REVIEW

Managing dengue fever in primary care: A practical approach

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Abstract

Dengue is a common cause of illness seen in primary care in the tropical and subtropical countries. An understanding of the course of disease progression, risk factors, recognition of the warning signs and look out for clinical problems during the different phases of the disease will enable primary care physicians to manage dengue fever in an appropriate and timely manner to reduce morbidity and mortality.

Introduction

Dengue is a common cause of illness seen in primary care settings in tropical and subtropical countries. It is endemic in more than 100 countries of Africa, America, Eastern Mediterranean, South-East Asia and Western Pacific.[1] It is caused by dengue virus—a mosquito-borne flavivirus and transmitted by *Aedes aegypti* and *Aedes albopictus*.[2] There are four distinct dengue serotypes, DEN-1, 2, 3 and 4.

A report had shown that 30% of deaths due to dengue had sought medical attention within 24 hours of onset and 67% by 72 hours.[3] Among the patients with dengue who were hospitalised, 83.9% had sought medical consultation at primary care level before admission and 68.7% had been seen on two or more occasions.[4] The mean duration between first contact with primary care and hospitalisation was 1.4 days. Therefore, primary care physicians play a very important role in the early recognition and management of dengue fever when patients progress through the different phases of illness.

Diagnosis of dengue fever

Dengue viruses cause symptomatic infections or asymptomatic seroconversion. Patients with asymptomatic infection are viraemic and thus may be a source of infection. Symptomatic dengue infection is a systemic and dynamic disease. The incubation period lasts for 5 to 7 days and the onset of the illness is abrupt. It has a wide clinical spectrum, which includes both severe and non-severe clinical manifestations.[5] Common presenting symptoms include high-grade fever, headache, retro-orbital pain, myalgia, arthralgia, nausea, vomiting and rash. The symptoms usually last for 2–7 days. As these symptoms are relatively undifferentiated in early stages, other differential diagnoses need to be considered in the first 72 hours. In patients with moderate-to-severe disease, the

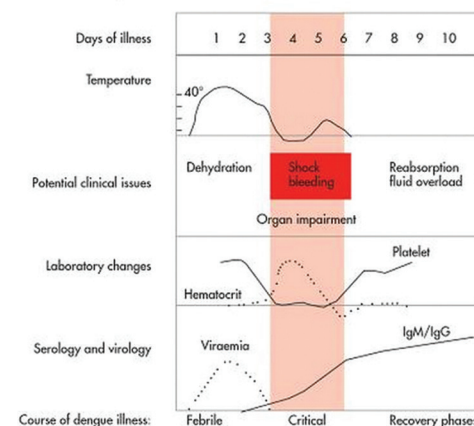course of the illness follows three phases: febrile, critical and recovery (Figure 1).

Figure 1. Course of dengue illness. (Yip WCL, 1980)[6]

The severity of the disease usually becomes apparent during defervescence, that is, during transition from the febrile to the afebrile phase. This often coincides with the onset of the critical phase, usually after 72 hours of fever. The critical phase is distinguished by the pathophysiological phenomenon of increased capillary permeability, which lasts approximately for 24 to 48 hours and is more frequently seen in secondary dengue infections. This phase is followed by the recovery phase. The key to achieve a good clinical outcome is to have an understanding of the different phases of the disease and be alert to the clinical problems that could arise during these phases.

Febrile phase of dengue

After the incubation period, the illness starts abruptly with high fever accompanied by non-specific symptoms such as facial

flushing, skin erythema, generalised body aches and headache. This febrile or viraemia phase usually lasts for 2 to 7 days. It can be clinically difficult to distinguish dengue from non-dengue febrile illnesses in the early febrile phase.

In a single-centre outpatient-based cohort study enrolling 214 patients aged 16 years and more with ≤72 hours of undifferentiated fever, 65% had a laboratory-confirmed diagnosis of dengue, whereas the rest were classified as other febrile illnesses (OFI).[7] Of the 140 patients with dengue, 11.4% developed dengue haemorrhagic fever (DHF), no patients developed dengue shock syndrome (DSS) and 37.1% of patients required hospitalisation. In addition to a recent history of dengue within the family or neighborhood, the three early clinical predictors of dengue at ≤72 hours of fever were nausea and/or vomiting, postural dizziness and lower total white cell count compared to patients with OFI. Symptoms such as headache, myalgia, arthralgia and retro-orbital pain that were frequently reported by patients with dengue fever were also observed in patients with OFI with no significant differences between the two groups. Similarly, children with dengue were more likely to report anorexia, nausea and vomiting. They had a positive tourniquet test, lower total white cell counts, absolute neutrophil and monocyte counts and higher plasma ALT and AST than the children with OFI.[8] Symptoms of upper respiratory tract infections such as injected pharynx and enlarged tonsils did not exclude dengue.[9]

After 2 to 3 days of high fever, anorexia and nausea, most patients may have varying degrees of dehydration and lethargy. The quality of life decreases to approximately 40% to 50% at the onset of fever with experiences of somatic pain and discomfort and difficulties in cognition, sleep, mobility, self-care and anxiety or depression.[9] Mild haemorrhagic manifestations such as petechiae and mucosal membrane bleeding (e.g., nose and gums) may be seen.[8,10] Easy bruising and bleeding at venepuncture sites are present in some cases. Massive vaginal bleeding (in women of childbearing age) and gastrointestinal bleeding may occur during this phase, although this is not common.[7] The liver may be enlarged and tender after a few days of fever.[4] The earliest change in the full blood count is a progressive decrease in white blood cell count, which should alert the physician to a high probability of dengue. This leucopenia is most likely due to a virus-induced down-regulation of haematopoiesis.

Critical phase

During the transition from febrile to afebrile phase, usually after day 3 or as late as day 7 of

fever, patients without an increase in capillary permeability improve without going through the critical phase. Their appetites improve and they feel better. Patients with increased capillary permeability, however, experience worsening of symptoms with the subsidence of high fever. Defervescence usually occurs on days 3 to 8 of illness when temperature drops to 38°C or less and remains below this level. Patients may have warning signs, mostly as a result of plasma leakage (Table 1). Warning signs usually precede the manifestations of shock and appear towards the end of the febrile phase, usually between days 3 and 7 of illness.

Table 1. Warning and danger signs and symptoms of dengue fever

Persistent vomiting >3 times a day
Severe abdominal pain
Lethargy and/or restlessness, sudden behavioural changes
Bleeding: epistaxis, black coloured stools, haematemesis, excessive menstrual bleeding, dark-coloured urine or haematuria
Postural hypotension—dizziness
Pale, cold clammy hands and feet
Not able to drink and less/no urine output for 4–6 h
Difficulty in breathing
Enlarged and/or tender liver
Clinical fluid accumulation
Rising HCT together with rapid fall in platelet count

In the full blood count picture, progressive leucopenia followed by a rapid decrease in platelet count usually precedes plasma leakage. An increasing haematocrit (HCT) above the baseline is another early sign.[11,12] The period of clinically significant plasma leakage usually lasts 24–48 h. The degree of plasma leakage varies. A rising haematocrit precedes changes in blood pressure (BP) and pulse volume. The degree of haemoconcentration above the baseline haematocrit reflects the severity of plasma leakage; however, this can be masked by early intravenous fluid therapy. Usually pleural effusion and ascites are clinically detectable only after an intravenous fluid therapy unless the plasma leakage is significant, which is a case of patient in a state of shock. A right lateral decubitus chest radiograph, ultrasound detection of free fluid in the chest or abdomen or gall bladder wall oedema may precede clinical detection. In addition to the plasma leakage, haemorrhagic manifestations such as easy bruising and bleeding at venepuncture sites

occur frequently. Shock occurs when a critical volume of plasma is lost through leakage; it is often preceded by warning signs. Some patients progress to the critical phase of plasma leakage and shock before defervescence. In these patients, a rising haematocrit and rapid onset of thrombocytopenia or the warning signs indicate the onset of plasma leakage. Most patients with dengue having warning signs recover from intravenous rehydration, although some will deteriorate to severe dengue.

Recovery phase

As the patient survives the 24- to 48-hour critical phase, a gradual reabsorption of extravascular compartment fluid takes place in the following 48 to 72 hours. During this time, patient's general well-being improves, appetite returns, gastrointestinal symptoms abate, haemodynamic status stabilises and diuresis ensues. Some patients may exhibit a confluent erythematous or petechial rash in small areas of normal skin described as "isles of white in the sea of red".[13] Some may experience generalised pruritus. Bradycardia and electrocardiographic changes are common during this stage. The haematocrit stabilises or may become 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 oedema or congestive heart failure may occur during the critical and/or recovery phases if excessive intravenous fluids have been administered. Table 2 summarises the complications that can be encountered in the various phases of dengue.

Table 2. Medical complications seen in the febrile, critical and recovery phases of dengue

No.	Phase	Complication
1	Febrile phase	Dehydration: High fever may cause neurological disturbances and febrile seizures in young children
2	Critical phase	Shock from plasma leakage: Severe haemorrhage and organ impairment
3	Recovery phase	Hypervolaemia (only if intravenous fluid therapy has been excessive and/or has extended into this period) and acute pulmonary oedema

The various risk factors associated with severe disease of dengue are listed as below:

- Infants
- Young children
- Pregnant women
- Diabetes mellitus
- Hypertension
- Haemolytic conditions
- Older persons
- Obese patients

The revised dengue case classification

The development of the revised dengue case classification into dengue (with or without warning signs) and severe dengue (D/SD) was introduced in 2009 (Figure 2).[14] The most recent systematic review compared the 1997 classification with the revised dengue case classification.[15] Five years after its introduction, the D/SD classification is able to detect disease severity with high sensitivity and thus assisting the clinical management and potentially contributing to reduce mortality. It is recommended that a clinical diagnosis of dengue (e.g., probable dengue based on case definition or laboratory confirmed dengue) should be made first and then the warning signs should be applied to help in triage.
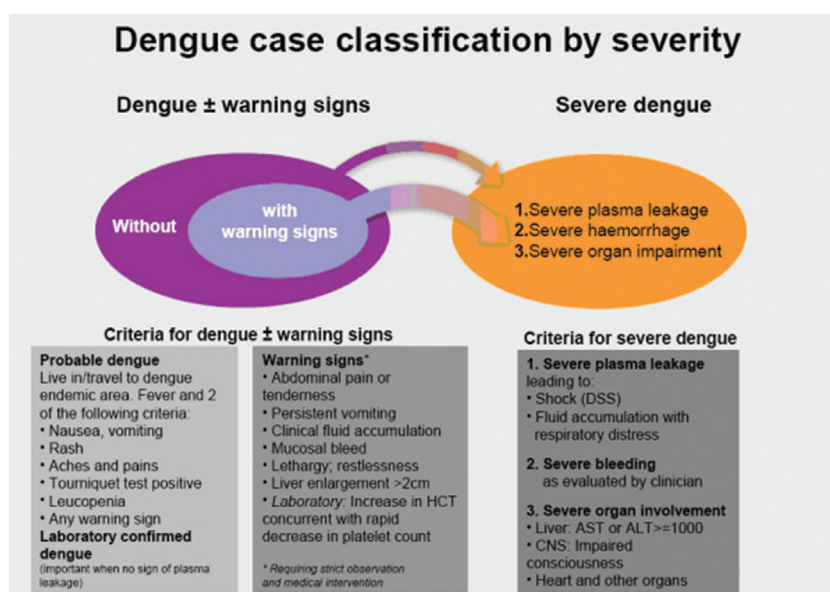
Dengue case classification by severity

Dengue ± warning signs   **Severe dengue**

Without | with warning signs → 1.Severe plasma leakage / 2.Severe haemorrhage / 3.Severe organ impairment

Criteria for dengue ± warning signs

Probable dengue
Live in/travel to dengue endemic area. Fever and 2 of the following criteria:
• Nausea, vomiting
• Rash
• Aches and pains
• Tourniquet test positive
• Leucopenia
• Any warning sign
Laboratory confirmed dengue
(important when no sign of plasma leakage)

Warning signs*
• Abdominal pain or tenderness
• Persistent vomiting
• Clinical fluid accumulation
• Mucosal bleed
• Lethargy; restlessness
• Liver enlargement >2cm
• *Laboratory*: Increase in HCT concurrent with rapid decrease in platelet count

* Requiring strict observation and medical intervention

Criteria for severe dengue

1. **Severe plasma leakage** leading to:
• Shock (DSS)
• Fluid accumulation with respiratory distress

2. **Severe bleeding** as evaluated by clinician

3. **Severe organ involvement**
• Liver: AST or ALT>=1000
• CNS: Impaired consciousness
• Heart and other organs

Figure 2. Dengue case classification by severity. (WHO, 2009)[14]

It is important to note that the warning signs should not be randomly applied without making a clinical diagnosis of dengue.

Clinical evaluation

Clinical evaluation of the patients involves four steps–history taking, clinical examination, investigations and diagnosis and assessment of disease phase and severity.

Step 1: A patient's history should include:

• Date of onset of fever onset (date is preferable to the number of days of fever)
• Other symptoms and severity
• Ask the 3 three golden questions:
  - Oral fluid intake—quantity and types of fluids
  - Urine output—quantify in terms of frequency and estimated volume and time of most recent voiding
  - Types of activities performed during this illness (e.g., can the patient go to school, work, market, etc?)

These questions, though not specific to dengue, give a good indication of patient's hydration status and how well the patient copes with his illness.

• Other fluid losses—such as vomiting or diarrhoea
• Presence of warning signs, particularly after the first 72 h of fever
• Family or neighbour with dengue or travel to dengue-endemic areas
• Medications (including non-prescription or traditional medicine) in use
  - List of medications and the time they were last taken
• Risk factors
• Jungle trekking or swimming in waterfall
  - Consider leptospirosis, typhus and malaria
• Recent unprotected sexual or drug use behaviour
  - Consider acute HIV seroconversion illness

Handout for homecare of dengue patients
(Important information to be given to family members at outpatient department)

A. What should patients do?
  • Adequate bed rest
  • Drink small volumes of fluids frequently. Types of fluids: include milk, fruit juice, isotonic electrolyte solution (ORS), rice water and, coconut water. Volume:
    - Young children at least 3 cups (~250 mL each) per day
    - Older children at least 4 cups per day
    - Adults at least 6 cups per day
  • Keep body temperature below 39°C. If temperature rises >39°C, give patients paracetamol. Paracetamol is available in tablets (500 mg per tablet) or syrup (120 mg per 5 mL syrup). The recommended dose is 10 mg/kg/dose, not more than 4–6 times in 24 hours and not more than 4 days.
  • Tepid sponging should be applied to the forehead, neck, armpits and inguinal regions. Lukewarm shower or bath is recommended for adults
  • Daily follow-up*
  • Watch out for warning/danger signs (Box 1)
  • Source reduction—clear breeding sites in and around house

> **Handout for homecare of dengue patients**
> (Important information to be given to family members at outpatient department)
>
> B. What should patients avoid?
>   • Aspirin or non-steroidal anti-inflammatory agents (NSAIDs)
>   • Too much paracetamol
>   • Intravenous fluid therapy at home is dangerous and will lead to complications

Figure 3. Handout for homecare of dengue patients

*   There are 8 parameters to be assessed: 3 of them relate to peripheral perfusion (capillary refill time, colour and temperature of extremities, and peripheral pulse volume), 2 to the cardiac output (heart rate and blood pressure), 2 to organ perfusion (brain and kidney) and 1 to respiratory compensation for shock. By holding patient's hand, you can evaluate 4 of these parameters.

Step 2: Physical examination

Assess:
• Mental state
• Hydration status
• Peripheral perfusion done by holding the patient's hand, assessing the colour, capillary refill time, temperature of the extremities, pulse volume and pulse rate (CCTVR)
• Haemodynamic status (Table 3)
• Tachypnoea/acidotic breathing/pleural effusion
• Abdominal tenderness/hepatomegaly/ascites
• Rash and bleeding manifestations
• Tourniquet test (repeat if previously negative or if there is no bleeding manifestation)

Table 4. Haemodynamic assessment—continuum of haemodynamic changes

*There are 8 parameters to be assessed: 3 of them relate to peripheral perfusion (capillary refill time, colour and temperature of extremities, and peripheral pulse volume), 2 to the cardiac output (heart rate and blood pressure), 2 to organ perfusion (brain and kidney) and 1 to respiratory compensation for shock. By holding patient's hand, you can evaluate 4 of these parameters.

Parameters	Stable circulation	Compensated shock	Hypotensive shock
Conscious level	Clear and lucid	Clear and lucid	Restless and combative
Capillary refill time	Brisk (<2 seconds)	Prolonged (>3 seconds)	Very prolonged and mottled skin
Extremities	Warm and pink	Cool peripheries	Cold and clammy
Peripheral pulse volume	Good volume	Weak and thready	Feeble or absent
Heart rate	Normal heart rate for age	Tachycardia	Severe tachycardia or bradycardia in late shock
Blood pressure	Normal blood pressure for age	Normal systolic pressure but rising diastolic pressure	Hypotension (see definition below)
	Normal pulse pressure for age	Narrowing pulse pressure (≤20 mm Hg) Postural hypotension	Unrecordable blood pressure
Respiratory rate	Normal respiratory rate for age	Tachypnoea	Hyperpnoea or Kussmaul's breathing (metabolic acidosis)
Urine output	Normal	Reducing trend	Oliguria or anuria

Step 3: Investigation

If facilities are available, a full blood count (FBC) should be done at the first visit to establish the baseline haematocrit. However, a normal FBC during the first 72 hours of illness does not exclude dengue infection. FBC should be repeated daily from the 3rd

day onwards until the critical phase is over. The haematocrit in the early febrile phase can be used as the patient's own baseline. A decreasing white blood cell and platelet count makes the diagnosis of dengue very likely. Leucopenia 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 haematocrit compared to the baseline, is suggestive of progress in the plasma leakage/critical phase of the disease. These changes are usually preceded by leucopenia (≤5000 cells/mm^3). In the absence of the patient's baseline haematocrit, age-specific population haematocrit levels can be used as a surrogate during the critical phase. There is however, no local data on the normal range of HCT in children and adults. In the absence of a baseline HCT level, a HCT value of >40% in female adults and children aged <12 years and >46% in male adults should raise the suspicion of plasma leakage.

If facilities for a FBC are not available or if resources are limited, such as in an outbreak, a FBC should be done at the first visit to establish the baseline. This should be repeated after the 3rd day of illness and in those with warning signs and with risk factors for severe disease.

Dengue-specific laboratory tests should be performed to confirm the diagnosis. However, it is not necessary for acute management of patients except in cases with unusual manifestations. Additional tests such as liver function test, glucose, serum electrolytes, urea and creatinine, bicarbonate or lactate, cardiac enzymes, electrocardiogram (ECG) and urine-specific gravity should be considered in patients with co-morbidities or in patients with clinically severe disease as indicated.

Step 4: Diagnosis, assessment of disease phase and severity

Based on the evaluations of history, physical examination and/or FBC and haematocrit, one could clinically determine the diagnosis of dengue, the phase patient is in, the presence or absence of warning signs, the hydration and haemodynamic state of the patient and whether the patient requires admission.

Disease notification and management decision

Disease notification

In dengue-endemic countries such as Malaysia, cases of suspected, probable and confirmed dengue should be notified by telephone within 24 hours to local health office so that appropriate public-health measures can be

initiated. Laboratory confirmation is not necessary before notification, but it should be obtained. In non-endemic countries, usually only confirmed cases should be notified.

Management decisions

Depending on the clinical manifestations and other circumstances, patients may either be sent home (Group A), referred for in-hospital management (Group B), or required emergency treatment and urgent referral (Group C).[16]

Group A (patients who may be sent home)

These are patients who can tolerate adequate volumes of oral fluids (at least 6–8 glasses depending on age), pass urine at least once every 6 hours and do not have any warning signs (particularly when fever subsides).

The key to successful ambulatory management is to give clear and definitive advice on the care that the patient needs to receive at home. These are bed rest, frequent oral fluids and fever management (Box 1). Patients with ≥3 days of illness should be reviewed daily for ability to drink adequate fluids and disease progression (indicated by decreasing white blood cell and platelet counts, increasing haematocrit, defervescence and warning signs) until they are out of the critical period.

Patients should be advised to return to the nearest hospital immediately if they develop any of the warning signs. They should be advised on the following action plan:

• Bed rest may relieve some of the physical discomforts in the febrile phase.

• Adequate oral fluid intake may reduce the number of hospitalisations.[17] Encourage oral intake to replace fluid loss from fever and vomiting. Small amount of oral fluids should be given frequently to the patients with nausea and anorexia. The choice of fluids should be based on the local culture like coconut water in some countries and rice water or barley water in others. 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 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 intake and urine output should be maintained and reviewed daily.

- Take paracetamol for high fever if the patient feels uncomfortable. 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, gastrointestinal tract bleeding and intramuscular hematoma.

- Instruct caregivers to bring the patient to a hospital immediately if any of the following occurs: 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 coffee-ground 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 risk factors. This group of patients should be followed up for daily assessment until they are 24 to 48 hours without fever.

Group B (patients who should be admitted for in-hospital management)

These patients should be admitted for close observation as they approach the critical phase. These include patients with:

- Warning signs only, with no evidence of shock

- Risk factors that may make dengue or its management more complicated (such as pregnancy, infancy, old age, obesity, diabetes mellitus, hypertension, heart failure, renal failure and chronic haemolytic diseases) and 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 shock. If the patient has dengue with warning signs or signs of dehydration, judicious volume replacement by intravenous fluid therapy (5 mL/kg of 0.9% saline for 1 h, then reduce rate to 3-4 mL/kg/hour for 1-2 h) from this early stage may modify the course and the severity of disease. These patients should be admitted for further observation as plasma leakage may progress during the next 24 to 48 hours.

Table 5. Admission criteria

Warning signs	Any of the warning signs for admission (Table 6)
Signs and symptoms related to dehydration and hypovolemia (possible plasma leakage)	Dehydrated patient, unable to tolerate oral fluids
	Dizziness or postural hypotension
	Profuse perspiration, fainting, prostration during defervescence
	Hypotension or cold extremities
	Difficulty in breathing/shortness of breath (deep sighing breaths)
Bleeding	Spontaneous bleeding, independent of the platelet count
Organ impairment	Renal, hepatic, neurological or cardiac
	Enlarged, tender liver, although not yet in shock
	Chest pain or respiratory distress, cyanosis
Findings through further investigations	Rising haematocrit with rapid decrease in platelet count (note that there is no "magic" level of platelet count to admit or not to admit a patient)
	Pleural effusion, ascites or asymptomatic gall-bladder thickening
Co-existing conditions	Pregnancy
	Co-morbid conditions, such as diabetes mellitus, hypertension, peptic ulcer, haemolytic anemia and others
	Overweight or obese (rapid venous access difficult in emergency)
	Infancy or old age
Social circumstances	Living alone
	Living far from health facility
	Without reliable means of transport

Table 6 . Warning signs for admission

Clinical	Laboratory
Severe abdominal pain	Rising haematocrit
Persistent vomiting	Sudden decrease in platelet count
Lethargy, restlessness	
Mucosal bleed	
Liver enlargement	

Group C (patients with severe dengue who require emergency treatment and urgent referral)

These are the patients who are in the critical phase of the disease and have:

- Severe plasma leakage leading to dengue shock
- Severe haemorrhages
- Severe organ impairment (hepatic damage, renal impairment, cardiomyopathy, encephalopathy or encephalitis)

Patient who is in shock should be transferred to the emergency department of the nearest hospital by ambulance and should be accompanied by a doctor. All patients with severe dengue should be admitted to a hospital with access to blood transfusion facilities. Judicious intravenous fluid resuscitation is essential and usually the sole intervention required. During the period of plasma leakage, the crystalloid solution used should be isotonic and the volume is just sufficient to maintain an effective circulation. Plasma loss should be replaced immediately and rapidly with isotonic crystalloid solution. In the case of hypotensive shock, a colloid solution is preferred. If possible, obtain haematocrit levels before and after fluid resuscitation. Intravenous fluid therapy of 5 to 10 mL/kg of 0.9% saline over 1 hour may be life-saving. This should be started as soon as possible. The rate of fluid infusion should be slowed down to 7 mL/kg/h for the second hour if the patient improves.

Post-dengue fever monitoring

Most patients with dengue fever after the recovery phase do not need to be reviewed. However, some patients with deranged liver function tests need a repeated test done after discharge from hospital to ensure if they feel well and the liver functions are recovering.

Conclusions

Dengue fever is a common disease encountered in primary care especially in the tropical countries. An understanding of the course of the disease progression and clinical problems to look out the different phases of the disease will enable primary care physicians to manage dengue fever in an appropriate and timely manner to reduce morbidity and mortality. With appropriate and timely treatment, the morbidity and mortality can be reduced. It is important for primary care doctors to adopt a practical approach to assess, classify and manage dengue fever. It is crucial to identify red flags and high-risk individual and refer them accordingly.

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Ethics approval

Not applicable.

Conflict of interest

None.

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