Indian Academy of Pediatrics (IAP)

STANDARD TREATMENT GUIDELINES 2022

Dengue in Children

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Dengue in Children

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Introduction

- ☑ Dengue fever is one of the most common causes of "undifferentiated tropical fevers" in hospitalized children across India. It is caused by dengue virus of *Flavivirus* family, and it has four serotypes: DENV-1, DENV-2, DENV-3, and DENV-4.
- ☑ In a prospective multicenter study done in 34 intensive care units ICUs across India, dengue (23%) emerged as the most common etiological diagnosis in patients presenting with acute febrile illness and systemic manifestations.
- ☑ Dengue fever is associated with higher morbidity and mortality especially in children. The risk of death is fourfold higher in children younger than 15 years of age.
- ☑ By virtue of early diagnosis and improvement in clinical management protocols, the case fatality ratio is declined from 3.3% in 1996 to 0.4% in 2010.

Case Definitions in Clinical Practice

- ☑ *Probable dengue fever (DF)/dengue hemorrhagic fever (DHF):* Acute febrile illness of 2–7 days with two or more of features such as "headache, retro-orbital pain, myalgia, arthralgia, rash, and hemorrhagic manifestations" during an outbreak.

  OR

  Nonenzyme-linked immunosorbent assay (non-ELISA) based nonstructural glycoprotein-1 (NS1) antigen/immunoglobulin M (IgM) tested to be positive.
- ☑ *Confirmed dengue fever:* A case compatible with the clinical description of dengue fever with at least one of the following:
  - Isolation of dengue virus by viral culture
  - Demonstration of IgM antibody against dengue virus by ELISA
  - Demonstration of dengue virus antigen (NS1) by ELISA

Case Definitions in Clinical Practice

- Immunoglobulin G (IgG) seroconversion in paired sera after >2 weeks with fourfold increase in titer
- Detection of viral nucleic acid by polymerase chain reaction (PCR)

☑ *Dengue with warning signs:* Probable or confirmed dengue fever with any of the following "warning signs"

- Abdominal pain or tenderness
- Persistent vomiting
- Clinical fluid accumulation
- Mucosal bleed
- Lethargy, restlessness
- Liver enlargement >2 cm
- *Laboratory:* Increase in hematocrit (HCT) concurrent with rapid decrease in platelet count

☑ *Severe dengue:*

- *Severe plasma leakage* leading to
  - Shock (DSS)
  - Fluid accumulation with respiratory distress
- *Severe bleeding:* As evaluated by clinician
- *Severe organ involvement:*
  - *Liver:* Aspartate transaminase (AST) or alanine transaminase (ALT) ≥1,000
  - Central nervous system (CNS)—impaired consciousness
  - Heart and other organs involvement

Natural History of Dengue Infection and Dengue Illness in Children

The clinical course of illness passes through the following three phases:

1. *Phase 1: Febrile phase:*
   i. Children are usually febrile throughout this phase and it lasts 2–5 days.
   ii. In some children the temperature can be biphasic.
2. *Phase 2: Critical phase:*
   i. Children enter the critical phase after 3–4 days of onset of the fever.
   ii. During this period, plasma leakage and hemoconcentration starts and patients may develop hemodynamic issues including hypotensive shock and progressive organ dysfunction.
3. *Phase 3: Convalescent phase:*
   i. During this phase, the extracellular fluid, which was lost due to capillary leakage, returns to the circulatory system and the patient's clinical status improves.
   ii. This phase usually starts after 6–7 days of fever and lasts for 2–3 days.

Investigative Approach to Diagnose Dengue Fever

☑ *NS1 antigen:*

- It is a highly conserved glycoprotein of dengue virus. It starts to appear in the infected patient at onset of symptoms and declines over the next few days.
- Both ELISA and immunochromatographic NS1 antigen tests are available whereas ELISA is preferred due to high sensitivity.

☑ *Dengue IgM:*

- IgM antibodies appear after day 5 and are present in close to 70% of patients by day 10 and 100% by day 14.
- IgM antibodies can continue to be detectable for even up to a year and this characteristic accounts for the lower sensitivity and specificity of IgM for diagnosis of dengue.

☑ *Dengue IgG:*

- Primary dengue is associated with appearance of "IgG antibodies" by 1–2 weeks that subsequently peak and then decline and persist for life.
- In secondary dengue, IgG antibody response is good and appears early within the first few days.

☑ *Molecular tests:*

- "Commercially available stand-alone dengue PCR" or "tropical fever multiplex PCR panel" can be used as a diagnostic tool in clinical practice.
- Sensitivity is high in early infections. However, molecular tests are not routinely indicated, as NS1 antigen estimation serves most purposes.

The best sensitivity in clinical practice is achieved by estimating for all NS1 antigens and IgM and IgG at the time of presentation. Molecular tests are not proven to be superior in diagnostic evaluation of dengue fever.

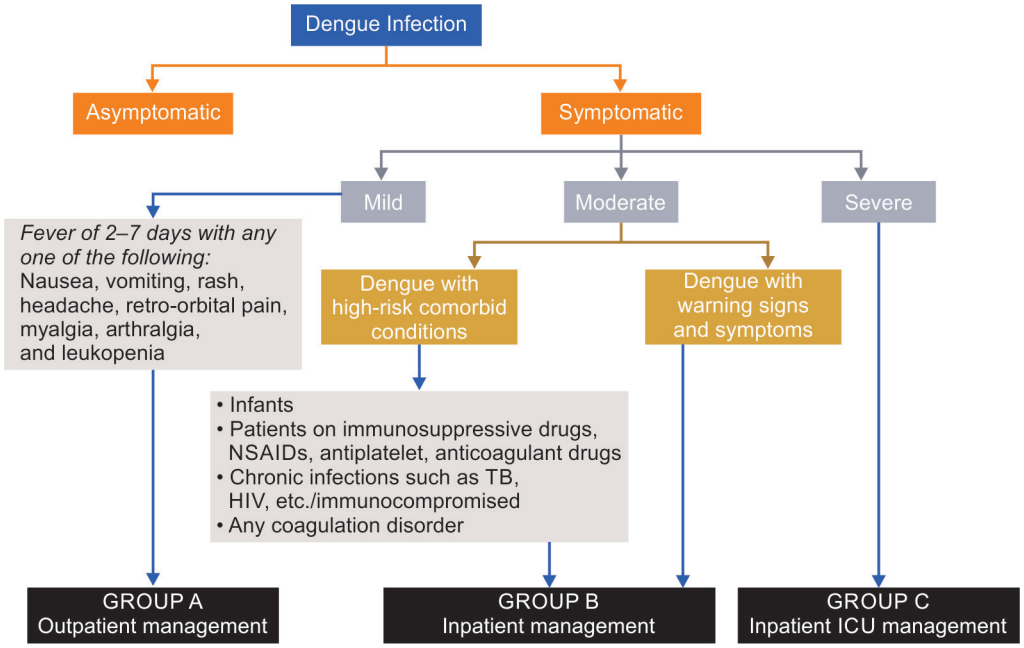
Basic Principles of Dengue Fever Management in Children

☑ Based on the clinical disease classification at the time of presentation to healthcare facility, we can decide the further care need for the child.

☑ **Flowchart 1** may function as a guide to differentiate children requiring out-patient management, hospitalized care and immediate critical care needs.

☑ We should not to forget that dengue in children especially during the critical phase of illness impose "minute-to-minute variation in clinical illness state" hence continuous monitoring is mandatory to secure the safe care of children.

Flowchart 1: Dengue fever: Clinical features and case classification based on severity.



(ICU: intensive care unit; HIV: human immunodeficiency virus; TB: tuberculosis)

Group A: Out-patient Management

☑ *During the febrile phase (2–7 days):*

- Fever management with paracetamol
- Watch for dehydration
- Watch for warning signs (clinical + laboratory)
- Watch for fever defervescence (indicates onset of critical phase)
- Complete blood count when clinically deemed necessary

Group B: Inpatient Management of Dengue Patients with Warning Signs

Children with warning signs warrant hospitalized treatment. Blood Investigations are done during this phase to guide differentiation from other closely mimicking undifferentiated febrile illnesses and to estimate disease severity to direct treatment.

Supportive Investigations to Manage Hospitalized Dengue Children

☑ *Hematocrit:*
- It is usually normal in uncomplicated disease whereas it is high when capillary leak starts.
- 20% rise over the baseline is considered to be clinically significant.
- Monitoring of hematocrit helps in titrating fluid therapy.

☑ *White blood cell count:*
- It is usually low to very low with reactive/atypical lymphocytes in peripheral smear.
- Rise in white cell count during recovery precedes the rise in platelet count.

☑ *Platelet count:*
- The platelet counts rapidly decline during critical phase.
- Clinical recovery is appreciated by rise in platelet count.

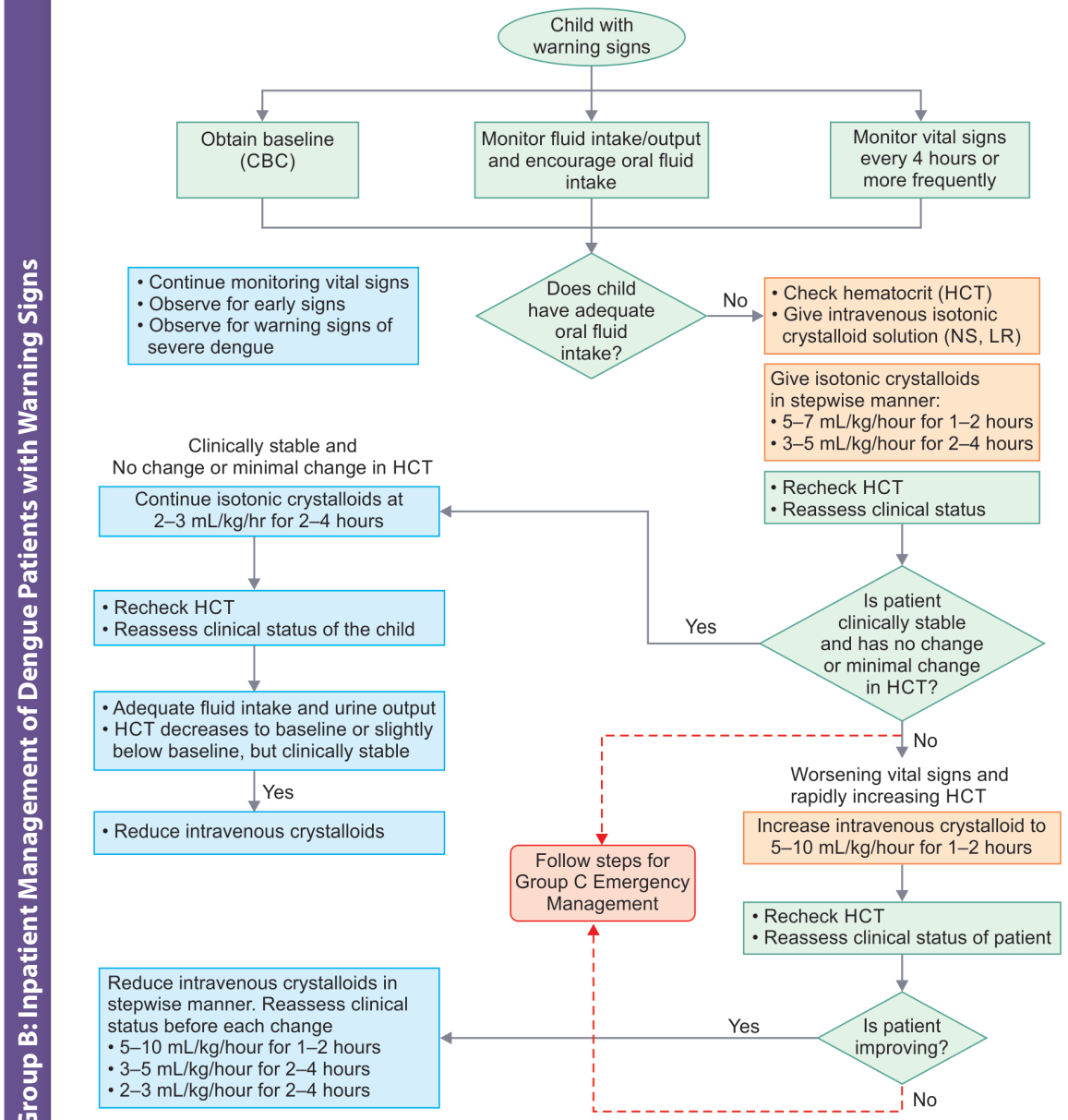
☑ *C-reactive protein (CRP):* It is normal or mildly elevated.

☑ *Liver function tests:*
- Mild elevation with serum glutamic-oxaloacetic transaminase (SGOT) > serum glutamic-pyruvic transaminase (SGPT)
- Higher levels since in severe disease
- Low albumin seen in severe disease due to capillary leak
- Coagulation abnormalities with low fibrinogen raised prothrombin time (PT)/ partial thromboplastin time (PTT) seen in severe diseases.

☑ *Ferritin:*
- Ferritin levels in dengue higher than in other febrile illnesses.
- Very high serum ferritin levels seen in severe disease and in dengue-associated hemophagocytic lymphohistiocytosis (HLH)
- Ferritin values need to be interpreted cautiously along with clinical condition of the index child.

☑ *Renal function tests:*
- Elevated creatinine, proteinuria, and hyponatremia are seen in severe diseases.
- Metabolic acidosis and elevated lactate levels seen in shock and help in prognostication.

Flowchart 2: Group B—inpatient management of dengue patients with warning signs.



(HCT: hematocrit; LR: lactated Ringers; NS: normal saline)

Source: Adapted from Dengue Case Management for Clinicians, Centers for Disease Control and Prevention, 2015.

☑ *Other microbiologic tests:*

- PS for MP, blood cultures, IgM/PCR for chikungunya, scrub typhus IgM, COVID-19 RT PCR, and SARS-COV-2 antibodies for MISC (these investigations are helpful only when we suspect coinfection state).
- **Flowchart 2** guides in managing children with warning signs and without shock during clinical presentation.

Group B: Inpatient Management of Dengue Patients with Warning Signs

- Cautious fluid resuscitation is very important to avoid overloading.
- When "capillary leak" progress, children have a tendency to develop "fluid creep" and worsening respiratory status.
- Fluid resuscitation at the cost of respiratory worsening may not culminate in good outcome.
- Apart from advanced monitoring methods such as lung ultrasonography (USG) for B lines and intra-abdominal pressure monitoring, **Figure 1** depicting *Chart 1* which can be used as an empiric guide for safe fluid therapy at bedside.

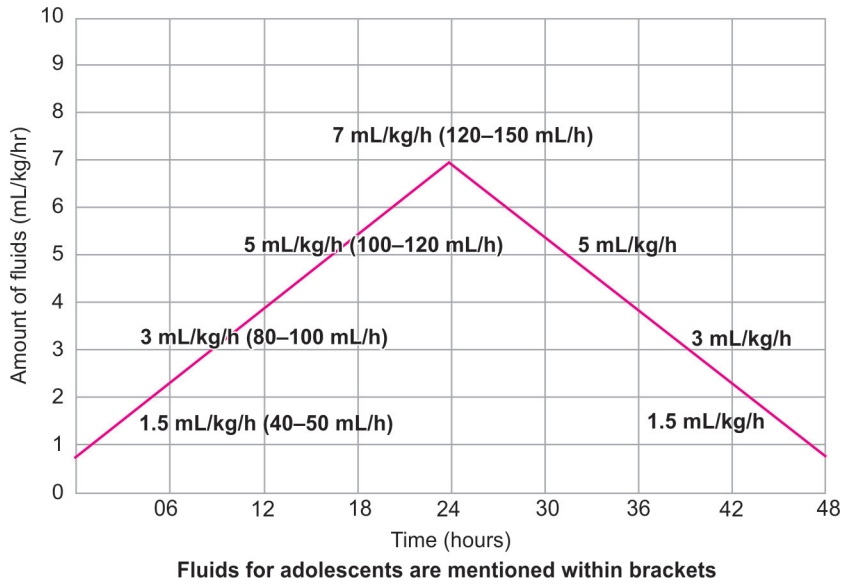


Fig. 1: Guide to rate of fluid intake in critical phase—without shock.
Courtesy: WHO Collaborating for Case Management of Dengue/DHF/DSS. Bangkok, Thailand: Queen Sirikit National Institute of Child Health.

Group C: Inpatient Management of Dengue Shock

- ☑ When a child is categorized to be in dengue shock (hypotensive or compensated) as per the physiological categorization in emergency room, preferably to be managed in pediatric intensive care unit considering the unpredictable clinical trajectory in next 24 hours.
- ☑ As per the current clinical practice standards in pediatric intensive care unit (PICU), hemodynamic assessment by echocardiography is considered after 20 mL/kg crystalloid or colloid resuscitation to ensure lung safe approach in fluid resuscitation.
- ☑ Wherever advanced monitoring is not immediately available, continuous clinical monitoring ensures safe resuscitation when we scale up fluid resuscitation.

Indications for Pediatric Intensive Care Unit Admission

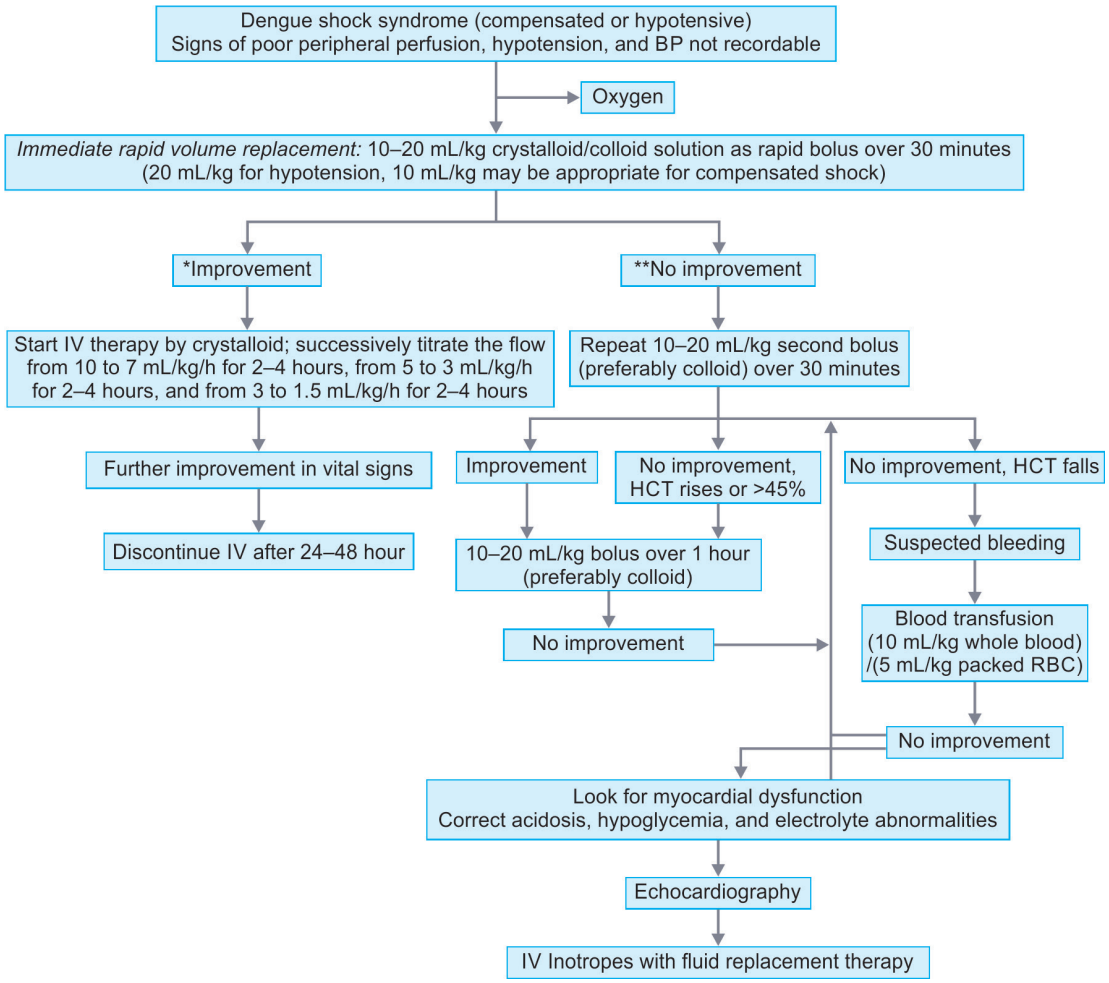
- ☑ Severe plasma leakage with hypoperfusion and hypotension
- ☑ Fluid accumulation with respiratory distress
- ☑ Severe bleeding

Group C: Inpatient management of Dengue Shock

☑ *Severe organ impairment:*

- Myocardial dysfunction
- Acute kidney injury
- CNS dysfunction (altered consciousness and seizures)
- Hepatic dysfunction (ALT/AST >1,000 IU)
- HLH

Flowchart 3: Group C—inpatient management of dengue patients with dengue shock.



(HCT: hematocrit; IV: intravenous; RBC: red blood cells)

☑ *Crystalloid:* Normal saline and Ringer lactate.

☑ *Colloid:* Dextran 40/degraded gelatin polymer (polygeline).

☑ *Unstable vital signs:* Urine output falls and signs of shock.

☑ In case of acidosis, hyperosmolar or Ringer's lactate solution should be avoided

☑ **Improvement:* HCT falls, pulse rate and blood pressure stable, urine output 0.5 to 1.0 mL/kg/hour

☑ ***No improvement:* HCT or pulse rate rises, pulse pressure falls below 20 mm Hg, urine output falls

Group C: Inpatient management of Dengue Shock

The *Chart 2* **(Fig. 2)** can be used as an empirical start point for cautious fluid titration after initial resuscitation in resource-limited setting without immediate access to advanced monitoring methods.

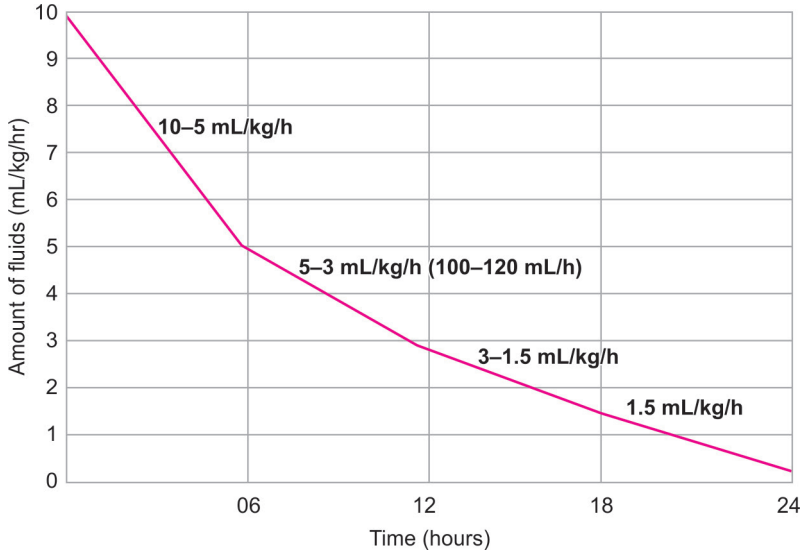


Fig. 2: Guide for the rate of IV fluids in profound shock after initial resuscitation.
Courtesy: WHO Collaborating for Case Management of Dengue/DHF/DSS. Bangkok, Thailand: Queen Sirikit National Institute of Child Health.

Patient Disposition

The following criteria should be fulfilled before discharge from hospital.

- ☑ No fever for at least 24 hours without the usage of antipyretic drugs
- ☑ Good general condition with improving appetite
- ☑ Normal HCT at baseline value or around 38–40 % when baseline value is not known.
- ☑ No distress from pleural effusions and no ascites
- ☑ Normal organ function workup results
- ☑ Platelet count has risen above 50,000 /mm^3.
- ☑ No other complications

Further Reading

- ☑ Centers for Disease Control and Prevention. (2015). Dengue Case Management for Clinicians. https://www.cdc.gov/dengue/resources/dengue-clinician-guide_508.pdf. [Last accessed December, 2022].
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