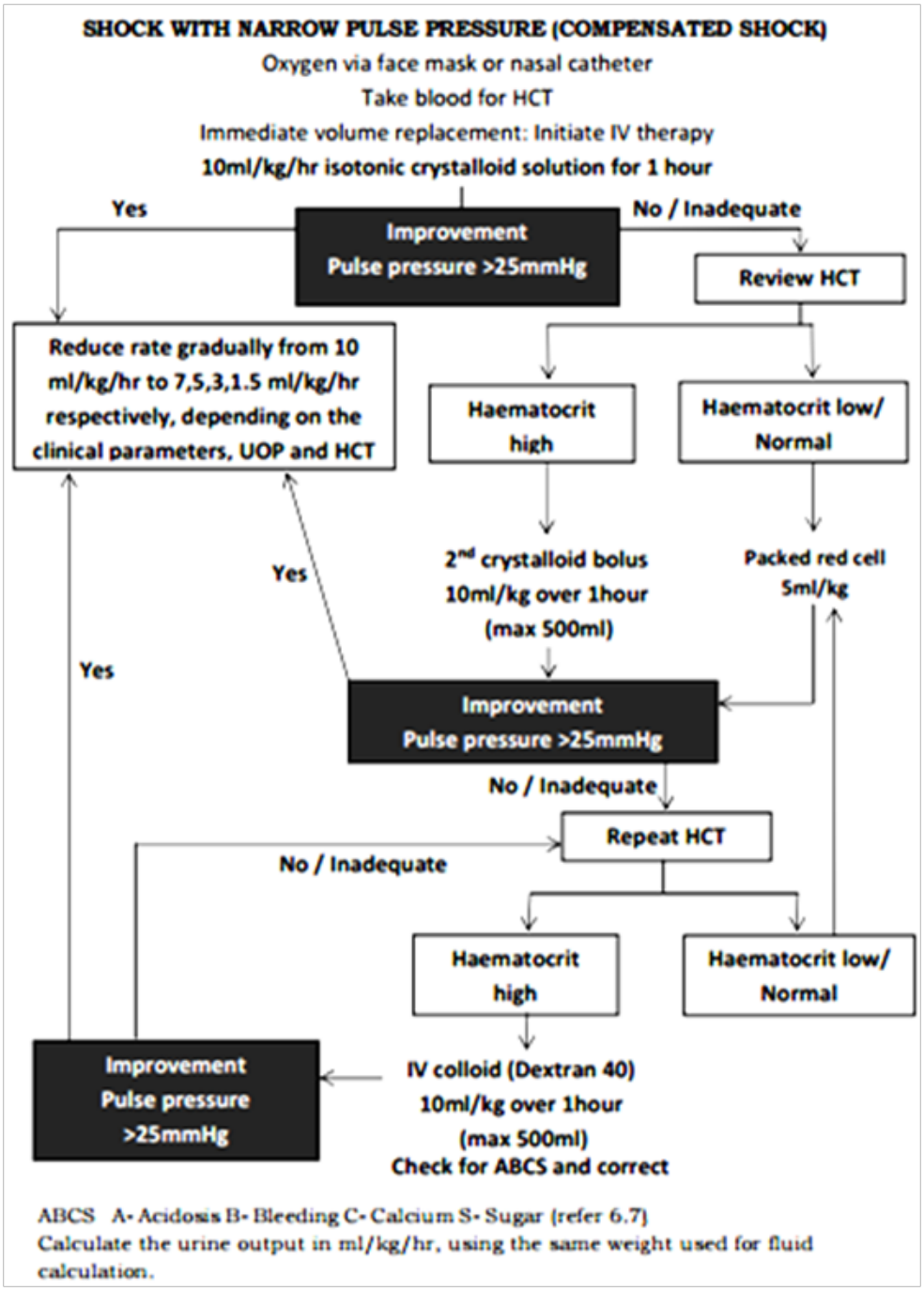

Figure 3.Management of compensated shock.[10] Source: www.epid.gov.lk/.../guidelines_for_the_management_of_df_and_dhf_in.Sri.

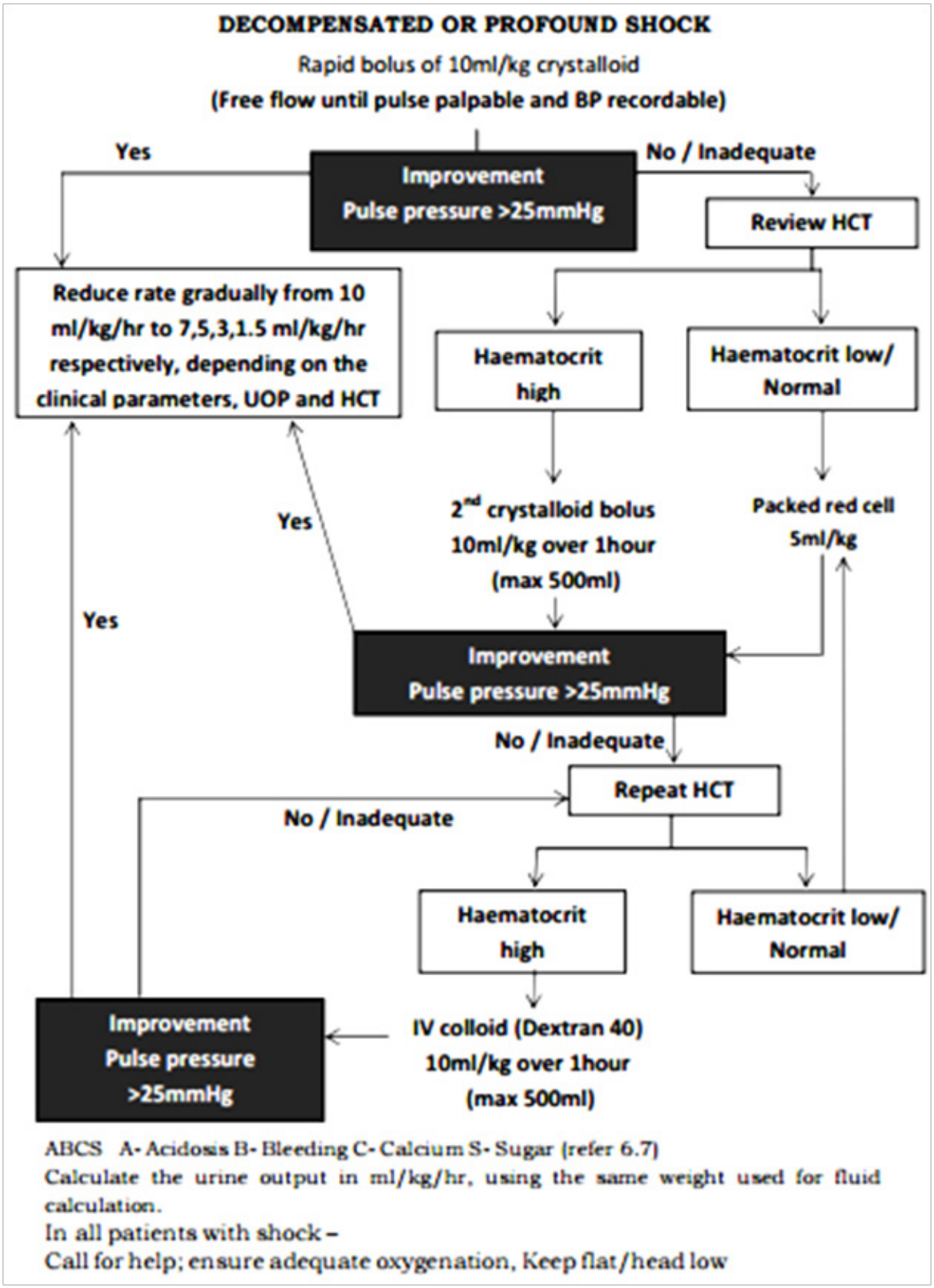

Figure 4. Management of decompensated shock.10Source: www.epid.gov.lk/.../guidelines_for_the_management_of_df_and_dhf_in.Sri.

Clinical parameters indicating adequacy of fluid resuscitation	
Improvement of general well-being	Improving pulse pressure
Good orientation & mental state	Reduction in tachycardia or normalization of heart rate
Warm peripheries	Increase in urine output
Capillary refill time ≤ 2 sec	Reducing in tachypnea or normalization of respiratory rate
Stable BP	

Laboratory parameters indicating adequacy of fluid resuscitation:

- Decrease in HCT (in face of hemodynamic stability
- Improvement in metabolic acidosis

Figure 5.Improvement in the following parameters indicates adequate fluid resuscitation:[11] Source: Dengue GCP Guideline 2012

Persistent shock

Persistent shock should be considered in patients who fail to improve despite adequate fluid resuscitation. Following causes of persistent shock must be considered and managed.

Following causes of persistent shock must be considered and managed:

Significant bleeding: (Often occult)

- Treat with packed cells (5ml/kg) or whole blood (10ml/kg) may be used. This is expected to increase the HCT by 5%. If HCT is >45% it must be decreased by giving iv fluids before using blood; even if bleeding is likely

Hypocalcemia: Treat with IV (10%) calcium gluconate @ 1 ml/kg (max 10mls diluted in equal volume of saline) as slow bolus over 10 minutes with cardiac monitoring (may be repeated 6 hourly). Empiric treatment with calcium may be given if patient fails to improve or deteriorates despite fluid resuscitation

Acidosis: If the arterial blood bicarbonate (HCO3) falls below 15 meq/l in the patients with decompensated shock, treat with NaHCO3 (8.4%) with an empiric dose of 1ml/kg, diluted in equal volume of saline in a slow infusion. (A bolus of not more than 10 ml /dose – maximum up to 5 doses). Shift the patient to HDU under expert supervision

Hypoglycemia: Treat with intravenous dextrose after bed side glucose measurement. If patient's is still in state of persistent shock despite all the above measures consider sepsis and cardiogenic shock

- Treat with I/V antibiotics: Use intravenous antibiotics as oral administration may worsen vomiting and result in erratic absorption. Choice of antibiotics should be sufficiently broad to provide cover for Gram+, Gram- and anaerobic organisms in keeping with the prevailing culture sensitivity pattern. Choice may later be reviewed in light of blood C/S result of the patient
- Consider inotropic support

Figure 6. Causes of persistent shock. Source: Dengue GCP Guideline 2012

Management of the convalescent phase

Plasma leakage ends within 24-48 hours from the time of onset, and is followed by reabsorption of extravascular fluid. This usually lasts 2-5 days[10,11] and by this time the patient's wellbeing improves, appetite returns to normal,gastrointestinal symptoms abate,haemodynamic status stabilizes and diuresis ensures. Some patients may have a classical rash of "isles of white in the sea of red". Some patients may experience generalized pruritus. Bradycardia and electrocardiographic changes are not uncommon during this stage. During this phase, HCT level may drop further due to reabsorption associated haemodilution. The recovery of platelet count is typically preceded by recovery of white cell count.[5,10,11]

Management of a fluid overload patient

Some degree of fluid overload is inevitable in patients with severe plasma leakage.4,10Recognized causes of excessive fluid overload are:

- excessive and/or too rapid intravenous fluid during the critical phase,
- incorrect use of hypotonic crystalloid solutions,
- inappropriate use of large volumes of intravenous fluid in patients with unrecognized severe bleeding,
- inappropriate transfusion of blood products,
- prolonged intravenous fluid therapy,i.e.continuation of intravenous fluids after plasma leakage has resolved
- co-morbid conditions such as congenital or ischaemic heart disease, heart failure, chronic lung disease and renal disease

The presence of features such as puffy eye lids, rapid breathing, suprasternal in-drawing, intercostals recession, difficulty in breathing, respiratory distress, wheezing, lungs crepitations, large pleural effusions, increased jugular venous pressure, tense ascites and persistent abdominal discomfort, pain and tenderness indicate early stages of fluid overload. Presence of pulmonary oedema and irreversible shock are late clinical features of fluid overload.[4,10,11] Fluid over-loading should be treated according to the haemodynamic status and the haematocrit (HCT) of the patient.[10,11,36]

- If the patient is in shock or has features of fluid overload(haemodynamically unstable) and has high HCT,a bolus of colloid (Dextran 40 or Tetrastarch)should be given as 10ml/kg over an hour.Frusemide 10-20mg should be given in the midway of the bolus, and can be repeated if necessary.[5,10,11]
- If the patient is in shock(haemodynamically unstable) and has a normal or low HCT, immediate blood transfusion is necessary. Until blood is available, a bolus of colloid (500 mL of Dextran or Tetrastarch) could be administered.[4,10,11]
- If the patient is haemodynamically stable and has a normal or low HCT,fluid should be restricted and the patient should be monitored carefully, as the patient is likely to improve within hours.The most probable reason for low HCT is haemo-dilution.However the possibility of concealed bleeding should be considered.If the patient develops features of pulmonary oedema, frusemide 10-20mg should be given intravenously and this dose can be repeated after half an hour accordingly.[10,11]
- If the patient is haemodynamically stable and has high HCT,fluid should be restricted and the patient needs careful fluid monitoring.
  It is likely that the patient will go to polyuric phase and the HCT will settle within several hours.[4,10,11]
- Therapeutic aspiration should be considered in a patient with evidence of fluid overload and poor peripheral circulation if there is gross ascites or massive pleural effusion.[10,11]

Management acute respiratory distress and failure

Causes of acute respiratory distress and failure are:

- Severe metabolic acidosis from severe shock
- Fluid overload-large pleural effusions and ascites
- Acute pulmonary oedema
- Acute respiratory distress syndrome (ARDS)

Severe metabolic acidosis from sever shock

Kussmaul's breathing will be observed in addition to tachycardia and other signs of shock.These patients should be given treatment as for hypotensive shock i.e.prompt resuscitation with fluid boluses and evaluate to ensure that respiratory effort has subsided and that other parameters of adequate circulation are present.[4,10,11] Otherwise the HCT needs repeating and the question of severe bleeding needs to be considered. If the patient is clinically acidotic one dose of 50mL of 8.4% sodium bicarbonate may be given empirically if blood gas cannot be assessed.[4,10]

Fluid Overload

Early clinical features of fluid overload are:

- rapid breathing;
- respiratory distress,difficulty in breathing;
- wheezing,crepitations;
- large pleural effusions;
- tense ascites, persistent abdominal discomfort/pain/tenderness;
- increased jugular venous pressure.[4,10,11]

Late clinical features are:

- pulmonary oedema(cough with pink or frothy sputum,wheezing and crepitations)
- irreversible shock(heart failure,often in combination with ongoing hypovolaemia)

Management of fluid overload depends on the patient's haemodynamic stability,intravascular volume status and was discussed previously.[4,10]

Acute pulmonary oedema and ARDS

These two conditions will cause life-threatening hypoxaemia.Pulmonary oedema is more common than ARDS.Both are aggravated by rapid infusion of fluid

during the critical phase. The goal of therapy is to optimize oxygenation and ventilation with respiratory support and stabilize the haemodynamic condition.[4,10,36]

Management of haemorrhagic complications

Mucosal bleeding may occur in any patient with dengue, but if the patient remains stable with fluid resuscitation, this should be considered as a minor case.[4,11] This bleeding usually improves rapidly during the recovery phase.In patients with profound thrombocytopenia, strict bed rest and protection from trauma should be ensured.There is no evidence to suggest the benefit of prophylactic platelet transfusion in haemodynamically stable patients.[4,10,11]

If sever bleeding occurs it is usually from gastrointestinal tract,and/or hypermenorrhoea.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-steroid ant-inflammatory agents;
- Have pre-existing peptic ulcer disease;
- Are on anticoagulant therapy;
- Have any form of trauma,including intramuscular injection.

Patients with haemolytic conditions are at high risk of acute haemolysis with haemoglobinuria and may require blood transfusion.[4,10,11]

Sever bleeding should be recognized in the following situations:[4,10,11]

- persistent and/or sever overt bleeding in the presence of unstable haemodynamic status, regardless of the HCT level;
- a decrease in haematocrit after boluses of fluid resuscitation together with unstable haemodynamic status;
- refractory shock that fails to respond to consecutive fluid resuscitation of 40-60mL/kg;
- hypotensive shock with inappropriately low/ normal haematocrit;
- persistent or worsening metabolic acidosis in patients with a well-maintained systolic BP, especially in those with severe abdominal tenderness or 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. 5mL/kg of fresh-packed red cells or 10mi/kg of fresh whole blood should be transfused at an appropriate rate and the clinical response should be observed.Blood transfusion should be repeated if there is further blood loss or HCT fails to rise adequately following bloodtransfusion.[4,10]

Management of hepatic encephalopathy

Hepatic dysfunction is a well recognized feature of dengue infections.Mild to moderate rise in liver enzymes is a common finding in dengue fever and in DHF.[10,11,37] This does not warrant any specific treatment.Higher rise of liver enzymes is usually due to ischaemic hepatitis caused by prolonged shock.If there are no features of hepatic encephalopathy,no specific treatment is indicated in these patients. [10,37,38]If there are features of encephalopathy such patients should be treated as for liver failure with the following:[10,11,38]

- Maintain adequate airway and oxygenation
- Infuse minimal intravenous fluids sufficient to maintain intravascular volume
- Use hyper-oncotic colloid solution early if HCT is increased
- Infuse Mannitol to reduce intracranial pressure if renal functions are normal
- Take measures to maintain serum sodium in-between 145-155 meq/L
- Maintain blood sugar above 60 mg/dL
- Give single dose of vitamin K 10mg IV
- Give lactulose to maintain 3-4 bowel motions per day.
- Treat with broad spectrum antibiotics, which are not excreted through liver,if secondary bacterial infection is suspected
- Oral metronidazole may be used
- Ventilate (IPPV)early,if the features of encephalopathy are getting worse.
- There are no strong evidence to support the use of L-arginine L-Ornithine (LOLA) or N-Acetyl Cysteine(NAC) in these patients.

Dengue in pregnancy

In the recent decade more cases of dengue in pregnancy are being reported.The clinical manifestations, treatment and outcome of dengue in pregnant women are similar to those of non-pregnant women but with some important differences.[4,10] Misdiagnosis or delayed diagnosis is not uncommon due to some of the overlapping clinical and/or laboratory features with the better recognized conditions of pregnancy.These include eclampsis or pre-eclampsia, haemolysis, elevated liver enzymes and low platelet counts (HELLP) syndrome, pneumonia, pulmonary embolism,various obstetric causes of per-vaginal bleeding and other infectious diseases. The diagnosis of plasma leakage may be difficult due to confusion with the normal physiological changes in pregnancy.[4,10,39] Therefore,the following baseline parameters should be noted as early as possible on the first day of illness.[4,10]

- Pulse,blood pressure(BP) and pulse pressure(baseline BP is often lower and pulse pressure wider and heart rate may be higher)
- Full blood count(Haemoglobin,HCT and platelet may be lower than in non-pregnant patient)
- SGOT/SGPT

A multi-disciplinary team consisting of an obstetrician, physician, anesthetist and paediatrician should be involved in the management. All pregnant patients

with fever more than 24 hours without a definite cause should be advised to get admitted to hospital.Urgent referral to the physician is essential if admitted to the obstetric ward.[4,10,40]

Challenges in recognition of dengue disease and plasma leakage in pregnancy

- Symptoms of hyper emesis during first trimester of pregnancy resemble the warning signs of severe dengue and this may delay the recognition of severe dengue.[4,10]
- After the second trimester it is normal to see an increase in circulatory blood volume with generalized vasodilatation, resulting in an increased baseline heart rate and lower baseline BP, as well as a lower baseline HCT. This can confuse the diagnosis of dengue and therefore clinicians need to be alert to the following:[4,10,40]
  - o The lower BP and tachycardia of normal pregnancy could be misinterpreted as hypotensive shock.
  - o The lower baseline HCT after the second trimester should be noted. Establishing baseline haematocrit during the first 2-3 days of fever is essential for early recognition of plasma leakage.
  - o Clinical signs of plasma leakage such as pleural effusion and ascites could be difficult to elicit in the presence of a gravid uterus.

Discharge criteria

The following criteria are to be taken into account while contemplating a discharge of a dengue patient.[11]

Discharge criteria

- Must be afebrile for 48 hours (without antipyretics)
- Stable general condition
- Recovery of appetite
- Stable haematocrit for at least 24 hours
- Rising trend in platelet count (minimum 40,000)
- No dyspnea or respiratory distress attributable to pleural effusion or ascites

Developing a vaccine for dengue

Until now, there is no approved drug or vaccine against dengue.[1,4] Several issues have prevented the development of a successful vaccine for dengue. Presence of four distinct serotypes of dengue virus, incomplete understanding of the pathophysiology of dengue fever, absence of animal model to recreate the disease process in human and technical difficulties in accurate measurement of neutralizing antibody titer following vaccination with current assay methods all contribute to the hindrance to developing a successful vaccine for dengue.[1,3,5] Several vaccine candidates are currently being evaluated in clinical studies. The candidate currently at the most advanced clinical development stage is live-attenuated tetravalent vaccine based on chimeric yellow fever-dengue virus(CYD-TDV), has progressed to phase III efficacy studies.[5]

Future directions

There is no vaccine for dengue available and one of the major areas for future research is development of a successful vaccine. Research into understanding the pathophysiology of dengue,mainly the mechanisms behind the capillary leakage and drop in platelet count, will help in accurate prediction of the critical phase,identifying patients at risk, and targeting specific immunomodulatory therapy. The role of immunosuppressive/immunomodulatory therapy in dengue has not been adequately explored and needs further research.[43,44] Innovative approaches to preventing transmission of the virus, such as modification of mosquito population, should be fostered.

CONCLUSION

Dengue is now endemic in more than 125 countries globally and approximately 2.5 billion of the world's population are at risk of infection.Though it is a short-lasting illness without any significant long-term sequelae,a severe infection can be lethal. There is no antiviral therapy or vaccination available for dengue at this time,leaving only early detection and symptomatic treatment with fluid resuscitation essential for management of severe cases.

Disclosure

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