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PRACTICE POINTER

Assessment and management of dengue

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What you need to know

- Consider dengue in patients with fever who reside in endemic regions or who have visited such regions in the past 14 days
- Some 20-40% of patients with dengue virus infection are thought to experience symptoms, including a high grade fever: these usually occur five to seven days after infection and last for between two and seven days
- Around 95% of those who experience symptoms of dengue will recover after a self limiting febrile illness. Around 5% will deteriorate into a critical phase, when they may develop warning signs and progress to severe dengue. Be alert to the warning signs in all patients with dengue, irrespective of disease phase
- Treatment for dengue is supportive, including paracetamol as an antipyretic and analgesia and advice regarding identification of warning signs and progression to severe dengue. Patients admitted to hospital will be monitored with careful management of fluid balance. Those with severe dengue may require organ support in an intensive care setting

Dengue (dengue fever, breakbone fever), an arboviral infection transmitted by *Aedes* mosquitos, is endemic in more than 100 countries in the World Health Organisation (WHO) regions of Africa, the Americas, the Eastern Mediterranean, South-East Asia, and the Western Pacific.[1] Although most patients are asymptomatic or recover after a febrile phase, 2-5% develop severe disease and may require intensive care.[2] Mortality is 5% among severe dengue.[2] Distribution of the four dengue virus serotypes (DENV-1, DENV-2, DENV-3, and DENV-4) varies geographically and over time.[3]

Previously limited to tropical regions, outbreaks now occur in subtropical and temperate regions, including high altitude areas (such as Kathmandu, Nepal).[2 4 5] In North America and Europe, where dengue is a common cause of fever in travellers returning from endemic areas,[6 7] autochthonous (locally acquired) cases have also been reported.[8 -10] Global warming, increased urbanisation, population increases, increased quantities of stagnant water, and increased trade, transit, and travel to and from dengue endemic areas have contributed to this geographical expansion.[4 11 12]

The advice we provide here is based on the most up to date guidelines issued by WHO global headquarters (the 2009 *Dengue guidelines for diagnosis, treatment, prevention and control*[13]) as well as updates from more recent regional WHO and CDC (Centers for Disease Control and Prevention) papers.[1 11 14 -18] It is relevant to all endemic and non-endemic countries.

Terminology and definitions

The classifications in box 1 replaced the 1997 WHO classifications of "dengue fever," "dengue haemorrhagic fever," and "dengue shock syndrome," but these older terms are still used in some regions, including by some WHO regional offices (such as the WHO South-East Asia Regional office).[15]

Box 1: Classifications of dengue

WHO (2009)[13]

- *Case definition*—Fever up to 40°C lasting at least two days; plus at least two of the following: rash, nausea or vomiting, aches, positive tourniquet test for capillary fragility,* leucopenia, the presence of any dengue warning sign (see box 2)[2 11 13]
- *Symptomatic dengue*—Categorised as dengue fever without warning signs, dengue fever with warning signs, or severe dengue[13]
- *Severe dengue*—One or more of: compensated or hypotensive shock,† respiratory distress, severe bleeding, severe organ impairment[2]
- *Group A/B1/B2/C classification*—Used for management (see table 2):
  - A: Dengue fever without warning signs, and with no high risk factors (box 2)
  - B1: Dengue fever without warning signs, with any high risk factor
  - B2: Dengue fever with any warning sign
  - C: Severe dengue.

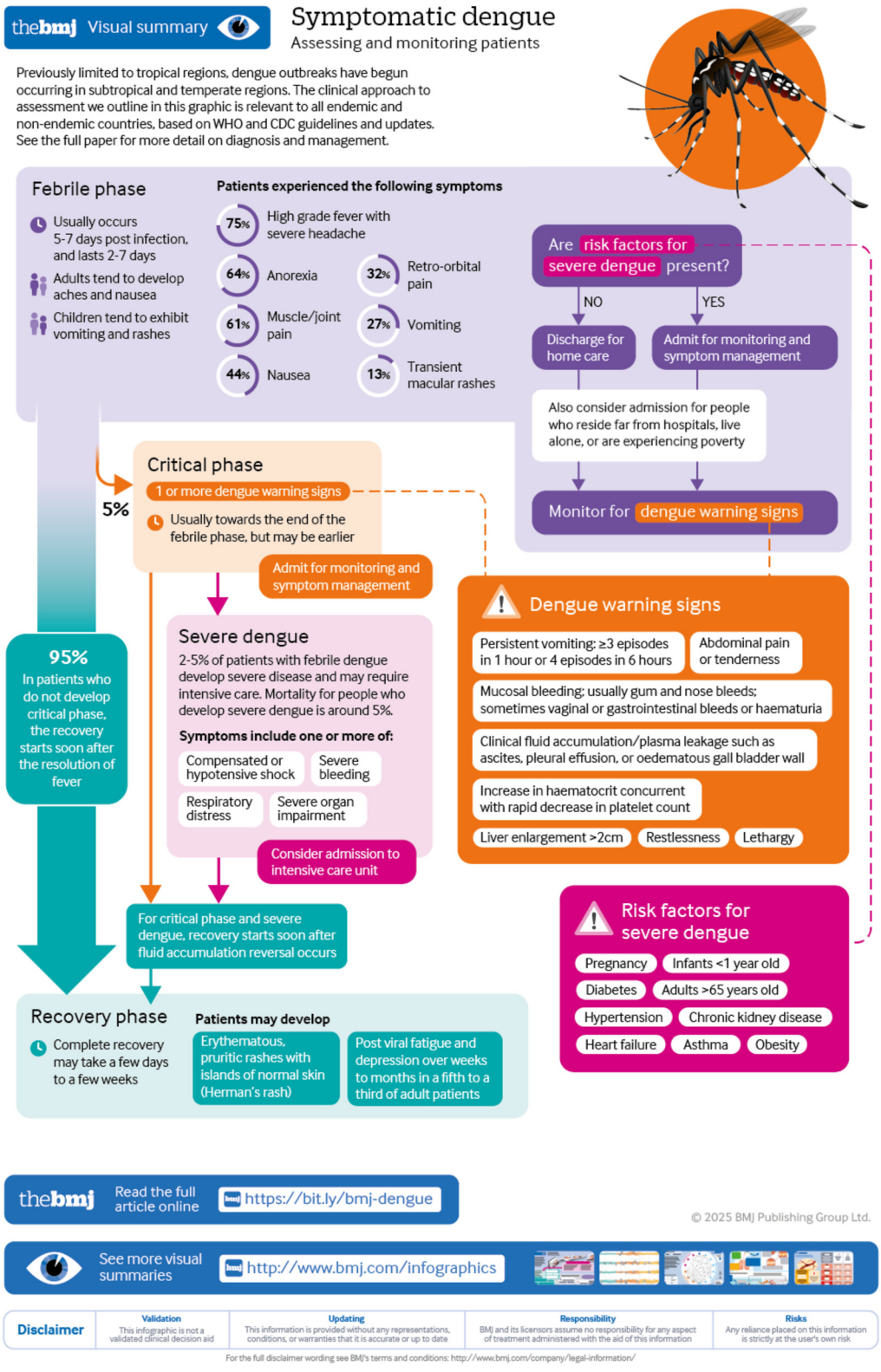
WHO (2009)[13] and CDC Yellow Book on traveller's health (2024)[14]

- *Disease course terminology*—Febrile, critical, and recovery phases (largely correlating with the classifications "dengue fever without warning signs," "dengue fever with warning signs," and "severe dengue")

* The tourniquet test entails inflating a sphygmomanometer cuff on the arm to a point midway between the patient's systolic and diastolic blood pressures and maintaining it for five minutes: in a positive result, ≥10 petechiae per square inch will appear in the cubital fossa 1-2 minutes after deflating the cuff[11]

† Maintained systolic blood pressure (>90 mm Hg) with pulse pressure <20 mm Hg indicates compensated shock, while systolic blood pressure <90 mm Hg indicates hypotensive shock[13]

In this article, we mainly use the terms "febrile, critical, and recovery phase" and, within that, "warning signs" and "severe dengue."



Primary and subsequent infections

In primary infections, antibodies specific to the causative DENV serotype provide long term immunity against that serotype, making re-infection with that serotype uncommon (but not impossible).[19 20] Cross-reacting antibodies against other serotypes are also generated, but, instead of providing partial immunity or neutralising the heterologous serotype, they bind to it, increasing viral entry into cells. This antibody-dependent enhancement can increase disease severity in secondary infections.[2 21 -23] Third and fourth infections are usually mild because more potent cross-neutralising antibodies have developed.[24 25]

How do symptomatic patients present?

Only 20-40% of patients are symptomatic, with most symptomatic people experiencing a self limiting acute febrile illness.[2 13 21]

Febrile phase

This phase is characterised by high grade fever (typically up to 40°C) with severe headache (75% of patients), anorexia (64%), muscle or joint pain (61%), nausea (44%), retro-orbital pain (32%), vomiting (27%), and transient macular rashes (13%, fig 1).[26] It usually occurs 5-7 days after infection, lasts 2-7 days, and, in around 95% of cases, is followed by the recovery phase.[2 11 13 14] Adults more commonly develop aches and nausea, while children more commonly experience vomiting and rashes (fig 1).[27]

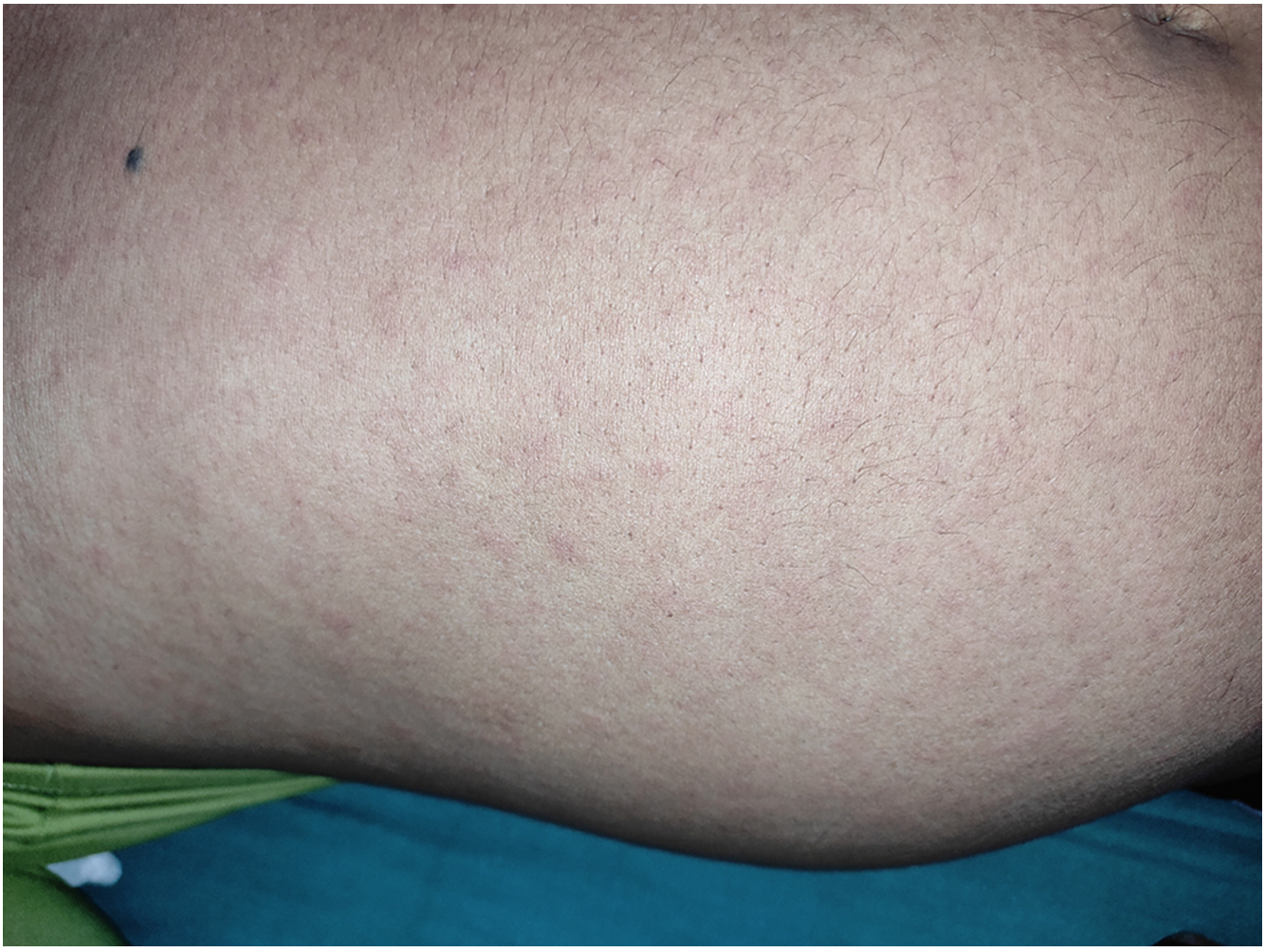


Fig 1 | Typical dengue rash on the abdomen of an adult during the febrile phase (note, the rash may be harder to spot in people with darker skin tones)

Consider differential diagnoses and co-infections according to geographical prevalence.[16 28 29] In travellers returning to non-endemic countries, consider dengue when acute undifferentiated febrile illness has been present for up to 14 days.[14]

- Examination[2 13 21]:
  - Normal blood and pulse pressures
  - Positive tourniquet test (see box 1).[11]
- Investigations[2 13 21]:
  - Full blood count may show leucopenia and/or thrombocytopenia
  - Record a baseline haematocrit
  - Consider ultrasound to look for subclinical fluid accumulation.[30]

Critical phase

Towards the end of the febrile phase but possibly earlier, about 5% of patients deteriorate into a critical phase,[11 22 31] when warning signs (box 2) are present and severe dengue (see box 1) may develop. The positive predictive values of individual warning signs for progression to severe dengue, range from 9% (for persistent vomiting) to 58% (fluid accumulation), but negative predictive values are higher (greater than 95% for each of the individual warning signs).[38] Unless organ support is needed (inotropic support, mechanical ventilation, and/or dialysis), the critical phase usually lasts 2-3 days.[2 13]

Box 2: Dengue warning signs and risk factors for severe disease[9 13 17]

Warning signs

- Abdominal pain or tenderness
- Persistent vomiting (≥3 episodes in 1 hour, or 4 episodes in 6 hours)
- Fluid accumulation from plasma leakage (such as ascites, pleural effusion, oedematous gall bladder wall, peripheral oedema)
- Mucosal bleeding (usually gum or nasal bleeding, sometimes vaginal or gastrointestinal bleeds or haematuria)
- Lethargy
- Restlessness
- Liver enlargement >2 cm
- Laboratory: increase in haematocrit, concurrent with rapid decrease in platelet count

Risk factors for severe disease

- Pregnancy[12 32]
- Infants <1 year old[33]
- Adults >65 years old[34]
- Underlying health conditions (diabetes, asthma, hypertension, chronic kidney disease, heart failure)[35 36]
- Obesity[37]
- Also consider people who reside far from hospitals, live alone, or experience extreme poverty (who may not receive adequate home care and be unable to attend follow-up)

- Examination[2 13 21]:
  - Monitor (every 2-4 hours) for the development of severe dengue by assessing airway, breathing, and circulation (including blood pressure, and urine output), and consciousness.
  - There might be fluid accumulation (from plasma leakage) (box 2) on examination or with bedside ultrasound.
  - In severe dengue:
    - Narrow pulse pressure occurs if systolic blood pressure decreases and diastolic increases
    - Cool, clammy extremities might indicate hypotensive or compensated shock
    - Assess for bleeding (mucosa, orifices, skin) that may occur with severe thrombocytopenia or coagulopathy
    - Consider severe bleeding if haematocrit decreases and the patient remains haemodynamically unstable (cool clammy extremities, low blood pressure, decreased urine output) despite intravenous fluids resuscitation
    - Assess for signs of organ impairment (such as hepatic failure, encephalopathy, cardiomyopathy).
- Investigations[2 13 21]:
  - Haematocrit increases, at least 20% from baseline concurrent with rapid thrombocytopenia (a low or normal haematocrit may indicate bleeding).
  - Liver function tests may show moderate elevation in transaminases.
  - Monitor kidney function and electrolytes.
  - If severe dengue develops:
    - Increased haematocrit with hypotensive or compensated shock indicates severe plasma leakage
    - Decreased haematocrit with hypotensive or compensated shock indicates severe bleeding
    - Aspartate and alanine transaminases >1000 units/L indicate severe hepatic impairment
    - Monitor blood glucose, kidney function, electrolytes, coagulation profile, and cardiac enzymes as indicated.

Recovery phase

The recovery phase starts soon after plasma leakage reversal, about 48-72 hours after the start of the critical phase. If patients do not enter a critical phase, recovery starts soon after defervescence (resolution of fever).[2 13 21] Complete recovery may take between a few days and a few weeks. Erythematous, pruritic rashes with islands of normal skin (Herman's rash) may develop. Improvement is usually rapid, but a fifth to a third of adult patients may develop post-viral fatigue and/or depression in the weeks and months after.[2 39]

- Examination[2 13 21]:
  - Stable blood pressure
  - Diuresis.
- Investigations[2 13 21]:
  - Haematocrit stabilises or might fall due to reabsorption of leaked fluid
  - White cell count and platelets begin to normalise.

What investigations confirm the diagnosis?

Consider tests as outlined in table 1.[2 13 21]

Table 1 | Diagnostic tests for dengue[2 13 21]

Test and method	Sensitivity and specificity[40]	Note
Days 1-5 of illness		
NS1 RDT	Sensitivity 76.5%* Specificity 100%*	Interpret negative tests with caution. Sensitivity lower in secondary infections.[41] Interpret patients' self tests with caution as many commercially available rapid tests are unreliable.[42]
NS1 ELISA	Sensitivity 82.4%* Specificity 94.3%*	
Virus/nucleic acid detection by culture or RNA detection (PCR)	Considered reference standard	
Day ≥3 of illness		
IgM RDT	Sensitivity 17.9% Specificity 97.1%	Many commercially available rapid tests are unreliable.[42]
IgM ELISA	Sensitivity 27.5% Specificity 91.4%	
IgG RDT or ELISA	In primary infection: positive after 7 days (unhelpful for acute illness) In secondary infection: positive after day 3.[43]	

ELISA = Enzyme linked immunosorbent assay. IgG = Immunoglobulin G. IgM = Immunoglobulin M. NS1 = Non-structural protein 1, a protein found in the blood of people infected with dengue and other flaviviruses. PCR = Polymerase chain reaction. RDT = Rapid diagnostic test.

*Compared with PCR.

How is it managed?

In the absence of warning signs or risk factors for severe disease (box 2), avoid hospital admission where possible (especially during outbreaks) to reduce overburden of health systems.[4] Instead, when it is safe to do so, discharge with detailed home care guidance and safety-netting advice (table 2).

Table 2 | Management recommendations based on WHO, PAHO (Pan American Health Organization), and CDC guidelines[2 11 13 14 17 21]

Disease phase, WHO group	Admit or discharge	Management
Febrile phase		
Group A (without warning signs or risk factors)	Discharge	Home care: tepid sponging (see considerations in text), paracetamol, oral fluids Advise patients to: - Aim for micturition at least every 4 hours[13] - Be alert to development of warning signs and severe dengue; seek urgent review if they develop - Prevent spread at home (vector control) - Reassure that about 95% of people with dengue in this phase recover without long term consequences or complications[11]
Group B1 (without warning signs, with a risk factor(s))	Admit	Symptom management Oral fluids 2-4 hourly monitoring of blood pressure and urine output Daily blood counts with haematocrit
Critical phase		
Group B2 (with warning sign(s))	Admit	Symptom management Intravenous fluids as per WHO algorithm (box 3) Counsel patients about possible deterioration into severe dengue 2-4 hourly monitoring of blood pressure, pulse pressure, urine output, and consciousness; if there is deterioration, manage as severe dengue 6-12 hourly bedside haematocrit; daily blood tests to monitor platelets, electrolytes, kidney and liver function; cardiac enzymes if myocarditis (a potentially serious complication of dengue) is suspected
Group C (severe dengue)	Admit (consider ICU[44])	Treat compensated or hypotensive shock as per WHO fluid resuscitation algorithm (box 3)* After stopping fluids, observe for deterioration for 24-48 hours Consider urgent blood transfusion for patients with severe bleeding (decreased haematocrit with hypotensive or compensated shock) Monitor organ function and manage severe organ impairment with organ support (mechanical ventilation, haemodialysis, or inotropic support) 1-2 hourly monitoring of blood and pulse pressure, and urine output (maintain output at >0.5 mL/kg/hr) Monitor haematocrit after every intravenous fluid bolus and if clinical deterioration Assess for fluid overload and pulmonary oedema, which can occur when plasma leakage reverses (stop fluid and give loop diuretics urgently if pulmonary oedema occurs[45])
Recovery phase		
	Discharge	Indications for discharge are absence of fever for ≥48 hours, improved wellbeing and appetite, normal vital signs, urine output >0.5 mL/kg/hr, increasing platelet count, stable haematocrit without intravenous fluids[11] Follow up in 1-2 months by hospital discharge team to assess for fatigue and depression

* We recommend monitoring for fluid accumulation before and during fluid resuscitation.13

Box 3: Highlights and principles of the WHO fluid resuscitation algorithm for dengue[13]

- *Warning signs*—Intravenous crystalloid fluid replacement (normal saline or Ringer's lactate) 5-7 mL/kg/hr for the first 1-2 hours, followed by 3-5 mL/kg/hr for the next 2-4 hours, then 2-3 mL/kg/hr or less based on the clinical response, to be stopped within 48 hours.
- *Hypotensive shock*—Restrictive fluid resuscitation with a 20 mL/kg bolus of crystalloid or colloid fluid over 15 minutes, followed by 10 mL/kg over the next hour if shock improves with the initial bolus. Can repeat 20 mL/kg colloid boluses twice if no improvement with increased haematocrit.[13 46]
- *Compensated shock*—Initial rate is 10 mL/kg crystalloid fluid over 1 hour.[13]
- When the shock is improved (systolic blood pressure >90 mm Hg, pulse pressure >20 mm Hg, or urine output >0.5 mL/kg/hr) rapidly reduce fluids (as in "warning signs" phase) and stop within 48 hours.
- Adopt a strict balance between under-treatment and over-treatment because, after 48-72 hours, leaked fluid is typically reabsorbed into the vascular system, risking fluid overload and pulmonary oedema.

No specific antiviral or disease-modifying treatment has proven beneficial to date. For all phases, in all regions, WHO recommends supportive treatment and reassurance, acknowledging there may be anxiety associated with symptoms such as high grade fevers,

severe aches, and cytopenia. In patients admitted to hospital, recommendations include regular monitoring of vital signs, urine output, and haematocrit (frequency dependent on illness phase/severity) and monitoring other bloods with consideration of blood transfusion/organ support when clinically indicated.[13] Table 2 shows a more detailed summary, according to illness phase.

Management considerations

Tepid sponging

Tepid sponging for fever control is recommended by all dengue guidelines.[13-15 17] However, UK NICE guidance does not recommend this for fever control in children under 5 years old.[47] We suggest discussing the potential effects of chills, goose pimples, and discomfort to patients when considering this.[48]

Paracetamol

Paracetamol is the antipyretic and analgesic of choice (for adults, 0.5-1 g every 4-6 hours, maximum 4 g per 24 hours).[13] However, a randomised, double-blind, placebo-controlled trial in Thailand showed raised hepatic transaminases without fever or pain reduction when median dose was 1.5 g/day.[49] We recommend using paracetamol with caution, and, based on our own practice, to discontinue if hepatic transaminases rise more than three times the upper limit of normal.

Limitations to the WHO fluid resuscitation algorithm

Researchers in Singapore and the US[50] have suggested some limitations of the WHO intravenous fluid resuscitation algorithm:

- No large scale, randomised controlled trials confirm the optimal intravenous fluid types and rates, and the monitoring strategies recommended for severe dengue
- WHO fluid recommendations are mainly extrapolated from small, randomised studies only on children
- Consensus is lacking on whether crystalloids or colloids (which can potentially worsen coagulopathy) are preferable for management of hypotensive shock.

Treatments without evidence to support their use

- We advise avoiding non-steroidal anti-inflammatory drugs as there is a theoretical risk of platelet dysfunction and bleeding in patients with thrombocytopenia. However, no randomised prospective studies assess this risk.[51]
- WHO advises avoiding empirical antibiotics[13 52]
- WHO advises avoiding prophylactic platelet transfusions because randomised trials showed no benefit, and because of the possibility of fluid overload[53]
- We also advise avoiding other non-evidence-based therapies that have been considered to increase platelets:
  - Thrombopoietin agonists[54]
  - Carica papaya extract.[55 56]

Hypothetical case vignette

Febrile phase—A 25 year old man in Nepal presented during the monsoon season with three days of fever, nausea, headache, eye pain, and body aches. "Dengue fever without warning signs" was diagnosed (see table below). He was discharged with paracetamol and asked to return if he developed abdominal pain, vomiting, lethargy, restlessness, bleeding, or decreased urine output.

Critical phase—On day 6, he returned with severe abdominal pain and vomiting. "Dengue fever with warning signs" was diagnosed (table) and he was given a proton pump inhibitor, antispasmodics, antiemetics, and 500 mL intravenous normal saline overnight. On day 7, the diagnosis was changed to "severe dengue" because of narrowed pulse pressure (table), and a 1000 mL normal saline bolus was given. The intravenous fluid rate was reduced with monitoring of blood pressure and haematocrit, and stopped in 24 hours.

Recovery phase—On day 8, signs and symptoms subsided. Blood pressure and urine output were monitored for 24 hours. On day 9, he was discharged with counselling about the possibilities of Herman's rash and increased urine output in the next 3-5 days, and fatigue and depression over the next few weeks. Secondary prevention advice was given.

| Examination and investigation findings for patient

Examination/test	Result			
	Day 3	Day 6	Day 7	Day 8
Temperature	101°F (38°C)	Afebrile	Afebrile	Afebrile
Blood pressure (mm Hg)	120/70	100/70	90/76 (100/70 after 1000 mL saline bolus)	110/70
Rapid diagnostic tests:				
Dengue	Positive for NS1	—	—	—
Scrub typhus, covid-19, leptospirosis, malaria	Negative	—	—	—
Blood culture	Negative	—	—	—
Leucocyte count (normal range 4000-11 000/µL)	3400	2700	2800	3600
Platelets (normal range 150 000-450 000/µL)	90 000	50 000	45 000	55 000
Haematocrit (normal range 40-54%)	42%	45%	50%	46%
Bedside ultrasound	—	Oedematous gall bladder wall, no ascites or pleural effusion	—	—
Urine output (normal range >0.5 mL/kg/hour)	—	0.8 mL/kg/hr over 12 hours	0.7-1	0.9-1.2

How can primary and secondary infections be prevented?

WHO-approved live-attenuated vaccines are available for people >9 years old who are seropositive after screening (Dengvaxia (CYD-TDV), three doses), and for children aged 6-16 years in endemic countries regardless of baseline serostatus (Qdenga (TAK-003), two doses).[18 57-59] A third live-attenuated vaccine is in development (Butantan-DV (TV003), single dose) which doesn't require prescreening and has just completed a phase 3 trial.[60]

- Effective vector control measures include[2]:
  - Mosquito repellents[11 13]

- Covering the arms and legs (especially during daylight, when *Aedes* mosquito are most active)[11 13]
- Insecticide-treated house screens and bed nets[61 62]
- Stagnant water removal (for example, regular drainage, improved water supply, mosquito-proofed water containers, adequate waste management)[13]
- Genetically modified mosquitoes (such as in Brazil and India).[63]
- Wolbachia infection of *Aedes* mosquitoes (as in Singapore and Thailand).[64]

Further research

Large randomised clinical trials are needed for validation and optimisation of treatments currently recommended by WHO. Also, clinical trials to discover effective antiviral agents and immunomodulators in the same manner as the RECOVERY trial for covid-19.[65]

Education into practice

- What diagnosis and treatment protocols are in place in your region?
- How do you balance reassuring patients with dengue while ensuring they remain alert to the possibility of developing warning signs?

How this article was created

PubMed was searched for studies published between January 2000 and March 2024 using the MeSH terms: "(epidemiology, diagnosis, therapy, guideline) *and* (dengue fever)." The Cochrane Database was searched for related systematic reviews. Relevant reports and educational material from the World Health Organization (WHO) and Centers for Disease Control and Prevention (CDC) and Pan American Health Organization (PAHO) were examined.

How patients were involved in the creation of this article

Based on the story of a patient who kindly shared her experience of having dengue, we amended the section now titled management considerations.

Contributors: SA and SB wrote the first draft. SH and BB reviewed and revised the draft. SA was the contact for patient involvement. All authors contributed to the literature review and approved the final manuscript. BB is the guarantor of this article.

Competing interests: *The BMJ* has judged that the authors have no disqualifying financial ties to commercial companies that are relevant to this paper. The authors declare no other competing interest.

Patient consent: Consent obtained for the image of dengue rash.

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