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Singapore National Dengue Clinical Guideline

National Centre for Infectious Diseases
NHG Health

ACADEMY OF MEDICINE SINGAPORE

CHAPTER OF INFECTIOUS DISEASE PHYSICIANS, COLLEGE OF PHYSICIANS, SINGAPORE

COLLEGE OF PUBLIC HEALTH & OCCUPATIONAL PHYSICIANS SINGAPORE

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Guidelines for Guidelines — Method Validated
An initiative by the Agency for Care Effectiveness

In validating the methodology for this guideline, ACE assessed that they meet the ACE Guidelines for Guidelines (G4G) standard for clinical guideline development in Singapore. This methodological validation applies for 5 years, unless amended or updated during this period, or otherwise specified. Note that responsibility for clinical decision-making remains with individual providers and health service providers.

EPIDEMIOLOGY, BURDEN OF DISEASE AND TRANSMISSION

Epidemiology

- Dengue is endemic in Singapore, with all four serotypes co-circulating.
- Infection by one serotype results in lifelong type-specific immunity but only a short-term cross-reactive immunity against the other three serotypes. [1]
- Dengue transmission in Singapore exhibits seasonal patterns with traditional dengue peak periods from May to October, correlating with environmental factors e.g. rainfall and temperature.

Updated information regarding dengue surveillance including dengue clusters and mosquito vector hotspots can be obtained from the dengue page of the National Environment Agency (www.nea.gov.sg/dengue-zika/dengue) and the myENV app.

Transmission of Dengue Virus

- *Aedes aegypti* and *Aedes albopictus* mosquitoes are the primary vectors responsible. They breed in stagnant water sources e.g. domestic containers, flowerpot trays, and discarded receptacles.
- Dengue virus is spread to humans by the bite of an infected *Aedes* mosquito. Preventing dengue transmission also involves reducing the risk of mosquitoes biting an infected person and then spreading the virus to others.
- Other rarer transmission modes include vertical transmission during late stage of pregnancy, organ transplantation, and blood transfusion. [2–4]

Guideline Recommendations

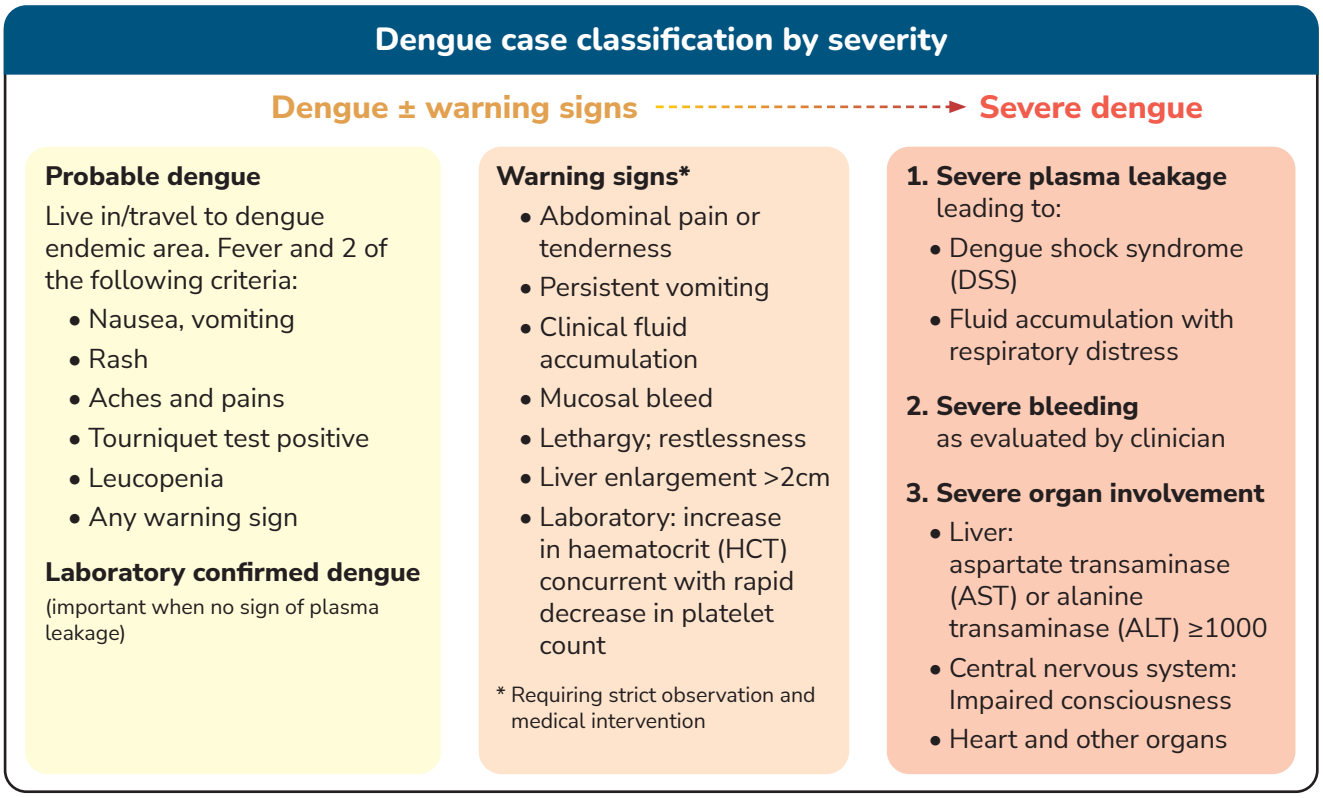
Recommendation 1	For the diagnosis of dengue infection, symptoms, signs and laboratory test results should be consistent with dengue infection. If there are inconsistencies, further evaluation should be pursued depending on the history, physical examination and/or laboratory test results.
Recommendation 2a	In the first 7 days from symptom onset of suspected dengue infection, tests to detect both dengue virus NS1 antigen and dengue IgM antibodies in human serum, plasma or whole blood OR a dengue polymerase chain reaction (PCR) test on whole blood or plasma should be requested. In primary infection, IgM antibodies are detectable in 50% in the first 3–5 days of illness and IgG at the end of the first week.
Recommendation 2b	After 7 days from symptom onset, dengue PCR test on whole blood or plasma generally should not be performed.
Recommendation 3	Dengue is a notifiable disease and should be reported by medical practitioners to the Communicable Diseases Agency using the appropriate platform when suspected and when confirmed through point-of-care tests. Development of dengue haemorrhagic fever requires re-notification within 24 hours from time of diagnosis.

INTRODUCTION TO DENGUE DIAGNOSIS AND CLASSIFICATION

Recommendation 1

For the diagnosis of dengue infection, symptoms, signs and laboratory test results should be consistent with dengue infection. If there are inconsistencies, further evaluation should be pursued depending on the history, physical examination and/or laboratory test results.

Figure 1. 2009 WHO Classification of dengue [5]



Warning signs are used in the diagnosis of dengue and are also used to guide right siting and management of patients.

Note: Lethargy, restlessness or abnormal behaviors may be manifestations of shock. Main caregivers of infants, children and elderly would be the most reliable to report any notable changes in mentation and activity level.

Special population: Elderly

- As it may be difficult to differentiate dengue from other febrile illnesses at presentation, a high index of suspicion is important, especially during periods of high local incidence of dengue.
- Atypical clinical features tend to occur more frequently in the elderly. Elderly patients tend to present commonly with isolated fever. [6] Delirium is also more common in the elderly as a presenting sign. [7]
- Compared to younger patients, elderly patients may have lower frequencies of fever, abdominal pain, headaches, bone pain, rashes, nausea and vomiting. [6–10] Elderly patients presenting with the following clinical features should prompt dengue infection as a differential diagnosis: unexplained fever, delirium, leucopenia or thrombocytopenia.
- Elderly dengue patients are at higher risk of haemorrhagic manifestations, severe dengue, renal dysfunction, liver dysfunction and bacterial coinfections, such as primary bacteremia and hospital-acquired infections. [7,10,11] Clues that may indicate presence of bacterial coinfections include prolonged fever (>5 days), acute renal failure, leucocytosis and neutrophilia. [10]
- Secondary dengue (evidenced by a positive dengue IgG during early presentation i.e. before day 7) which is more common in the elderly, [12] may be a risk factor for severe disease. [13]

Special population: Pregnant Individuals

- As it may be difficult to differentiate dengue from other febrile illnesses at presentation, a high index of suspicion is important, especially during periods of high local incidence of dengue.
- Diagnostic testing for dengue should be considered in a pregnant patient early in the presentation, even in the absence of at least 3 cardinal symptoms (i.e. fever and two additional clinical symptoms) to guide subsequent appropriate management.

Special population: Infants and children

- Dengue commonly presents as an undifferentiated febrile illness or febrile exanthem in infants and children. [14] Younger children and infants are less able to report typical dengue symptoms of headache, myalgia and retroorbital pain. Warning signs of vomiting and abdominal pain may be misconstrued as presenting features of other common illnesses in childhood, such as gastroenteritis. As such, a high index of suspicion for evolving signs and symptoms of dengue infection is crucial, especially in the presence of epidemiological risk factors or during periods of high local disease incidence.
- Respiratory tract symptoms, nausea/vomiting, petechial rash, hepatomegaly and splenomegaly are more common in infants and in young children with dengue, compared to older children with dengue. Neurological manifestations such as seizures, are also more common in infants with dengue. [15,16,17]
- Leucopenia, thrombocytopenia, haemoconcentration and raised transaminases also occur in children, although these are often less pronounced than in adults. [18] However, up to half of infants with dengue can have platelet counts below 80 x 10^9/L. [15]

POSSIBLE DIFFERENTIAL DIAGNOSIS

As symptomatic dengue infection generally presents as an acute febrile illness, several infectious and non-infectious differential diagnoses need to be considered. It is important to obtain an accurate travel history to guide the determination of plausible differential diagnoses. Co-infections with dengue may also occur. Table 1 below summarises a non-exhaustive list of infectious differential diagnoses.

Non-infective ones to consider include immune thrombocytopenia, acute leukaemia, haemophagocytic lymphohistiocytosis. Specific to the paediatric population, considerations should also include Kawasaki disease and multisystem inflammatory syndrome in children. Given endemicity of dengue in Singapore, patients may also present with more than one illness. Outside of special populations as described earlier, symptoms, signs and laboratory features should be fully consistent with dengue.

Laboratory features consistent with dengue infection:

- Full blood count – Leucopenia, thrombocytopenia
  - In the first few days of dengue fever, thrombocytopenia may not be apparent
- Liver function test if performed – AST > ALT

Table 1. Possible differentials

Infectious conditions	Possible distinguishing features	Helpful diagnostic tests
Chikungunya	Joint pain and joint swelling	PCR and/or serology
Zika	Conjunctivitis	PCR
Viral hepatitis	Generally, ALT > AST in acute viral hepatitis (unlike dengue illness wherein AST > ALT)	PCR and/or serology
Acute human immunodeficiency virus (HIV) seroconversion	Lymphadenopathy, relevant sexual history	HIV antigen-antibody test
Influenza/COVID-19/Other respiratory viruses	Predominance of URTI symptoms	PCR, rapid antigen testing
Other viral haemorrhagic fevers e.g. Ebola virus disease, etc.	Relevant travel history	PCR
Measles	Koplik spots in first few days of illness, non-itchy rash, incomplete vaccination (receipt of <2 doses of measles vaccine)	PCR and/or Serology
Bacterial infections e.g. bacteraemias/enteric fever	Elevated neutrophil and other inflammatory markers	Blood cultures
Rickettsial	Epidemiological exposure, eschar	Serology
Leptospirosis	Conjunctival suffusion, may see elevated bilirubin out of proportion with level of transaminases	PCR and/or Serology
Malaria	Relevant travel history	Blood film for malaria parasites, PCR

NATURAL COURSE OF DENGUE ILLNESS AND INTERPRETATION OF DENGUE DIAGNOSTIC TESTS

Recommendation 2a

In the first 7 days from symptom onset of suspected dengue infection, tests to detect both dengue virus NS1 antigen and dengue IgM antibodies in human serum, plasma or whole blood OR a dengue polymerase chain reaction (PCR) test on whole blood or plasma should be requested. In primary infection, IgM antibodies are detectable in 50% in the first 3–5 days of illness and IgG at the end of the first week.

Recommendation 2b

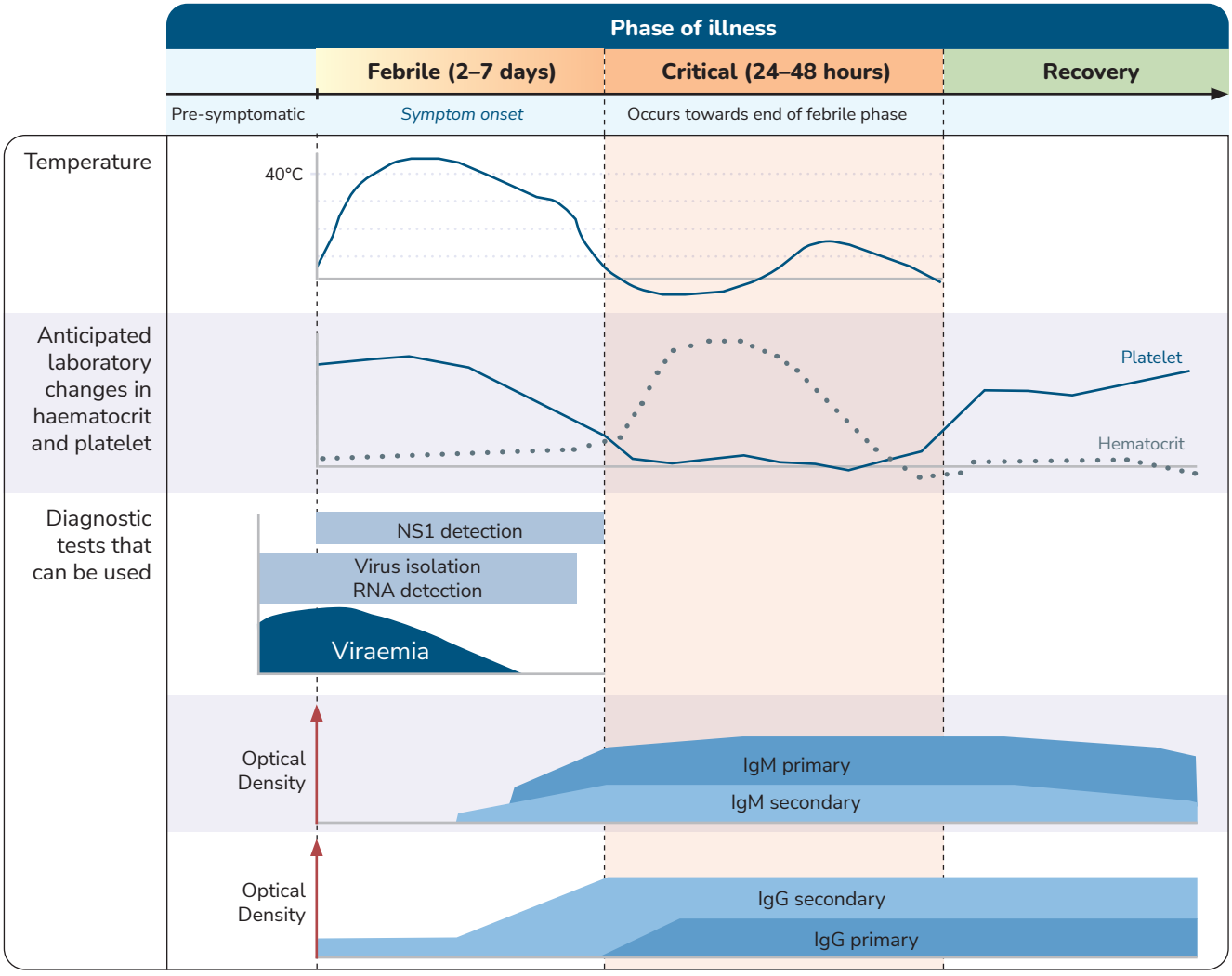
After 7 days from symptom onset, dengue PCR test on whole blood or plasma generally should not be performed.

Recommendation 3

Dengue is a notifiable disease and should be reported by medical practitioners to the Communicable Diseases Agency using the appropriate platform when suspected and when confirmed through point-of-care tests. Development of dengue haemorrhagic fever requires re-notification within 24 hours from time of diagnosis.

There are 3 phases in dengue illness: febrile, critical and recovery. Interpretation of dengue diagnostic test results depends on which time point the test is performed. Dengue diagnostic test results should be correlated clinically with the expected timing of detection of the dengue NS1 antigen, IgM and IgG. In primary infection, IgM antibodies are detectable in 50% in the first 3–5 days of illness and IgG antibodies at the end of the first week. In secondary infection, IgG antibodies may be detected earlier. False positives may occur due to antigenic or serological cross-reactivity, [20–23] or non-specific IgM reactivity.

Table 2. Natural course of dengue illness and dengue diagnostic methods [1]



DENGUE CASE MANAGEMENT AND RIGHT SITING OF CARE

	Phase of illness		
	Febrile (2–7 days)	**Critical (24–48 hours)**	**Recovery**
	Symptom onset	Occurs towards end of febrile phase	
Potential complications	• Dehydration	• Plasma leakage leading to shock • Occult and overt bleeding • End organ impairment	• Fluid overload
Overall recommendations	✔ Upon suspicion of dengue infection, counsel the following: ▪ Possible / confirmed diagnosis of dengue and importance of follow-up ▪ Dengue warning signs to empower patients with knowledge on when to return to medical care earlier ▪ Disease trajectory of dengue ✔ **Assess for high risk patient features that may influence right siting of care**[a] ✔ A full blood count (FBC) should be performed at the first opportunity when dengue is diagnosed or suspected. This may be normal in early disease and can serve as a baseline. HCT should then be monitored regularly and closely for haemoconcentration until patient is in recovery. ✖ Avoid nonsteroidal anti-inflammatory drugs (NSAIDs) and intramuscular injections ✔ Consider use of paracetamol for fever and pain relief if liver dysfunction is not suspected. Alternatively, use tepid sponging for fever and low dose tramadol for pain. ✔ Encourage oral hydration[b] ✔ Monitor urine output[c] ✔ If available, consider patients' previous BP trends and FBC to contextualize current BP and haematological findings	• ~10% of patients may progress into critical phase even with ongoing fever • Saddleback fever may occur	

	Phase of illness		
	Febrile (2–7 days)	**Critical (24–48 hours)**	**Recovery**
	Symptom onset	Occurs towards end of febrile phase	

Recommendations specific to **Outpatient care**

✔ Outpatient management is suitable for patients who fulfil the following:

Able to adhere to outpatient monitoring **AND** Dengue without warning signs **AND** Able to maintain adequate oral intake and adequate urine output[c]

Clinical assessment

✔ Regular[d] review till patient is in recovery phase whilst monitoring for the following:

- Phase of illness, presence of complications and warning signs
- Vital signs (including postural hypotension and relative hypotension if clinically indicated)
- Urine output[c]

Laboratory assessment

✔ Regular[d] FBC to monitor HCT trend and platelet trend until patient is in recovery phase

Recommendations specific to **Inpatient care**

✔ Inpatient management is recommended for patients with:

Dengue with warning signs **OR** Severe dengue **OR** High-risk patient features[a]

Clinical assessment

Febrile (2–7 days)	Critical (24–48 hours)	Recovery
Regular vital signs monitoring e.g. Q4H	**More intense vital signs monitoring e.g. Q1-2H may be required**	Frequency of vital signs monitoring can be decreased as clinically appropriate
Postural blood pressure (BP) should be monitored	**Strict input/output charting with Q4-6H assessment of urinary volume**	If fever persists / re-occurs during recovery phase, evaluate for other causes; e.g. severe dengue hepatitis, severe transaminitis, secondary bacterial infections, haemorrhagic manifestations or haemophagocytic lymphohistiocytosis
Strict input/output charting including urinary volumes	Monitor for warning signs including mental assessment, peripheral[6] and central perfusion, end organ function, and bleeding	
Monitor for defervescence, warning signs including mental assessment, peripheral[5] and central perfusion, and end organ function	**Suspect and evaluate for metabolic acidosis as clinically indicated especially for patients who are tachypnoeic or breathless despite good oxygen saturations on room air**	
	Where available, point-of-care ultrasound offers a valuable addition to traditional clinical evaluation	
	Close monitoring should last 24–48 hours minimally until patient has entered into recovery phase	

Laboratory assessment

Febrile (2–7 days)	Critical (24–48 hours)	Recovery
Regular[d] FBC to monitor HCT trend and platelet trend	**More frequent FBC monitoring may be required (Q6-12H and before and after fluid replacement) to monitor HCT trend and haemoglobin (Hb) trend especially in patients with active plasma leakage or suspected bleeding**	Ensure HCT is stable before cessation of fluid replacement
Blood glucose levels, electrolytes, liver transaminases, coagulation panel, and other tests should be performed as clinically indicated e.g. if patient has diabetes, gastrointestinal losses, or poor oral intake etc.	Blood glucose levels, electrolytes, liver transaminases, coagulation panel should be performed as clinically indicated e.g. if patient has diabetes, gastrointestinal losses or poor oral intake etc	Reactive lymphocytosis generally appear before platelet trend improves

	Phase of illness		
	Febrile (2–7 days)	**Critical (24–48 hours)**	**Recovery**
	Symptom onset	Occurs towards end of febrile phase	
Recommendations specific to **Inpatient care**	**Fluid management**		
	■ Oral fluids[b] are encouraged. If unable to tolerate oral fluids, consider balanced intravenous (IV) crystalloids (e.g. Hartmann's solution, Ringer's lactate, Plasma-lyte, 0.9% NaCl) [24] at maintenance rate[e,f] and reassess a few hours later with aim to stop IV fluids if able to tolerate orally	■ IV fluid resuscitation should be initiated in the presence of warning signs, compensated shock or decompensated shock[g] ■ IV fluid resuscitation is usually required only for 24–48 hours as this is the time period when plasma leakage occurs ■ Regular reassessment of the patient is key, including reassessment of HCT to guide fluid resuscitation rates ■ Early consideration of vasopressors is warranted should there be inadequate response to appropriate fluid resuscitation ■ Rate of IV fluids should be reduced gradually as plasma leakage improves and this is indicated by improving urine output and decreasing HCT in a stable patient ▶ *Refer to section "Dengue: Fluid management for hospitalised patients" for IV fluid resuscitation algorithms and more details*	
	Transfusion of blood and blood products		
		■ If the patient fails to respond adequately to appropriate fluid resuscitation, with concomitant falling HCT, consider occult bleeding in the absence of overt clinical bleeding. Transfuse red blood cells and correct coagulopathy accordingly. ■ Red blood cell transfusion should be considered if overt/occult bleeding is suspected in shock regardless of haemoglobin level. ■ Coagulation factor replacement (e.g. fresh frozen plasma, cryoprecipitate) should be given before invasive procedures or if overt/occult bleeding is suspected ■ Platelet transfusion for thrombocytopenia should only be given before invasive procedures or if clinically significant bleeding is present ▶ *Refer to section "Dengue: Blood product use in hospitalised patients" for more details*	

	Phase of illness		
	Febrile (2–7 days)	**Critical (24–48 hours)**	**Recovery**
	Symptom onset	Occurs towards end of febrile phase	
Recommendations specific to **Inpatient care**	**Others**		
		☐ All patients presenting with severe dengue and/or hypotension should be considered for prompt referral to the intensive care unit (ICU) or high dependency unit (HDU) for further evaluation and support ☐ If bacterial co-infection is suspected, take blood cultures and commence empirical antibiotics as clinically indicated	**Criteria for Discharge:** ✔ Good general condition, stable vital signs, improving appetite ✔ Stable HCT without need for IV fluids ✔ Improving organ dysfunction if any ✔ Increasing platelet count **Follow-up:** ☐ Repeat FBC or liver transaminases outpatient until resolution of abnormalities ☐ Liver transaminases abnormalities are generally expected to resolve 2–4 weeks after illness

[a] Examples of high-risk features include pregnancy, presence of co-morbidities, obesity (BMI >30), age <1 year of age or >65 years and above, social factors e.g. at risk of defaulting close outpatient reviews or lack of support. This list is non-exhaustive and any patient whose medical background may exacerbate the expected pathophysiological changes in dengue, or whose underlying condition may deteriorate due to dengue infection should be considered as high-risk, requiring inpatient management.

[b] Small frequent oral fluids should be prescribed for those with anorexia, nausea and vomiting. A variety of fluids are acceptable e.g. such as oral rehydration solution, fruit juices and soup, avoiding drinks with high sugar content (>5% sugar) as they may exacerbate hyperglycaemia from the physiological stress or those with underlying diabetes mellitus.

[c] For a person with normal renal function, oral intake is deemed adequate if there is good volume of urinary output at least 4–6x/day, once every 6 hours

[d] A local study has shown that the time window from development of warning signs to progression to severe disease is the day before or same day in ~68% of dengue patients. As such the frequency of review should be based on clinical judgment and understanding of the disease progression. [25]

[e] Use ideal body weight (IBW) to calculate fluid requirements for overweight / obese adults:

- Male: 50.0 kg + 0.91(height–152.4) cm
- Female: 45.5 kg + 0.91(height–152.4) cm

Height (cm)	Estimated IBW for adult men (kg)	Estimated IBW for adult women (kg)
150	50	45.5
160	57	52
170	66	61.5
180	75	70

[f] Use Holliday-Segar formula to calculate daily fluid **maintenance** requirement in children:

- 4 mL/kg per hour for the first 10 kg of body weight
- 2 mL/kg per hour for the next 10 kg of body weight
- 1 mL/kg per hour for each kilogram of additional body weight

IBW (kg)	5	10	15	20	25	30	35	40	50	60	70	80
Maintenance (mL/hour)	20	40	50	60	65	70	75	80	90	100	110	120

[g] Features of compensated and decompensated shock:

Parameters	Stable	Compensated shock	Decompensated shock
Urine output (UO)		New onset decrease in urine output <0.5mL/kg/hr for adults or <1mL/kg/hr for children	
Conscious level	Clear and lucid	Clear and lucid	Change (restless, combative etc)
Capillary refill time (CRT)[1]	≤3 seconds for adults ≤2 seconds for children	Prolonged	Very prolonged, mottling of skin
Extremities	Warm and pink	Cold	Cold and clammy
Peripheral pulse volume	Normal	Weak and thready	Feeble or absent
Heart rate	Normal for age	Tachycardic[2]	Tachycardic to bradycardic
Blood pressure	Normal for age	Normal systolic with rising diastolic[2]	Hypotension
		Narrowing of pulse pressure (systolic BP - diastolic BP) ≤20 mmHg (consider 25mmHg for pregnant adults)[3]	
		Adults: Reduction in SBP of >40mmHg from baseline[2,4]	
		Adults: New onset postural BP drop of 20 mmHg (systolic) or 10 mmHg (diastolic), for patients not known to have pre-existing postural hypotension	
Respiration rate	Normal for age	Tachypnoea	Tachypnoea to Kussmaul's breathing
Full blood count		Increase in haematocrit ≥20% compared with baseline values	

[1] How to measure capillary refill time:

i. Place the patient in a semi-recumbent position.
ii. Firmly press on the ventral surface of the finger's distal phalanx until the skin blanches, holding for 10 seconds.
iii. Release the pressure and use a timer or stopwatch to count the seconds it takes for the skin colour to return to normal.
iv. A return time of 3 seconds or less is considered normal for adults, and 2 seconds or less is considered normal for children

[2] Refer to Table 4 for range of normal vital signs for children according to age.

[3] Narrowing of pulse pressure is an early sign in children but can be a late sign in adults.

[4] In children, hypotension is late sign of shock.

[h] Colloids may be preferred for fluid resuscitation in patients with dengue shock [26,27]

Special population: Elderly

- As polypharmacy is common in the elderly, frequent medication chart review to assess potential risks and benefits of continuing certain medications (e.g. anti-hypertensives, diuretics, anti-platelet agents, anticoagulation, non-steroidal anti-inflammatory drugs) during the febrile and critical phases is essential. [28,29]
- Elderly patients are at higher risks of fluid overload from overzealous fluid therapy, especially with pre-existing cardiac/renal/liver disease. Fluid administration rates should be adjusted based on hydration status and urine output, with prompt discontinuation of IV fluids once in recovery phase.

Special population: Pregnant Individuals

- The indication to hospitalise pregnant patients with dengue is no different from that in other patient populations. Where possible, pregnant patients requiring inpatient care should be admitted to institutions with obstetrics support. The diagnosis of dengue should be made known to the patient's obstetrician, so that care may be taken during follow-up to monitor for known complications of dengue in pregnancy, such as low birth weight.
- Patients with high-risk pregnancies should be managed together with the patient's obstetrician until the patient enters the recovery phase.
- Patients should be reviewed for warning signs of dengue, which should not be dismissed as symptoms related to pregnancy. [15]
- There must be heightened vigilance for signs of intravascular fluid depletion and blood loss, as these may be masked by physiologic changes of pregnancy. It is important to review patient's vital signs, signs and symptoms in the context of these changes and the trimester of pregnancy she is in. **A narrow pulse pressure of 25mmHg** (rather than 20mmHg as in the general population)**, should be considered a threshold for intravenous fluid replacement** [15], particularly in the first and second trimesters.

Table 3. Expected changes in pregnancy

	1st trimester Preconception to 12 weeks	**2nd trimester 13 to 26 weeks**	**3rd trimester 27 to 40 weeks**
Cardiovascular	Widened pulse pressure	Widened pulse pressure Increase in plasma volume	BP and HR increases Peak in plasma volume at 34 weeks, then decreases
Haematological	Leucocytosis, although lymphocyte count may decrease Fall in haemoglobin (and haematocrit) due to rise in plasma volume	Leucocytosis Increased platelet count Decreased erythrocyte count Increased hypercoagulability	Leucocytosis Decrease in platelet counts Increased erythrocyte count
Respiratory	Increased minute ventilation and tidal volume	Compensated respiratory alkalosis Increased oxygen consumption (more susceptible to acute pulmonary oedema and hypoxia)	Compensated respiratory alkalosis Increased oxygen consumption (more susceptible to acute pulmonary oedema and hypoxia)
Thermoregulatory	Slight increase in body temperature	Slight decrease in body temperature	Body temperature ranges between 35.3–37.3°C
Impact on diagnosis	May not present with leucopenia	May not present with leucopenia, thrombocytopenia nor fever	May not present with fever
Impact on management	IV fluids may need to be initiated earlier • Threshold of narrowed pulse pressure is 25mmHg, instead of 20mmHg • The rise in haematocrit is not as apparent, due to lower baseline haematocrit	IV fluid replacement may need to be initiated earlier • The threshold of narrowed pulse pressure is 25mmHg, instead of 20mmHg • The rise in haematocrit is not as apparent, due to lower baseline haematocrit	Heightened vigilance for intravascular volume depletion and blood loss when there is a drop in blood pressure from baseline, even if it does not fulfil the cut-off of systolic BP <90mmHg

Special population: Infants and children

- Infants have higher risk for severe dengue and are at high risk of mortality compared to older children. [15]
- Infants born to women who are not dengue naive at time of pregnancy are especially at risk due to placental transfer of dengue antibodies. This risk for antibody dependent enhancement to occur is highest at 2 months after birth. [15]
- Thus, clinicians should be vigilant in reviewing infants and children for warning signs, which may mimic symptoms of other common childhood illnesses, such as gastroenteritis.
- Clinicians should take note of age-specific references for vital parameters and laboratory values in children (refer to tables below). When measuring BP, appropriately-size blood pressure cuffs should be used. [30]

Table 4. Normal HR, respiratory rate and Systolic BP by Age

Age	Heart Rate (beats/min)	Respiratory Rate (breaths/min)	Systolic Blood Pressure (mmHg)
Neonate	120–180	40–60	60–80
Infant (1 mth to 1 yr)	110–160	30–40	70–90
Toddler (1–2 yr)	100–150	25–35	80–95
Young child (2–7 yr)	95–140	25–30	90–110
Older child (7–12 yr)	80–120	20–25	100–120

References: KKH The Baby Bear Book

Table 5. Haematocrit ranges according to age

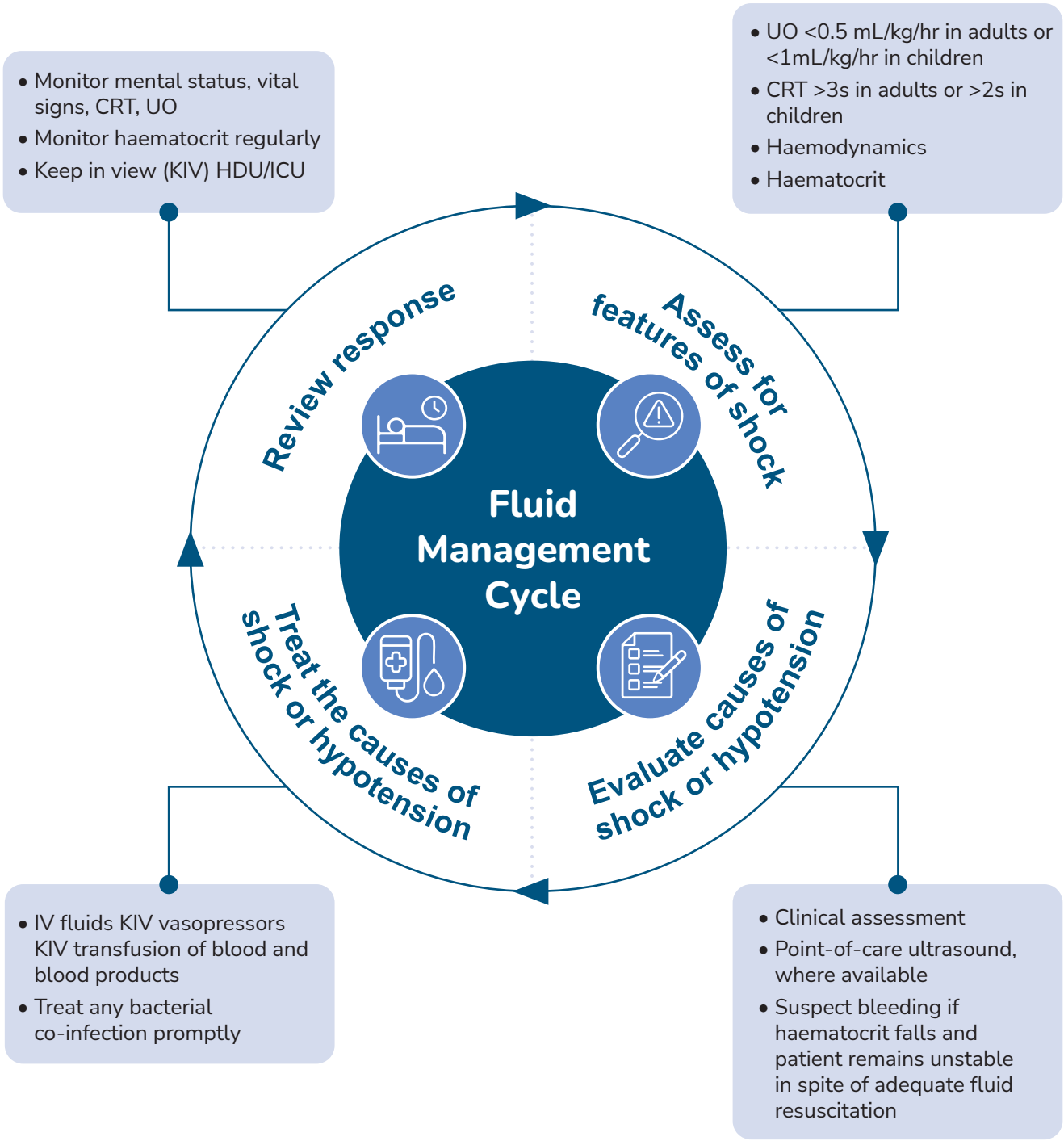
From Age	To Age	Minimum Haematocrit	Maximum Haematocrit
0 min	3 days	45%	75%
3 days	1 month	45%	67%
1 month	3 months	33%	53%
3 months	1 year	30%	40%
1 year	2 years	30%	38%
2 years	7 years	32.8%	41.1%
7 years	12 years	34.5%	42.2%

References: KKH Haematology Lab, KKH Full Blood Count (FBC)

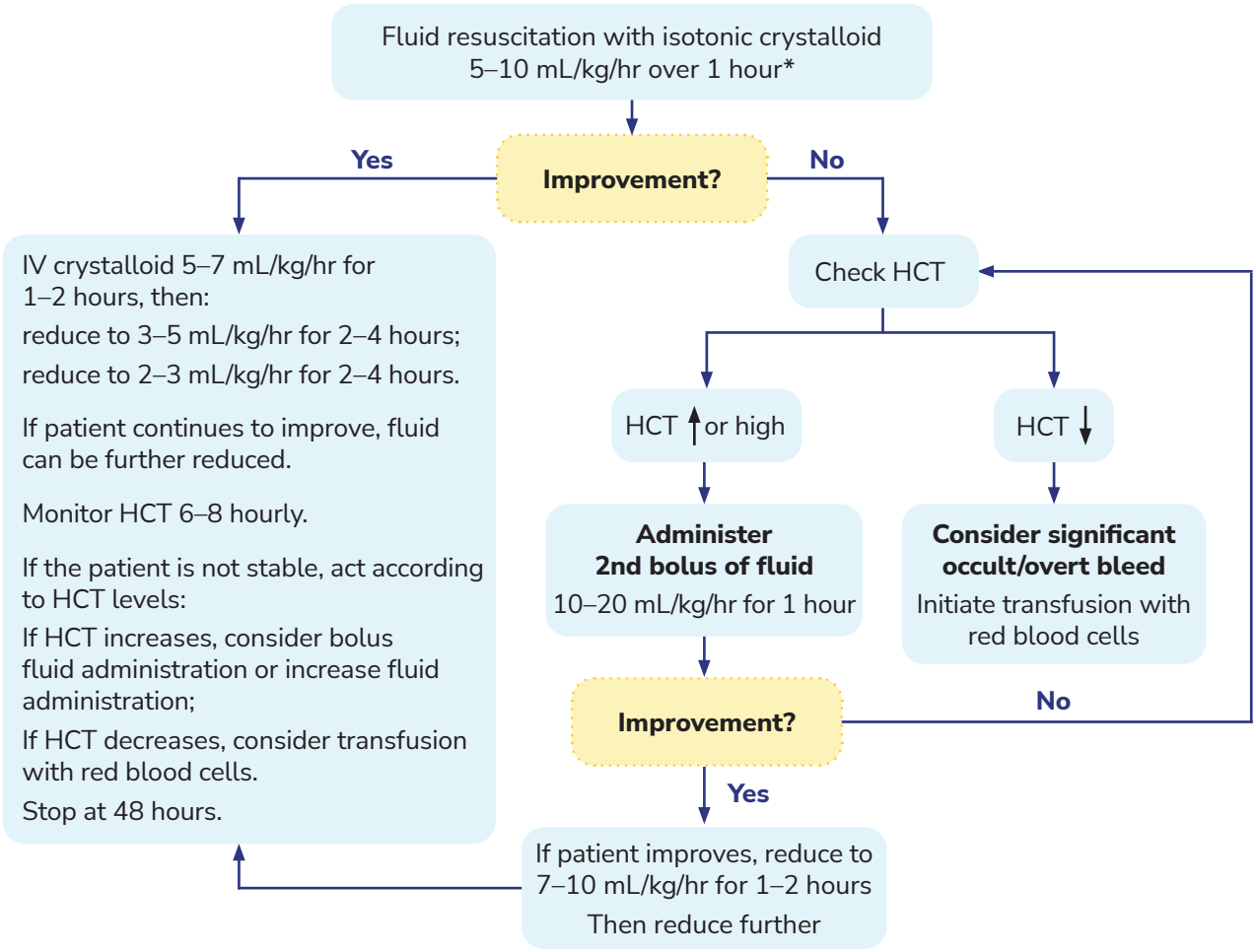
DENGUE: FLUID MANAGEMENT FOR HOSPITALISED PATIENTS

Prompt identification of plasma leakage, treatment and re-assessment are necessary to improve clinical outcomes of dengue. Clinicians should also avoid over-hydrating patients and should not administer intravenous fluids unnecessarily after patients have passed the critical phase. The figure below shows the fluid management cycle for patients with dengue.

Figure 2. Fluid management cycle

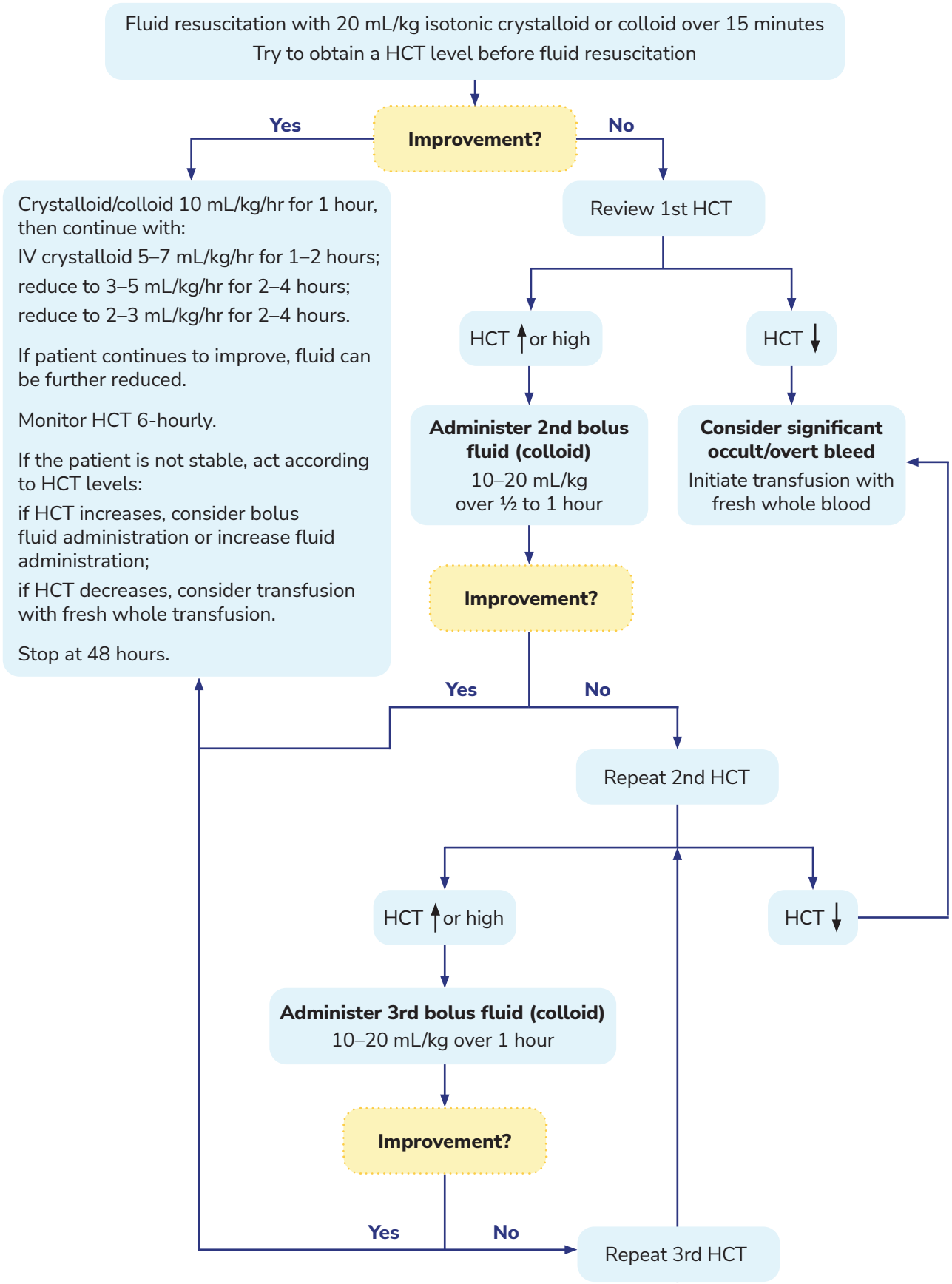


Compensated shock
(systolic pressure maintained but has signs of reduced perfusion)



* For infants and children to consider up to 20mL/kg/hr at initiation for compensated shock.

Hypotensive shock



DENGUE: BLOOD PRODUCT USE IN HOSPITALISED PATIENTS WITH DENGUE

When facing a scenario requiring massive transfusion, it is advisable to consult haematology. Once bleeding is under control, specific laboratory targets can guide further correction e.g. maintaining fibrinogen level between 1 to 1.5 g/L (or above 2 g/L in major obstetric haemorrhage), ensuring a partial thromboplastin time no more than 1.5 times upper limit of normal, and keeping platelet counts above 50 × 10^9/L (or above 100 × 10^9/L if bleeding persists). [31]

Table 4. Appropriate use of blood products in patients with dengue.

<table>
<tr><th>Blood product</th><th>Recommendations for prophylactic and pre-procedure blood product use in adults</th><th>Recommendations for adults with overt/occult bleeding</th><th>Guidance for children</th></tr>
<tr><td>Red Blood Cell</td><td>1) For a stable patient who is not bleeding: to consider transfusion if Hb is less than 7 g/dL.
2) If a patient is not bleeding but has septic shock: consider transfusion if Hb is less than 7 g/dL, with provision to transfuse up to 10 g/dL to overcome circulatory shock.
3) For a patient at risk of AMI, consider transfusion if Hb is less than 8 g/dL, with provision to transfuse up to 10 g/dL to overcome circulatory shock.</td><td>1) For a patient with circulatory shock and falling haematocrit trend, clinicians should look for internal and external haemorrhage. Consider red blood cell transfusion if bleeding is present, regardless of Hb levels.
2) For a patient with active bleeding, to replace estimated blood loss as Hb measurements may not be accurate in the acute phase.
3) If a patient is on an anti-coagulant and bleeds, stop the anticoagulant. Consider giving vitamin K, fresh frozen plasma, prothrombin complex concentrate, or a specific reversal agent (consult a haematologist if required).</td><td>General considerations for blood product transfusions are similar in children. Clinical judgment is required to determine Hb target for those children who have a background of stable iron deficiency anemia who have lower baseline Hb.
Hematocrit ranges according to age
<table>
<tr><th>From Age</th><th>To Age</th><th>Min HCT</th><th>Max HCT</th></tr>
<tr><td>0 min</td><td>3 days</td><td>45%</td><td>76%</td></tr>
<tr><td>3 days</td><td>1 mth</td><td>45%</td><td>67%</td></tr>
<tr><td>1 mth</td><td>3 mths</td><td>33%</td><td>53%</td></tr>
<tr><td>3 mths</td><td>1 yr</td><td>30%</td><td>40%</td></tr>
<tr><td>1 yr</td><td>2 yrs</td><td>30%</td><td>38%</td></tr>
<tr><td>2 yrs</td><td>7 yrs</td><td>32.8%</td><td>41.1%</td></tr>
<tr><td>7 yrs</td><td>12 yrs</td><td>34.5%</td><td>42.2%</td></tr>
</table>
Volume of packed cells required (mLs) = change in Hb desired (g/dL) × weight (kg) × 3.5 (4mL/kg of packed cells expected to increase Hb by 1g/dL in absence of ongoing bleeding)</td></tr>
<tr><td>Coagulation factors (fresh frozen plasma; cryoprecipitate)</td><td>1) Fresh frozen plasma or cryoprecipitate should not be administered in the absence of bleeding and/or invasive procedures.
2) For patients with coagulopathy undergoing an invasive procedure (e.g., central line insertion), consult the proceduralist. Note that standard coagulation tests are poorly predictive of bleeding risk prior to invasive procedures.
3) Fresh frozen plasma may be considered prophylactically before a major procedure or surgery. The appropriate dose of plasma depends on the clinical indication and is typically 12 to 15 mL/kg.</td><td>1) With regards to bleeding in the setting of anticoagulation use, a haematologist should be consulted for reversal options.
2) Fresh frozen plasma may be considered therapeutically when there is severe bleeding. The appropriate dose depends on the clinical indication and is typically 12 to 15 mL/kg.
3) Cryoprecipitate can be considered for treatment of patients with acquired hypofibrinogenemia (fibrinogen level <1.0 g/L) who are clinically bleeding or who have planned interventions associated with high bleeding risks.
4) In the setting of massive blood loss or major haemorrhage, a higher fibrinogen threshold of <1.5 g/L may be used. 10 units of cryoprecipitate (or 2 units of pre-pooled cryoprecipitate) will increase fibrinogen in an average-sized adult by approximately 1 g/L, with repeat doses guided by fibrinogen levels.
5) Local or surgical arrest of the bleed and use of tranexamic acid may be considered.</td><td>General considerations for coagulation factors are similar in children.
Cryoprecipitate: 5mL/kg or 1u/4kg body weight</td></tr>
<tr><td>Platelets
Platelet counts are a continuous variable and can fluctuate rapidly in patients with dengue haemorrhagic shock</td><td>1) No bleeding and no procedures/surgeries: no requirement for prophylactic transfusion regardless of platelet level.
2) For patients undergoing insertion of central venous catheter: prophylactic platelet transfusion if platelet level is less than 20 × 10^9/L.
3) For patients undergoing other procedures/surgeries: consult proceduralist on preferred platelet threshold for transfusion.</td><td>1) If a patient is on anti-platelet agents and bleeds, stop the antiplatelet drug. Consider platelet transfusion.
2) Oropharyngeal bleeding or epistaxis <30min or self-resolving: No recommendations for platelet transfusion. Use local compression and adjunct methods to mitigate bleed.
3) Bleeding in GIT, GU tract, respiratory tract, body cavity, muscle or soft tissue, which does not require red cell transfusion: Keep platelet level above 30 × 10^9/L
4) Bleeding in GIT, GU tract, respiratory tract, body cavity, muscle or soft tissue, which requires red cell transfusion: Keep platelet level above 50 × 10^9/L
5) Bleeding involving polytrauma, eye or brain: Keep platelet level above 100 × 10^9/L</td><td>General considerations for platelets are similar in children.
Platelets: 10–15mL/kg; 1 unit Cold-Stored Platelets (CSP) or 4 units of platelets in adult-sized adolescents</td></tr>
</table>

Methods

In Singapore, the burden of dengue disease is mostly in the primary healthcare setting, with a smaller proportion requiring admission. Adult residents disproportionately bear the burden of disease of dengue compared to other countries in the region, wherein dengue occurs mainly in the paediatric population. Furthermore, more complicated dengue disease requiring hospitalisation, severe disease requiring Intensive Care Unit monitoring and support, and deaths occur in the adult population. [33] It is against this backdrop and based on previous national dengue death audits that the need for a local guideline on dengue management was identified. To ensure wide representation of views, a multidisciplinary expert group (EG) of 13 members was appointed. The EG included primary care doctors, adult and paediatric ID physicians, intensivists, and pathologists. The composition of the EG was formed so to include private and public healthcare professionals (the latter, with representation across all three local clusters). A Chairperson was appointed based on leadership skills, ability to facilitate discussions and involvement in the national dengue death audits. Each EG member declared potential conflicts of interest (COI); declarations were assessed by the Chairperson and secretariat to avoid undermining the objectivity of the guideline and to ensure the scope of the guideline is not influenced by personal, financial and or professional interests. Members with COI recused themselves from voting when relevant. The EG convened with the goal to develop a dengue clinical guideline presenting concise best practices for the acute care of dengue patients from outpatient to inpatient care, as well as high acuity care if needed. The main objective was to optimise acute dengue clinical management and to reduce unwarranted variation in practice. Management options that are not yet commercially available in Singapore or are still under trial and investigation were not included (e.g. diagnostic tests, biomarkers, antivirals, specific intravenous fluids, and vaccines).

Evidence review and development of recommendations

Recommendations were developed by adapting from two guidelines from the World Health Organisation (WHO):

- WHO (2009) Dengue Guidelines for diagnosis, treatment, prevention and control: new edition
- WHO (2012) Handbook for Clinical Management of Dengue

These source guidelines were identified as they offer a scientifically robust and globally recognised source of recommendations. When relevant, critical review of the literature was conducted, with emphasis on local scientific evidence or institutional-level guidances. Additional information was sourced and included from learning points that arose from the national dengue death audit conducted in 2019-2020 (unpublished data) and relevant circulars from the Ministry of Health. As Dengue is a neglected tropical disease, there are areas where there is little-no evidence to inform the discussion and as such expert opinion was relied upon. Based on the totality of the evidence, recommendations and best practices were drafted using the following key factors to guide the strength and wording of the recommendations:

1. Quality of evidence (as based on the hierarchy of evidence)
2. Balance of benefits and harms wherein the benefits should clearly outweigh the harms for strongly worded recommendations and a weak recommendation is made when the balance is uncertain
3. Resource use and feasibility to incorporate the practicalities of implementing the recommendation
4. Values and preferences of the affected populations should be taken into consideration

The draft guideline was collated and then reviewed by the entire EG across four rounds. The RAND/UCLA voting method was applied to detect consensus. The aims of the reviews were to have clear and concise language, actionable steps, and avoid being too restrictive without compromising on basic principles in the care and management of the dengue patient.

Relevant stakeholders and external experts were engaged on the draft guideline via a comprehensive consultation process; feedback was sought from relevant Colleges and Chapters under the Academy of Medicine, Singapore, the College of Family Physicians Singapore, NCID Paediatrics ID workgroup, NCID Clinical Management Committee, National Environment Agency, and Communicable Diseases Agency.

Guideline updating process

As there have not been significant changes to acute dengue management evidence over the past decade, this guideline will be updated on an ad-hoc basis, should new literature emerge that will impact outcomes and clinical management of acute dengue. Changes in local healthcare practices or epidemiology will be monitored and assessed vis-à-vis the need to update the guideline or in 3–5 years.

GLOSSARY

ALT: alanine transaminase

AMI: acute myocardial infarction

AST: aspartate transaminase

BP: blood pressure

CRT: capillary refill time

FBC: full blood count

GIT: gastrointestinal tract

GU: genitourinary

GP: general practitioner

Hb: haemoglobin

HCT: haematocrit

HDU: high-dependency unit

HR: heart rate

IV: intravenous

ICU: intensive care unit

KIV: keep in view

MAP: mean arterial blood pressure

NSAIDs: non-steroidal anti-inflammatory drugs

PCR: polymerase chain reaction

SBP: systolic blood pressure

UO: urine output

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Prepare · Prevent · Protect

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