GUIDELINES

ISCCM Position Statement: Management of Severe Dengue in Intensive Care Unit

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Abstract

Dengue is one of the commonest causes of undifferentiated acute febrile illness in India as well as South East Asia. Nearly two-fifths of the world population is at risk of infection, and nearly 96 million infections reported worldwide, it is a major cause of concern across the globe. The ISCCM leadership felt that there have been no new directives/guidelines except the MOH guidelines for the management of dengue fever since 2014. Under the auspices of the Indian Society of Critical Care Medicine (ISCCM), an expert group of 14 intensivists from across the country, was formed. The task force members formulated questions that needed to be answered. These questions were validated by the members of ISCCM attending research conclave 2023. All the members systematically searched PubMed, MEDLINE, and Science Direct for original articles on different aspects of dengue management between January 1, 2000, and July 1, 2023. From the collected articles, duplicates were removed. Based on the evidence collected, the expert group members prepared statements/answers to the questions. Since most of the evidence is of moderate to low quality, a consensus was generated amongst the members of the task force. Each statement was agreed upon by 70% of the task force. The statements presented in the article are consensus statements as answers to queries raised.

Keywords: Critically ill patients, Dengue, Intensive care unit.

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Introduction

Dengue is one of the commonest causes of undifferentiated acute febrile illness in India as well as South East Asia. Nearly two-fifths of the world population is at risk of infection, and nearly 96 million infections reported worldwide, it is a major cause of concern across the globe.[1] It is caused by *flavivirus*, which is transmitted by Aedes Aegypti/albopictus mosquitos. There are four known serotypes of dengue virus (DENV 1, DENV 2, DENV 3, and DENV 4), and all strains are efficient in causing critical disease due to dengue hemorrhagic fever (DHF)/dengue shock syndrome (DSS). The fifth serotype, DENV 5, follows the sylvatic cycle, unlike the other four serotypes which follow the human cycle. Apart from mosquitoes, the various may be transmitted through blood products, needle stick injury, and mucocutaneous exposure.[2] A large number of studies and treatment guidelines have tried to provide effective approaches for managing severe dengue infections, yet there seem to be some concerns regarding them. Very limited data from high-quality randomized control trials make the evolution of effective, evidence-based treatment strategies difficult. The mortality amongst severe dengue virus-infected adult patients admitted in intensive care unit (ICU) is reported to be as high as 20%. The presence of shock, respiratory failure, and renal dysfunction are important causes associated with adverse outcomes.[3] To address this issue, Indian Society of Critical Care Medicine (ISCCM) leadership decided to constitute an expert group to evaluate the evidence and come out with a position statement regarding management approaches for critically ill dengue patients admitted to the ICU.

Need for Position Statement

The ISCCM leadership felt that there have been no new directives/guidelines except the MOH guidelines for the management of dengue fever since 2014. A committee of experts was constituted during the research conclave 2024 to address the common issues

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raised by intensivists across the country during teaching webinars. During the conclave, the committee pondered over the possible questions to be addressed. After due deliberations, a list of questions was prepared and presented to the delegates present during the conclave. The suggestions ions provided by the ISCCM members regarding points to be addressed were incorporated as questions to be addressed.

Methodology

Under the auspices of the ISCCM, an expert group of 14 intensivists, was formed. The task force included members representing different regions of India and working in a mix of public and private institutions. The members were selected based on their profile in education, interest, or research in dengue. The expert group members were given the responsibility of developing consensus on the management of severe dengue cases in the ICU. The Delphi technique was employed to develop a consensus position statements. All the expert group members systematically searched PubMed, MEDLINE, and Science Direct for original articles on different aspects of dengue management between Jan 1, 2000, and July 1, 2023. The search string used for the literature search included "dengue, management, guidelines" OR "dengue/severe dengue/dengue shock syndrome/dengue hemorrhagic fever" AND "fluid resuscitation" OR "complications". The list of search strings is provided in the annexure. The members of the expert group collected the articles, duplicates were removed. Based on the evidence collected, the expert group members prepared statements/answers to the questions. These were sent to 4 reviewers (AB, HS, VS, and LY) at PGIMER. These were deliberated upon and a set consensus statement was developed. These were then circulated amongst all the members of the expert group and their opinion was sought. All these statements have been approved/agreed on by at least 70% of the expert group members. These statements are consensus statements based on "low to moderate quality of evidence", mostly as expert group opinion/national guidelines.

Pathophysiology of Dengue Virus Infection

The expert group did not deliberate much on pathogenesis since it is nearly very well agreed on. Some of the newer pathogenesis mechanisms proposed for hematological alterations are still being evaluated.

The pathogenesis of dengue virus infection and immune-mediated complications following it, is still evolving. The critical step for virus infectivity is mediated by major viral protein (E) glycoprotein that binds with host cells.[4] The clinical manifestations of dengue virus infection are attributed to direct viremia and the subsequent immune response, resulting in a continuum or a biphasic illness.[3] Dengue virus infections cause illnesses ranging from mild, nonspecific fever (classic dengue fever) to life-threatening complications like DHF and DSS. Primary infection with one serotype generally provides lifelong immunity to infection with the same serotype. Virus protein cross-reactivity to serotypes may cause a secondary immune response resulting in complications in the form of organ dysfunction during secondary infection. Although less than 1% of all infections result in severe dengue, DHF, and DSS the sheer number in a short span of time overwhelms the healthcare facilities. The cardinal feature of severe dengue infection is "Capillary leak syndrome", which is characteristically absent in mild disease (Fig. 1). This pathophysiologic abnormality arises due to endothelial/vascular permeability and glycocalyx disruption due to toxic mediators.[4,5] Large number of mediators have been implicated in severe dengue infections.[5] The prominent ones are nitric oxide (NO), IL 6, IFN gamma, and free vascular endothelial growth factor (VEGF).[5] A complex interplay of various biochemical mediators and endothelium is responsible for clinical manifestations and complications in dengue.[6] The hematological predominant abnormalities include elevated levels of von

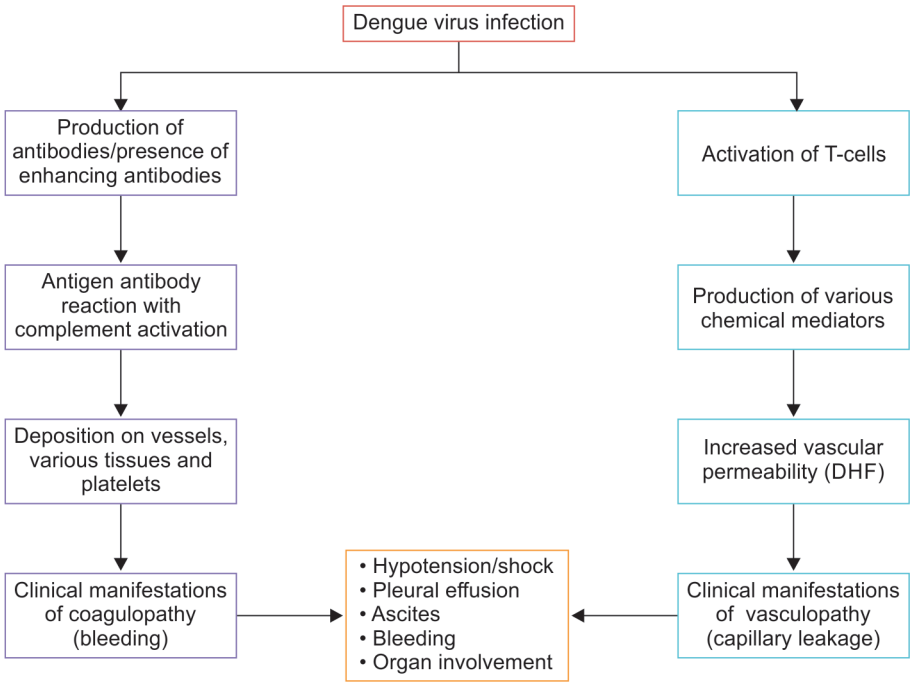


Fig. 1: Pathophysiology of dengue virus infection

Willebrand factor, tissue factor, tissue plasminogen activator, and platelet factor inhibitor.[7,8] Dengue being a hepatotropic virus, some amount of liver dysfunction is evident in all patients. In the absence of severe abnormalities in hepatic synthetic functions, frank coagulopathy is rarely seen except in patients with shock and MODS.[8] The combination of vasculopathy, endothelial dysfunction, and thrombocytopenia predisposes to bleeding manifestations.[8]

Clinical Presentation of Dengue Virus Infection

The clinical presentation of dengue virus infection has been described systematically by the World Health Organization and the expert group did not feel any need to change the same.

There are 3 clinical phases of dengue virus infection.[6]

- Febrile phase (day 2–7)
- Critical phase (day 4–5)
- Recovery phase (beyond day 6)

Febrile phase is characterized by acute onset fever, with headache, body ache, retro-orbital pain, URI-like symptoms, and occasionally GI symptoms. Flushing of skin or rash may appear on days 4–5. Starts from the neck and face, progresses to the periphery, and may disappear when the fever disappears. In some patients, itching and rash may persist even after the fever disappears.

Critical phase is characterized by the capillary leak. This results in fluid accumulation in the pleura, and peritoneum and is confirmed by hemoconcentration. Fluid leak results in shock and decreased organ perfusion. Abnormal hemostasis may result in clinically overt bleeding or falling HCT with clinical deterioration. Organ dysfunction becomes manifest. This period normally lasts for 36–48 hours. This is the stage at which the patient may seek hospital care/critical care.

Recovery phase is characterized by the return of extravascular fluid to a vascular compartment with improving organ function. There is clinical improvement in symptoms. It starts after day 7 and lasts for 2–3 days. In some patients (DHF/DSS) longer convalescence may be expected. Some patients may pass on to an expanded dengue phase with persisting organ dysfunction.

Definitions

Dengue virus infection has been divided into various categories depending on the severity of the illness by the guidelines issued by the Ministry of Health in 2014 (Tables 1 and 2).[9] It was discussed and decided to keep the same case definitions to maintain uniformity in defining various clinical stages of dengue virus infection.

- Dengue: Acute febrile illness of 2–7 days duration with, mild to moderate grade fever with myalgia, arthralgia, headache, retro-orbital pain, rash, or cutaneous bleeding. There may be the appearance of rash at defervescence.
- Severe dengue: Severe dengue is defined as dengue fever with a capillary leak, bleeding, shock, or organ dysfunction.
- Dengue with warning symptoms: Dengue fever with persistent vomiting, abdominal pain or discomfort, mild bleeding, evidence of pleural effusion/ascites, cold and clammy extremities, decreased urine output, tachycardia, hypotension, rapid fall in platelet count or hematocrit >45%, is classified as dengue with warning signs.
- Dengue hemorrhagic fever: Dengue fever with hemorrhagic manifestations (positive tourniquet test, petechiae, purpura, mucosal bleeding), evidence of capillary leak or thrombocytopenia (platelet <10,000 mm^3).
- Dengue shock syndrome: Dengue hemorrhagic fever with tachycardia, low pulse pressure, hypotension cold clammy skin, and restlessness.
- Expanded dengue: Dengue fever with more than usual manifestations of organ dysfunction, CNS (encephalitis), CVS

Table 1: Clinical features of dengue fever and severity

Clinical features of DF

An acute febrile illness of 2–7 days duration with two or more of the following manifestations: Headache, retro-orbital pain, myalgia, arthralgia, rash, hemorrhagic manifestations.

Dengue hemorrhagic fever (DHF)

a) A case with clinical criteria of dengue fever

Plus

b) Hemorrhagic tendencies evidenced by one or more of the following:
   1. Positive tourniquet test
   2. Petechiae, ecchymosis purpura
   3. Bleeding from mucosa, gastrointestinal tract, injection sites or other sites

Plus

c) Thrombocytopenia (<100,000 cells per cumm)

Plus

d) Evidence of plasma leakage due to increased vascular permeability, manifested by one or more of the following:
   1. A rise in average hematocrit for age and sex 20%
   2. A more than 20% drop in hematocrit following volume replacement treatment compared to baseline
   3. Signs of plasma leakage (pleural effusion, ascites, hypoproteinemia)

Dengue shock syndrome (DSS)

All the above criteria for DHF with evidence of circulatory failure manifested by rapid and weak pulse and narrow pulse pressure (–5.20% mm Hg) or hypotension for age, cold and clammy skin and restlessness.

Note: Evidence of plasma leakage is important for diagnosis of DHFI DSS.

Table 2: Expanded dengue syndrome

System involved	*Clinical manifestations*	*Proposed workup*	*Treatment*
CNS	Encephalopathy (multifactorial/metabolic)	Electrolytes, RFT, LFT	Correct metabolic abnormality
	Encephalitis (altered mentation)	MRI, CSF	Supportive T/T
	Seizures (encephalitis)	MRI	BZD, Antiepileptics
	IC Bleed (focal deficits)	NCCT, CECT, MRI	Supportive T/T
GI tract	Hepatitis	LFT, Coagulogram, Sr Ferritin	Avoid paracetamol, supportive T/T
	FHF	LFT, Coagulogram, serum ammonia	NAC infusion, supportive T/T
	Acute pancreatitis	Sr. Ferritin, LDH, TG	Supportive T/T
	Acute cholecystitis (a calculus)	CE CT Abdomen, Sr Amylase, Lipase USG abdomen	Supportive T/T
Renal	AKI/ATN (reduced urine output)	RFT, Sr. Electrolytes,	Fluid resuscitation
	HUS/TTP	Urine R/E	Diuretics
		Peripheral smear	Supportive T/T
		(Retic count, schistocytes to R/O HUS/TTP)	
CVS	Myocarditis (CCF/Arrhythmias)	Cardiac biomarkers	Guided IV fluids
	Pericardial effusion	Echocardiography	Ionotrops
	(s/o capillary leak)	ECG monitoring	Antiarrhythmic
		Echocardiography	Supportive T/T
Respiratory	Pleural effusion	CXR, USG chest	Supportive T/T
	Pulmonary edema	CXR, Cardiac biomarkers, Echocardiography	Oxygen,
	(SOB, Hypoxia)	CXR, HRCT chest	Diuretics
	ARDS (SOB, Hypoxia)	Serial Hb, HCT	Supportive T/T
	Pulmonary hemorrhage	CXR, CECT chest	Oxygenation
	(SOB, Hypoxia, Falling HCT)		Supportive T/T
			Blood and platelet transfusion
			Supportive T/T
Eyes	Visual loss	Visual acuity	Platelet transfusion
	(Macular hemorrhage, optic neuritis)	Fundus examination	Supportive therapy
		Platelet count	Steroids
	Conjunctival hemorrhage		

(myocarditis), GI (pancreatitis), hepatic (FHF), renal (AKI), RS (ARDS), or eye (Table 2).

Initial Assessment: Q1 in Triage/ER, What all should be Assessed in Suspected/Conformed Dengue Patient?[6] (Fig. 2)

The expert group suggests an initial assessment of the patient in triage or emergency for vital signs like temperature, blood pressure, pulse rate, respiratory rate, and peripheral perfusion. Peripheral perfusion is to be assessed by pulse volume, peripheral temperature, color of extremities, and capillary refill time.

The expert group recommends that all patients with only fever, no abnormal vital signs, and no warning symptoms, should be managed at home and not admitted in hospital/ICU. The expert group strongly recommends that these patients should be made aware of the warning symptoms and should be asked to report to the ER/ED at the first warning symptom.

The expert group suggests that all the patients in the "High-risk Group" should be observed or admitted in a hospital setting (Fig. 2).

The expert group suggests that patients with suspected or proven dengue fever with two or more abnormal vitals, the patient should be triaged "Yellow" and observed. Such patients should be evaluated for the presence of signs of organ system dysfunction.

The expert group recommends that high-risk patients and patients with two or more abnormal vital signs and those with reduced peripheral perfusion/shock, should be triaged "Red" and admitted to ICU.

It has been observed that the majority of patients, except those at "High Risk" usually have milder illnesses which can be easily managed at home with oral fluid supplements, antipyretics, and other supportive therapy.[6,9] Some of these patients will eventually go on to develop warning symptoms like pain abdomen, persistent vomiting, persistent headache, or ongoing fever even at the end of day 5, these patients will likely transit into a critical phase and should ideally be observed in a hospitalized setting.[9] A small number, around 10%, eventually end up with severe dengue fever, DHF, or DSS. This patient should be identified early and should be admitted ideally in an ICU.[9] Since dengue is a seasonal illness and a large number may overwhelm the health care services in a shorter time, specialized wards or observation units may be created in health care facilities. Those with severe dengue (>2 organ system dysfunction), expanded dengue and DSS may be referred in time to a facility with advanced management capabilities.[6,9]

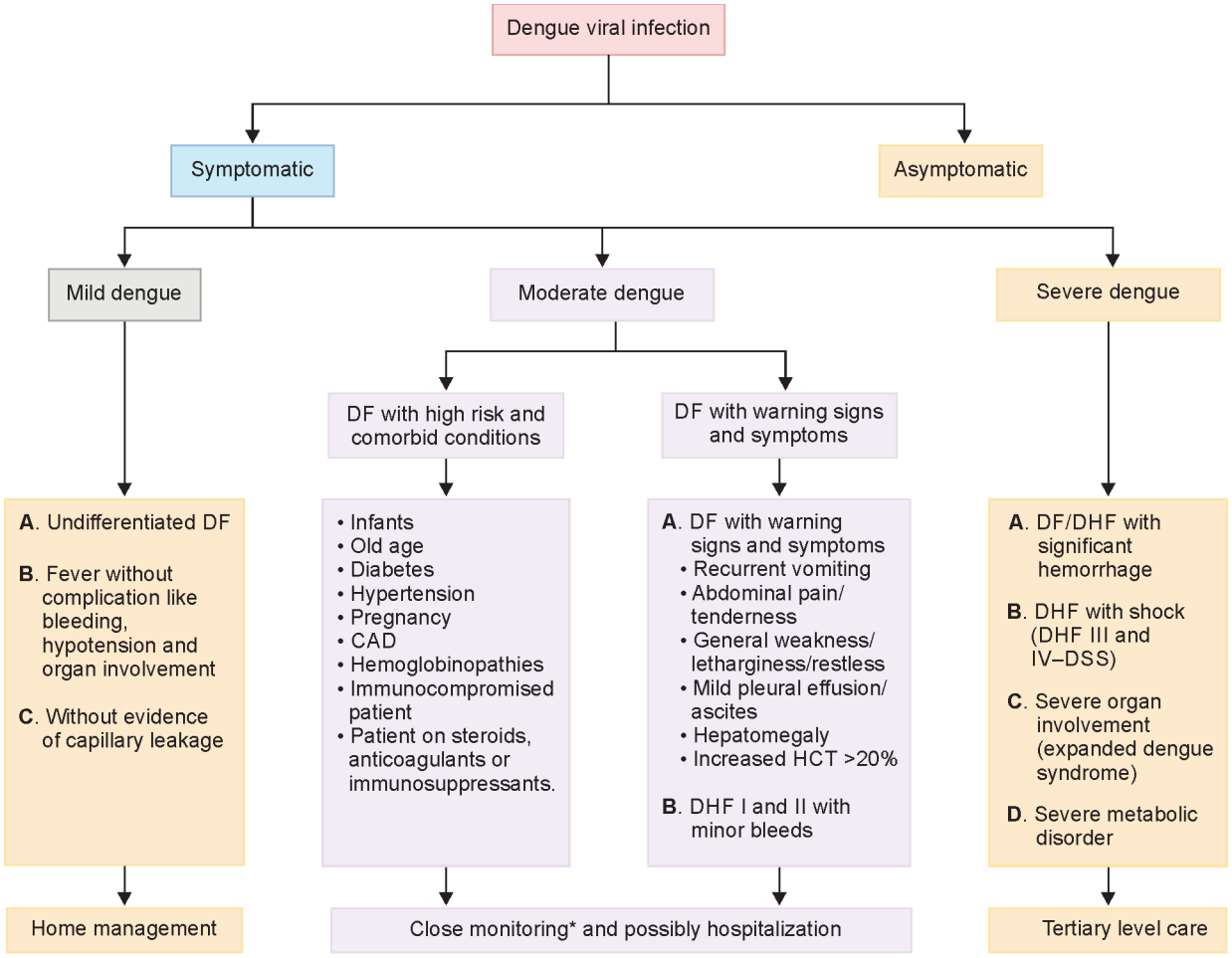


Fig. 2: Dengue virus infection and proposed triage protocol

Warning Signs Q2: What are all the Warning Signs the Clinicians should Look for? (Table 2)[6,9]

The clinician should be looking for clinical as well as worsening biochemical parameters in patients admitted to the wards or under observation.

The warning signs to look for are:

- No clinical improvement or worsening of the clinical conditions/ vitals just before or during the transition from a febrile to an afebrile phase.
- Persistent vomiting or inability to retain food/liquids/inability to drink liquids.
- Severe abdominal pain.
- Lethargy and/or restlessness, sudden behavioral changes.
- Bleeding: Epistaxis, black stool, hematemesis, excessive menstrual bleeding, dark-coloured urine (hemoglobinuria), or haematuria.
- Giddiness.
- Pale, cold, and clammy hands and feet.
- Less/no urine output for 4–6 hours.

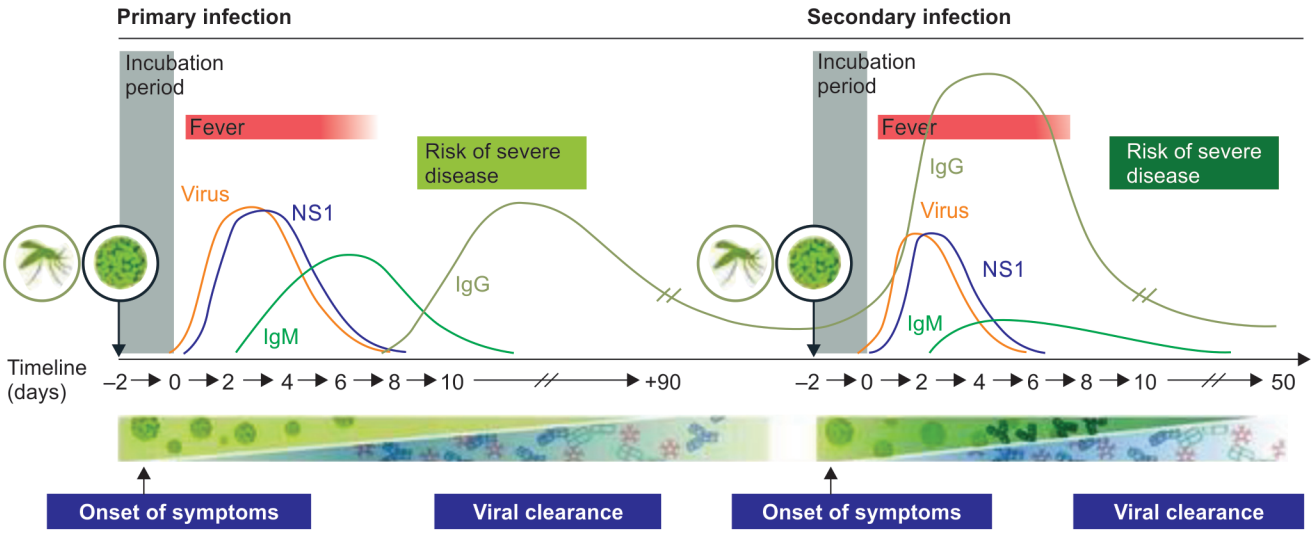
The expert group recommends that patients with warning signs/ symptoms should be admitted for observation in the observation unit attached to the ER or in the wards. These patients should be monitored frequently for abnormal vitals and organ system dysfunction.

Diagnosis of Dengue Fever and Severe Dengue

Dengue fever should be clinically suspected as per the case definition (Tables 1 and 2). The diagnosis can be confirmed by appropriate laboratory tests.

Laboratory diagnosis of dengue is made by detection of the virus or its components (PCR, Antigen test) or by detection of the serological responses after infection (IgM and IgG levels). During the febrile phase (day 1 to day 5 of fever onset), PCR (within 48 hours) or NS1 Ag can be used. For all practical purposes, the NS1 Ag test is preferred. Both enzyme-linked immunosorbent assay (ELISA) and rapid commercial tests are available for NS1 Ag detection. The sensitivity and specificity of NS1 antigen capture is to the tune of 80–100% respectively.[10,11]

A single serum sample collected after day 5 of fever onset is useful for IgM determination. Commercial anti-dengue IgM kits have reported sensitivities of 21–99% and specificities of 77–98%.[12] Serological cross-reactivity may be responsible for false positive results due to other *Flaviviruses* infections (Japanese encephalitis virus and West Nile virus). False-positive results may also be



Adapted from Kerkhof K, et al. Trends Microbiol. 2020

Fig. 3: Diagnosis of dengue fever

observed in patients with malaria, scrub typhus, or past Flavivirus infections (Fig. 3).[13]

Diagnosis: Q3: How should the Diagnosis of Dengue Fever be Confirmed in ER/ED?[6,9]

- The expert group recommends performing NS1 antigen test in the first 5 days of patients presenting with clinical features consistent with dengue.
- The expert group recommends performing dengue IgG in patients presenting with clinical features consistent with dengue accompanied by organ dysfunction within the first seven days or earlier, of illness.
- The expert group recommends performing dengue IgM levels for establishing diagnosis after day 7 of onset of clinical symptoms consistent with dengue fever.
- The expert group recommends against performing dengue IgM before day 7 of illness.
- The expert group recommends that PCR for virus detection should be performed only for surveillance/research purposes.

Q4: How should the Clinician/Intensivist Confirm the Diagnosis of Severe Dengue in ICU? [6,9]

Most of the patients develop severe dengue/complications in dengue fever after day 7 of illness. If the patient with confirmed dengue fever gets admitted/shifted to ICU with complications, there is no need to repeat/reconfirm the diagnosis.

In case the patient has been admitted to ICU with complications, without the diagnosis of dengue being established, the following should be done:

- For patients admitted with ongoing fever after day 7 with organ system dysfunction/shock, the expert group recommends IgM and IgG antibody test for dengue virus to be ordered.
- For patients admitted within five days of fever onset with organ system dysfunction/shock, the expert group recommends that apart from ruling out malarial infection (RDT for malaria), dengue NS1 antigen and IgG antibody test should be performed/ordered.
- If the patient gets admitted between days 5 and 7 of onset of fever with complications, the expert group recommends ruling out malarial infection and performing an IgG antibody test, as NS1 antigen is likely to disappear and IgM antibody may not have yet appeared.
- The expert group recommends against performing an NS1 antigen test after day 5 of the onset of fever.

Since the NS1 antigen test is the earliest to appear and IgM appears only after 7–10 days, a single positive value of NS1 antigen detected or an IgM seroconversion should be taken as a marker for acute dengue virus infection. In patients with secondary dengue, WHO recommends that a single value of IgG 1240 could suggest a secondary dengue.[6] A fourfold rise in the titers of IgG in paired sera, or IgG: IgM ratio of >1.10 is a better indicator than a single IgG value for secondary dengue infection.[14]

Admission Criterion: Q5: Which Patient with Dengue Fever (Confirmed/Suspected) should be Admitted in Intensive Care Unit?

- The expert group suggests that all the "high-risk" patients with dengue fever and warning symptoms should be admitted to the ICU.
- The expert group recommends admitting all patients diagnosed with dengue fever having two or more abnormal vital signs with warning symptoms to the ICU.
- The expert group recommends admitting diagnosed severe dengue patients (with 2 or more organ system dysfunction) to ICU.
- The expert group recommends all patients with DSS/DHF be admitted in ICU.
- The expert group recommends admitting all patients with dengue fever with warning signs in an observation unit/ward and carefully monitoring for organ system dysfunction.
- The expert group recommends against admitting patients with thrombocytopenia without any warning signs or hemorrhage in ICU.
- In the absence of a definitive diagnosis, the expert group recommends admitting patients with acute febrile illness (<7 days duration) with documented two or more organ system dysfunction/shock, especially during monsoon and post-monsoon season, to evaluate for tropical illnesses including dengue fever.

The recent GOI guidelines on admission to ICU also stress admitting high-risk patients and organ system dysfunction to ICUs where the facility for noninvasive as well as invasive monitoring is available.[15] It also suggests that patients requiring supportive therapy in the form of ventilation, renal replacement, or cardiovascular support, should be admitted to the ICUs.[15]

Evaluation: Q6: What Clinical and Laboratory Parameters should be Monitored in Severe Dengue Fever Admitted to ICU?

The expert group recommends detailed clinical evaluation to look for evidence of organ dysfunction and complication daily in patients admitted in the ICU. This includes vitals, looking for signs of dehydration and impaired perfusion (Capillary refill time, skin turgor, urine output), jaundice, and mental status.

Monitoring in Admitted Patients

- General condition, appetite, vomiting, mucosal bleeding (mucosal/skin/oral cavity), and mentation should be monitored every 6–8 hourly.
- Peripheral perfusion (pulse rate, blood pressure, CRT, and urine output) (early indicator of shock). Should be monitored every 2–4 hours.
- Vital signs such as temperature, pulse rate, respiratory rate, and blood pressure monitoring at least every 4–6 hours in non-shock patients.

Patients admitted to ICU with severe dengue have existing 2 or more organ failures, which could be clinical (jaundice, reduced urine output, coma) or abnormal laboratory tests. Two very important markers to evaluate reduced peripheral perfusion and reduced organ perfusion are capillary refill time and serum lactate.[16] These can guide fluid management in severe dengue patients as in severe sepsis. Since there is a potential chance of developing new organ dysfunction or worsening existing dysfunction, it is relevant to frequently monitor different laboratory parameters. Since most of the parameters will not change much in 10–12 hours, a single value every day is likely to be sufficient and should be ordered. More frequent monitoring of laboratory values should be done in patients with ongoing or worsening shock resulting in abnormal/decreased organ perfusion. Clinical monitoring and worsening/improving clinical parameters should guide the clinician regarding laboratory tests to be ordered.

Patients with Shock

These patients should be on continuous vital monitoring in the ICU. If this is not possible, vitals should be recorded as frequently as possible, preferably every 30 minutes. Since most of the cases can be monitored using noninvasive measures (Noninvasive blood pressure, pulse oximetry, POCUS for fluid resuscitation). Due to the inherent risk of bleeding while establishing invasive lines in patients with thrombocytopenia, these should be avoided, however, if clinically indicated all precautions must be taken while establishing arterial or central venous access.

- Serial hematocrit should be performed at least every 6–8 hours in stable cases and should be more frequent in unstable patients or those with suspected bleeding. It should be noted that hematocrit should be done before fluid resuscitation. If this is not possible, then it should be done after the fluid bolus but not during the infusion of the bolus.
- Urine output should be monitored at least every 6–8 hours in uncomplicated cases and on an hourly basis in patients with profound/prolonged shock or those with fluid overload. To maintain urine output around 0.5 mL/kg/h.

Biochemical Tests: Q7: Which Biochemical Parameters should be Monitored in Severe Dengue Patients Admitted in ICU? [9]

- The expert group recommends performing a baseline hemogram (with hematocrit) and routine biochemistry at admission in all suspected/confirmed patients with severe dengue.
- The expert group recommends that in DSS/DHF/dengue with warning signs routine tests (biochemistry and CBC; especially hematocrit) be repeated daily. More frequent monitoring may be done if clinically indicated.
- The expert group recommends performing baseline USG for evidence of a capillary leak in patients with dengue fever with warning signs, severe dengue, and DSS.
- The expert group recommends performing radiological imaging (CXR) at baseline in patients with severe dengue.
- The expert group suggests performing advanced radiological imaging (CT scan/MRI/echocardiography) in selected cases as and when clinically indicated.
- The expert group recommends against frequently (> twice) repeating platelet counts in dengue patients without clinically overt bleeding and a platelet count of >10,000/mm^3, however, hematocrit may be repeated frequently to access hydration status/bleeding in patients with DSS/DHF.
- The expert group recommends evaluation for secondary HLH in diagnosed dengue patients with persistent fever/recurrence of fever beyond day 7 with new-onset organ dysfunction. The recommended investigations include CBC, serum ferritin (>3000 IU significant), serum LDH, CRP, serum triglycerides, and bone marrow examination, if indicated. "H Score" should be calculated and used for the management of these patients.[17]

Recommended Blood Investigations[9]

- Complete blood count (CBC)
- Blood glucose
- Serum electrolytes
- Blood gas analysis, blood lactate levels
- Blood urea and creatinine
- Liver function tests
- Coagulation profile (PT, aPTT, INR)
- Chest radiograph
- Group and match for fresh whole blood or fresh packed red cells
- Cardiac enzymes or ECG if indicated, especially in adults
- Serum amylase and ultrasound if abdominal pain does not resolve with fluid therapy
- Any other test, if clinically indicated

Treatment: Q8: What are the Treatment Priorities in Severe Dengue Virus Infection?

The expert group strongly recommends that fluid supplementation/management should be the first and most important priority in severe dengue fever.

The majority of the complications associated with dengue fever start with the patient transiting into the critical phase instead of mild symptoms followed by recovery.[6] The major culprit is the "capillary leak", or third space fluid loss which results in reduced intravascular

fluid and resultant hemoconcentration. Hemoconcentration combined platelet functional abnormalities resulting in platelet sequestration in capillaries, resulting in rheological changes in blood flow causing organ system dysfunction secondary to compromised perfusion.[8,9] Therefore restoring perfusion by supplementing fluid becomes the first priority in the management of severe dengue fever.[9]

Type of Fluids: Q9: What should be the Preferred Fluid for Supplementation/Resuscitation in Severe Dengue Patient?

The Expert group strongly recommends that crystalloids should be preferred agents for replacement/resuscitation.

The expert group recommends that albumin infusion may be judiciously used when a large number of crystalloids are required and there is a risk of 3rd space loss.

The expert group suggests that balanced fluids may be judiciously used wherever clinically indicated.

There is no clear advantage of colloids over crystalloids based on the previous RCTs in outcomes. However, colloids may be the preferred choice if the blood pressure has to be restored urgently, i.e. in those with pulse pressure less than 10 mm Hg.[9] Colloids have been shown to restore the cardiac index and reduce the level of hematocrit faster than crystalloids in patients with intractable shock; however, the risk associated with Dextran/HES, far outweighs the benefits.[9] These agents are also not being recommended as preferred agents in fluid resuscitation in sepsis.[17] Isotonic solutions such as 0.9% saline and Ringer lactate should be preferred. Balanced fluids have an advantage and can reverse metabolic acidosis effectively but are expensive.[18] In select patients requiring very high quantities of crystalloids, albumin may be tried to prevent excessive fluid administration and reduce third space loss.[19]

Fluid Management: Q10: What should be Fluid Resuscitation Strategy in Severe Dengue with Warning Signs, without Shock?[9] (Annexure 1)

With Warning Signs Without Shock

The expert group suggests starting with 5–7 mL/kg/hr for 1–2 hours, then reducing to 3–5 mL/kg/hr for 2–4 hr, and then reducing to 2–3 ml/kg/hr or less according to clinical response.

The expert group recommends reassessing clinical status by repeating HCT at frequent intervals (2–4 hours):

- If HCT remains the same or rises only minimally -> continue with 2–3 mL/kg/hr for another 2–4 hours;
- If worsening vital signs and rapidly rising HCT: increase the rate to 5–10 mL/kg/hr for 1–2 hours.

The expert group recommends reviewing fluid infusion rates according to the clinical status (CRT), POCUS, and HCT as and when clinically indicated.

- Reduce intravenous fluids gradually when the rate of plasma leakage decreases towards the end of the critical phase.

This is indicated by:

- Adequate urine output and/or fluid intake
- HCT decreases below the baseline value in a stable patient.

Monitoring: How should the patient be monitored
The expert group recommends monitoring:

- Vital signs, peripheral perfusion (1–4 hourly until the patient is out of critical phase)
- Urine output (4–6 hourly)

Table 3A: Administration of maintenance fluid

The maintenance fluid should be calculated using the Holiday and Segar formula as follows:	
Body weight in kg	Maintenance volume for 24 hours
<10 kg	100 mL/kg
10–20	1000 + 50 mL/kg body weight exceeding 10 kg
More than 20 kg	1500 + 20 mL/kg body weight exceeding 20 kg

- HCT (before and after fluid replacement, then 6–12 hourly)
- Blood glucose
- Other organ functions (renal profile, liver profile, coagulation profile, as clinically indicated).

Since the government of India and WHO guidelines have discussed fluid management in dengue fever extensively, the expert group feels that there is no need to deviate from these guidelines.[6,9] The expert group also felt that enough evidence has been generated (in sepsis management) to recommend conservative fluid strategies as compared to liberal fluid strategy for resuscitation.[17] Therefore, a balanced approach of 10 mL/kg to a maximum of 20 mL/kg fluid bolus, as recommended in the Indian national guidelines should be followed, (Annexures 1 to 3) however, a POCUS guided resuscitation is indicated for elderly and patients with pre-existing compromised cardiac, respiratory, renal and liver function.[9]

Treatment of Compensated Shock: Q11: What should be Fluid Resuscitation Strategy in Severe Dengue with Warning Signs and Compensated Shock?[9] (Annexure 2)

The expert group recommends starting IV fluid resuscitation with isotonic crystalloid solutions at 5–10 mL/kg/hr over 1 hour and reassessing patients' condition.

The expert group recommends assessing the clinical status and resuscitation of the patient clinically (Pulse, BP, CRT, Urine output), laboratory parameters (Hematocrit), or by using POCUS.

If the patient improves: IV fluids should be reduced gradually to 5–7 mL/kg/hr for 1–2 hours, then to 3–5 mL/kg/hr for 2–4 hours, then to 2–3 mL/kg/hr for 2–4 hours and then reduced further depending on hemodynamic status.

The expert group recommends maintaining IV fluid administration for up to 24–48 hours, depending on the clinical condition and POCUS results (Tables 3A and B).

If the patient is still unstable clinically: The expert group recommends:

- Checking HCT after the first bolus;
- If HCT increases/still high (>50%), repeat a second bolus of crystalloid solution at 10–20 mL/kg/hr for 1 hour;
- If there is improvement after the second bolus, reduce the rate to 7–10 mL/kg/hr for 1–2 hours and continue to reduce as above;
- If HCT decreases, this indicates bleeding and the need to cross-match and transfuse blood as soon as possible.

Treatment of Hypotensive Shock Q12: What should be Fluid Resuscitation Strategy in Severe Dengue with Shock/DSS?[9] (Annexure 3)

The expert group recommends initiating IV fluid resuscitation with a crystalloid or colloid solution at 20 mL/kg as a bolus for 15 minutes.

If the patient improves: give a crystalloid/colloid solution of 10 mL/kg/hr for 1 hour, then reduce gradually as above.

If patient is still unstable:

Table 3B: Maintenance fluid replacement according to body weight

Body weight (In kgs)	*Volume of fluid to be given in 24 hrs maintenance + 5% deficit*	*Rate of fluid (mL/hours)*				
		Regimen 1 1.5 mL/kg	*Regimen 2 3 mL/kg*	*Regimen 3 6 mL/kg*	*Regimen 4 10 mL/kg*	*Regimen 5 20 mL/kg*
5	500 + 250 = 750	8	15	30	50	100
10	1000 + 500 = 1500	15	30	60	100	200
15	1250 + 750 = 2000	23	45	90	150	300
20	1500 + 1000 = 2500	30	60	120	200	400
25	1600 + 1250 = 2850	38	75	150	250	500
30	1700 + 1500 = 3200	45	90	180	300	600
35	1800 + 1750 = 3550	53	105	210	350	700
40	1900 + 2000 = 3900	60	120	240	400	800
45	2000 + 2250 = 4250	68	135	270	450	900
50	2100 + 2500 = 4600	75	150	300	500	1000
55	2200 + 2750 = 4950	83	165	330	550	1100
60	2300 + 3000 = 5300	90	180	360	600	1200

- Review the HCT taken before the first bolus;
- If HCT was low (50%), continue colloid infusion at 10–20 mL/kg as a third bolus over 1 hour, then reduce to 7–10 mL/kg/h 1–2 hours, then change back to crystalloid solution and reduce rate as above.

The expert group recommends using norepinephrine as the preferred inotropes in patients nonresponsive to fluid therapy.

Since the majority of data regarding inotropes use in shock comes from trials in severe shock, a pathology very similar to what is seen in severe dengue and dengue shock. The evidence is in favor of norepinephrine as the preferred inotropy in fluid unresponsive shock.[20] This strategy will help limit excessive fluid administration in patients with capillary leaks.

Treatment of Hemorrhagic Complications: Q13: What should be the Transfusion Triggers in Dengue Hemorrhagic Fever?

The expert group recommends observing for overt bleeding and hematocrit.

If overt bleeding is absent, falling hematocrit in an unstable patient may be an indicator of occult bleeding or fluid overload.

The expert group strongly recommends against transfusion of fresh blood/PCV in patients with mucosal/skin bleeding with hemoglobin >8 gm/dL.

The expert group recommends infusing 5–10 mL/kg of fresh packed red cells or 10–20 mL/kg of fresh whole blood in presence of fresh bleeding with a hemoglobin of <8 gm/dL.

The expert group recommends looking for falling hemoglobin or hematocrit as markers for occult bleeding in a clinically deteriorating severe dengue patient.

Steroids: Q14: What is the Role of Steroids in Severe Dengue Fever?

- The expert group recommends against the use of steroids in patients with severe dengue/dengue with warning signs.
- The expert group recommends against the use of any pharmaceutical agents for augmenting platelet counts.
- The committee suggests using experimental unproven therapies in severe dengue only under research settings with appropriate institute clearances.

Blood and Blood Products: Q15: What should be Indication of Platelets and FFP Transfusion in Severe Dengue or DHF?

- The expert group strongly recommends against prophylactic transfusion of platelets.
- The expert group recommends against transfusing blood in a severe dengue patient in the absence of active bleeding.
- The expert group recommends against transfusing blood in patients with hemoglobin of > 8 gm/dL in the absence of overt bleeding or an underlying systolic cardiac dysfunction.
- The expert group recommends transfusing platelets at platelet counts below 50,000 in the presence of clinically overt bleeding.
- The expert group suggests that clinicians should use his/her judgement for transfusing platelets when the platelet count is <10,000, there is a need for a surgical/minimally invasive intervention (diagnostic/therapeutic).
- The expert group recommends against prophylactic transfusion of FFP/Cryoprecipitate in severe dengue with coagulation abnormalities.
- The expert group recommends that clinicians should use his/her clinical judgement for transfusing blood products (FFP/Cryoprecipitate) in patients with coagulation abnormalities/overt bleeding.

Administration of blood, platelets, and fresh frozen plasma is a topic of controversy in dengue. There is ample evidence available against the use of prophylactic transfusions in patients with severe dengue with thrombocytopenia.[21] Various guidelines recommend considering prophylactic platelet transfusion below a platelet count of <10,000.[6,9,22] In the presence of overt bleeding, platelet transfusion, and FFP transfusion may be considered.[23,24] Packed cell transfusion and whole blood may be transfused if >10% of the total blood volume is lost or if there is falling HCT in the presence of clinical deterioration in spite of adequate fluid resuscitation.[23,24] Overt or occult bleeding in severe dengue/DHF patients having a cardiac compromise, transfusion should be done to keep a hemoglobin as close to 10 gm/dL as possible.[24]

CAM for Thrombocytopenia: Q16 Can Complementary and Alternative Therapies be Used in Severe Dengue/ Thrombocytopenia (To Increase Platelet Count)?

- The expert group recommends against the use of unproven CAM therapies in patients with severe dengue admitted to ICU. This includes papaya leaf extract.
- The expert groups recommend against routinely using anti-D immunoglobulins, romiplostim, and eltrombopag in patients with dengue having thrombocytopenia.
- The expert groups suggest using anti-D immunoglobulins, Romiplostim, and Eltrombopag in patients with dengue having thrombocytopenia strictly under research settings with appropriate ethical/institutional clearances.

There is some evidence available in the form of case reports and very small randomized trials, demonstrating significant benefits, however, the expert group feels that the evidence is not strong enough to recommend any of these agents.[25–27] The understanding of the pathophysiology of severe dengue has also changed over time. It is now well understood that the correction of organ system dysfunction is far more important than the correction of thrombocytopenia. It has been observed that unwarranted prophylactic platelet transfusion has resulted in complications like fluid overload and TRALI, causing far more damage and increasing morbidity in severe dengue patients. Therefore, prophylactic platelet transfusion should at best be avoided.[6,9]

Q17: What are the Indications for Use of Extracorporeal Therapies for Cytokine Removal/ Plasmapheresis in Severe Dengue?

- The expert group recommends against routinely using such therapies in severe dengue.
- The expert group suggests using experimental/unproven therapies (like extracorporeal removal of cytokines, and plasmapheresis) in severe dengue only under research settings with appropriate institute/ethical clearances.

Since unregulated cytokine storm is the root cause of multiple organ dysfunction in severe dengue, it is logical to think about cytokine removal to control the damage, however, none of the trials has demonstrated a significant benefit in patients with sepsis and is therefore not a part of surviving sepsis guidelines. The expert group feels that these therapies cannot be recommended as standard of care in severe dengue. Since plasma exchange has been used extensively as a bridge to liver transplant, it could be tried if needed in selected patients with dengue virus related acute liver failure.[28,29]

Disposition Q18: When should the Dengue Patient be Shifted from ICU to the Ward?

The expert group recommends shifting the patient to the ward/ observation unit from ICU once there is no fever is observed for 24 hours and clinical improvement is noted.

The following criterion may guide shifting to the ward:

Shock should have resolved (for >24 hours), no overt bleeding (>24 hours), static or improving organ dysfunction, including platelet count (>24 hours).

Q19: When should the Patient be Discharged from ICU/Ward?

The expert group recommends discharging the patients from the ward/ICU when the following criteria are met:

- Clinical: No fever for 48 hours. Improvement in clinical status (general well-being, appetite, hemodynamic status, urine output, no respiratory distress).
- Laboratory: Stable hematocrit without intravenous fluids.
- Increasing trend of platelet count.

Special Population Q20: Should the Management of Severe Dengue Differ in Elderly and Pregnant Females?[30] (Table 4)

The management of severe dengue does not differ much in pregnancy; however, shock may lead to compromised fetal circulation and thrombocytopenia may result in bleeding in any

Table 4: Dengue management in pregnancy

Gestational age	*Uninfected*	*Infected*	*Changes in management*
1st trimester	Wide pulse pressure	Narrow pulse pressure Increased capillary leak Increased chances of pulmonary edema Reduced plasma volume Increased risk of pre-eclampsia and eclampsia Fever may induce abortion	Frequent vital monitoring Guided rational fluid resuscitation POCUS for fluid overload Fetal well-being on USG Control febrile peak
2nd trimester	Wide pulse pressure Reduced pulse rate, SBP and DBP Increased plasma volume	Risk of complications more than in general population Increased risk of pre-eclampsia and eclampsia	Frequent monitoring for maternal and fetal well-being Guided rational fluid resuscitation POCUS for fluid overload
3rd trimester	Rising heart rate but <100 Plasma volume increases till 34 weeks SBP and DBP rises	No increased risk to mother or fetus if no shock or bleeding Fever may cause preterm labor Careful monitoring for capillary leak	Frequent monitoring Guided rational fluid resuscitation Control fever POCUS for fluid overload Fetal well-being on USG
Postpartum	Return to normal prepregnant state in 2 weeks Heart rate gradually decreases BP rises till day 5–7 postpartum, later decreases to normal	No specific altered physiology Thrombocytopenia may increase risk of postpartum bleeding	Vital monitoring Watch for abnormal bleeding Rational fluid resuscitation

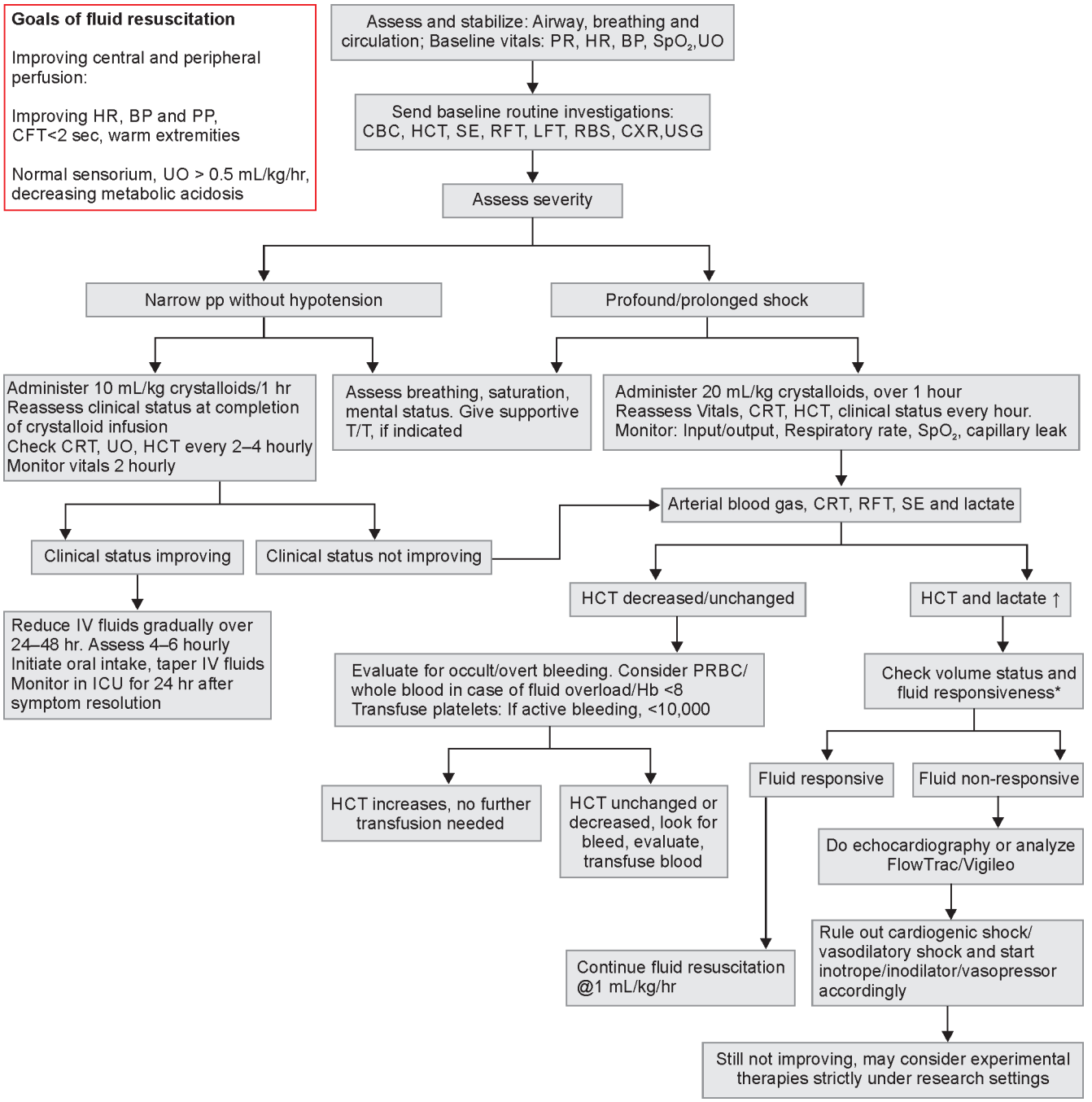


Fig. 4: Showing algorithm for ICU management of dengue

*Fluid responsiveness can be assessed by SPV, PPV, SVV, fluid challenge test, endotracheal tube occlusion test, passive leg raise test

BP, blood pressure; CBC, complete blood count; CFT, capillary filling time; CVP, central venous pressure; CXR, chest X-ray; HCT, hematocrit; HR, heart rate; hr, hour; IBP, invasive BP; LFT, liver function test; PP, pulse pressure; PPV, pulse pressure variation; RBS, random blood sugar; RFT, renal function test; RRT, renal replacement therapy; SE, serum electrolytes; SpO_2, pulse oximetery; SPV, systolic pressure variation; SVV, stroke volume variation; UO, urine output

trimester. In a large study, dengue manifestations did not differ much in pregnant dengue-infected patients from non-infected.

The expert group recommends admission of pregnant females in ICUs for frequent/continuous monitoring of maternal and fetal well-being (fetal USG).

Expert group recommends, stringent control of fever as fever may precipitate labor.

An expert group recommends guided fluid therapy in dengue-infected pregnant females to avoid dehydration and fluid overload.

The expert group recommends platelet transfusion at any stage when overt bleeding PV is documented.

The elderly (>65 years old), especially the ones having underlying diabetes or cardiac dysfunction, should be carefully monitored, either in the observation units or in the ICU, in case 2

or more organ system dysfunction is documented clinically or in investigations. The threshold for ICU admission and continuous monitoring should be lower in any patient >75 years old, even if single organ system dysfunction is documented.

The expert group recommends admission of the elderly, especially those with comorbidities, to the ICU for better monitoring.

The expert group recommends guided fluid therapy (POCUS/CVP) in the elderly to avoid shock and fluid overload.

Expanded Dengue Syndrome (Table 2)

The expert group recommends that along with the usual etiological workup for the clinical syndromes, dengue serology should be performed in patients presenting with these atypical manifestations during the monsoon or post-monsoon seasons or whenever there is a dengue fever outbreak in a geographic area.

The expert group recommends that all the patients presenting with atypical manifestations, which could be life-threatening, during the monsoon or post-monsoon seasons or whenever there is a dengue fever outbreak in a geographic area, should be admitted to ICUs.

The expert group suggests that all the patients presenting with atypical manifestations, which could be life-threatening, during the monsoon or post-monsoon seasons or whenever there is a dengue fever outbreak in a geographic area, should be admitted to an observation unit/ward with monitoring facilities in case intensive care beds are not available.

Dengue fever with more than usual manifestations of organ dysfunction which occur during the critical phase of the illness with symptoms referable to CNS, cardiovascular system, gastrointestinal tract, hepato-biliary system, renal, respiratory system, and eyes (Table 2). The dysregulated immune response rather than acute viremia may be responsible for these symptoms. Since there is no specific, evidence-based, immune modulation currently recommended, the management of these conditions is symptomatic and supportive. The expert group purposes a set of management measures outlined in Table 2 for guiding the intensivists regarding the management of expanded dengue syndrome (Fig. 4).

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References

1. Bhatt S, Gething PW, Brady OJ, Messina JP, Farlow AW, Moyes CL, et al. The global distribution and burden of dengue. Nature 2013;496(7446):504–507. DOI: 10.1038/nature12060.
2. Chen LH, Wilson ME. Transmission of dengue virus without a mosquito vector: Nosocomial mucocutaneous transmission and other routes of transmission. Clin Infect Dis 2004;39(6):e56–e60. DOI: 10.1086/423807.
3. Amancio FF, Heringer TP, de Oliveira Cda C, Fassy LB, de Carvalho FB, Oliveira DP, et al. Clinical profiles and factors associated with death in adults with dengue admitted to intensive care units, Minas Gerais, Brazil. PLoS One 2015;10(6):e0129046. DOI: 10.1371/journal.pone.0129046.
4. Mukhopadhyay S, Kuhn RJ, Rossmann MG. A structural perspective of the flavivirus life cycle. Nat Rev Microbiol 2005;3(1):13–22. DOI: 10.1038/nrmicro1067.
5. Sahaphong S, Riengrojpitak S, Bhamarapravati N, Chirachariyavej T. Electron microscopic study of the vascular endothelial cell in dengue hemorrhagic fever. Southeast Asian J Trop Med Public Health 1980;11(2):194–204. PMID: 7434071.
6. World Health Organization. Dengue: Guidelines for diagnosis, treatment, prevention and control, New edition. WHO: Geneva. 2009. Available from: http://www.who.int/tdr/publications/documents/dengue-diagnosis.pdf?ua=1.
7. Srikiatkhachorn A, Green S. Markers of dengue disease severity. Curr Top Microbiol Immunol 2010;338:67–82. DOI: 10.1007/978-3-642-02215-9_6.
8. Srichaikul T, Nimmanitaya S, Artchararit N, Siriasawakul T, Sungpeuk P. Fibrinogen metabolism and disseminated intravascular coagulation in dengue hemorrhagic fever. Am J Trop Med Hyg 1977;26(3):525–532. DOI: 10.4269/ajtmh.1977.26.525.
9. National guidelines for clinical management of Dengue. MOH guidelines India. 2014. Available from: https://ncvbdc.mohfw.gov.in/WriteReadData/l892s/Dengue-National-Guidelines-2014.pdf.
10. Kumarasamy V, Wahab AHA, Chua SK, Hassan Z, Chem YK, Mohamad M, et al. Evaluation of a commercial dengue NS1 antigen-capture ELISA for laboratory diagnosis of acute dengue virus infection. J Virol Methods 2007;140:75–79. DOI: 10.1016/j.jviromet.2006.11.001.
11. Dussart P, Petit L, Labeau B, Bremand L, Leduc A, Moua D, et al. Evaluation of two new commercial tests for the diagnosis of acute dengue virus infection using NS1 antigen detection in human serum. PLoS Negl Trop Dis 2008;2(8):e280. DOI: 10.1371/journal.pntd.0000280.
12. Hunsperger EA, Yoksan S, Buchy P, Nguyen VC, Sekaran SD, Enria DA, et al. Evaluation of commercially available diagnostic tests for the detection of dengue virus NS1 antigen and anti-dengue virus IgM antibody. PLoS Negl Trop Dis 2014;8(10):e3171. DOI: 10.1371/journal.pntd.0003171.
13. A-Nuegoonpipat A, Panthuyosri N, Anantapreecha S, Chanama S, Sa-Ngasang A, Sawanpanyalert P, et al. Cross-reactive IgM responses in patients with dengue or Japanese encephalitis. J Clin Virol 2008;42(1):75–77. DOI: 10.1016/j.jcv.2007.10.030.
14. Changal KH, Raina AH, Raina A, Raina M, Bashir R, Latief M, et al. Differentiating secondary from primary dengue using IgG to IgM ratio in early dengue: An observational hospital based clinico-serological study from North India. BMC Infect Dis 2016;16(1):715. DOI: 10.1186/s12879-016-2053-6.
15. GOI guidelines for admission in intensive care units. Available from: https://dghs.gov.in/Uploaddata/Final%20Guidelines%20for%20ICU%20Admission%20and%20Discharge%20Criteria%2023.12.2023.pdf.
16. Kattan E, Hernández G. The role of peripheral perfusion markers and lactate in septic shock resuscitation. J Intensive Med 2021;2(1):17–21. DOI: 10.1016/j.jointm.2021.11.002.

17. Giang HT, Banno K, Minh LH, Trinh LT, Loc LT, Eltobgy A, et al. Dengue hemophagocytic syndrome: A systematic review and meta-analysis on epidemiology, clinical signs, outcomes, and risk factors. Rev Med Virol 2018;28(6):e2005. DOI: 10.1002/rmv.2005.
18. Rawat N, Sahni N, Yaddanapudi L. Comparison of commercially available balanced salt solution and ringer's lactate on extent of correction of metabolic acidosis in critically ill patients. Indian J Crit Care Med 2020;24(7):539–543. DOI: 10.5005/jp-journals-10071-23488.
19. Zhou S, Zeng Z, Wei H, Sha T, An S. Early combination of albumin with crystalloids administration might be beneficial for the survival of septic patients: A retrospective analysis from MIMIC-IV database. Ann Intensive Care 2021;11(1):42. DOI: 10.1186/s13613-021-00830-8.
20. Georger JF, Hamzaoui O, Chaari A, Maizel J, Richard C, Teboul JL. Restoring arterial pressure with norepinephrine improves muscle tissue oxygenation assessed by near-infrared spectroscopy in severely hypotensive septic patients. Intensive Care Med 2010;36(11):1882–1889. DOI: 10.1007/s00134-010-2013-3.
21. Khan Assir MZ, Kamran U, Ahmad HI, Bashir S, Mansoor H, Anees SB, et al. Effectiveness of platelet transfusion in dengue Fever: A randomized controlled trial. Transfus Med Hemother 2013;40(5):362–368. DOI: 10.1159/000354837.
22. British Committee for Standards in Haematology, Blood Transfusion Task Force. Guidelines for the use of platelet transfusions. Br J Haematol 2003;122(1):10–23. DOI: 10.1046/j.1365-2141.2003.04468.x.
23. Kaur P, Kaur G. Transfusion support in patients with dengue fever. Int J Appl Basic Med Res 2014;4(Suppl 1):S8–S12. DOI: 10.4103/2229-516X.140708.
24. Vlaar AP, Oczkowski S, de Bruin S, Wijnberge M, Antonelli M, Aubron C, et al. Transfusion strategies in non-bleeding critically ill adults: A clinical practice guideline from the European Society of Intensive Care Medicine. Intensive Care Med 2020;46(4):673–696. DOI: 10.1007/s00134-019-05884-8.
25. Dimaano EM, Saito M, Honda S, Miranda EA, Alonzo MT, Valerio MD, et al. Lack of efficacy of high-dose intravenous immunoglobulin treatment of severe thrombocytopenia in patients with secondary dengue virus infection. Am J Trop Med Hyg 2007;77(6):1135–1138. DOI: 10.4269/ajtmh.2007.77.1135.
26. Zhang F, Kramer CV. Corticosteroids for treating dengue shock syndrome. Cochrane Database Syst Rev 2014;(7):CD003488. DOI: 10.1002/14651858.CD003488.pub3.
27. Chakraborty S, Alam S, Sayem M, Sanyal M, Das T, Saha P, et al. Investigation of the efficacy and safety of eltrombopag to correct thrombocytopenia in moderate to severe dengue patients – A phase II randomized controlled clinical trial. E Clinical Medicine 2020;29–30:100624. DOI: 10.1016/j.eclinm.2020.100624.
28. Kumarasena RS, Mananjala Senanayake S, Sivaraman K, de Silva AP, Dassanayake AS, Premaratna R, et al. Intravenous N-acetylcysteine in dengue-associated acute liver failure. Hepatol Int 2010;4(2):533–534. DOI: 10.1007/s12072-010-9176-4.
29. Schwartz J, Winters JL, Padmanabhan A, Balogun RA, Delaney M, Linenberger ML, et al. Guidelines on the use of therapeutic aphaeresis in clinical practice-evidence-based approach from the Writing Committee of the American Society for Apheresis: The sixth special issue. J Clin Apher 2013;28(3):145–284. DOI: 10.1002/jca.21276.
30. AICOG guidelines for management of Dengue in Pregnancy. 2014. Available from: http://www. ACOG+guidelines+dengue+2014.

Annexures: Search Strategy, Search Terms and Search Strings for Severe Dengue Management in Intensive Care Unit

Keywords and Search Strings for Severe Dengue

Keywords:
Dengue fever
Severe dengue
Dengue shock syndrome
Dengue hemorrhagic fever
Thrombocytopenia
Coagulation protein disorders/virology
Disseminated intravascular coagulation
Hepatitis

Keywords and Search String for Dengue and Fluid Resuscitation

Severe dengue fever
Intravenous fluids
Management
Therapy
Dengue hemorrhagic shock
Dengue shock syndrome
MeSH terms (Search from year 2001 onwards till date)

Term 1: Intravenous fluids and severe dengue fever
- PubMed search yielded 38 results till date
- 2 results after application of filter meta-analysis, clinical trials and RCTs

Term 2: Severe dengue fever management
- PubMed search yielded 523 results till date
- 16 results after application of filters of meta-analysis, clinical trials and RCTs

Term 3: Severe dengue fever and intravenous fluids
- PubMed search yielded 38 results till date
- 3 results after application of filters of meta-analysis, clinical trials and RCTs

Term 4: Severe dengue fever therapy
- PubMed search yielded 454 results till date
- 27 results after application of filters of meta-analysis, clinical trials and RCTs

Term 5: Dengue hemorrhagic shock management
- PubMed search yielded 269 results till date
- 8 results after application of filters of meta-analysis, clinical trials and RCTs

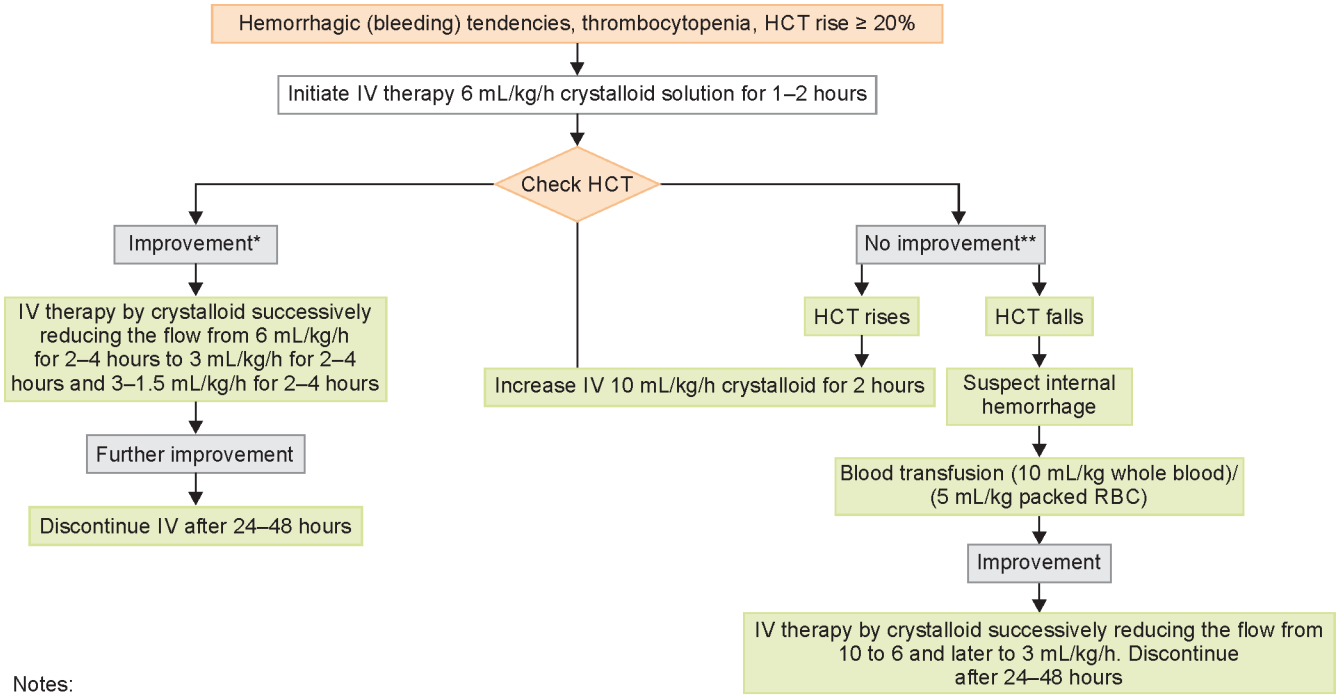
Term 6: Dengue hemorrhagic shock and intravenous fluids
- PubMed search yielded 44 results till date
- 4 results after application of filters of meta-analysis, clinical trials and RCTs

Term7: Dengue shock syndrome and intravenous fluids
- PubMed search yielded 58 results till date
- 3 results after application of filters of meta-analysis, clinical trials and RCTs

Term 8: Intravenous fluids in dengue shock syndrome
- PubMed search yielded 57 results till date
- 4 results after application of filters of meta-analysis, clinical trials and RCTs

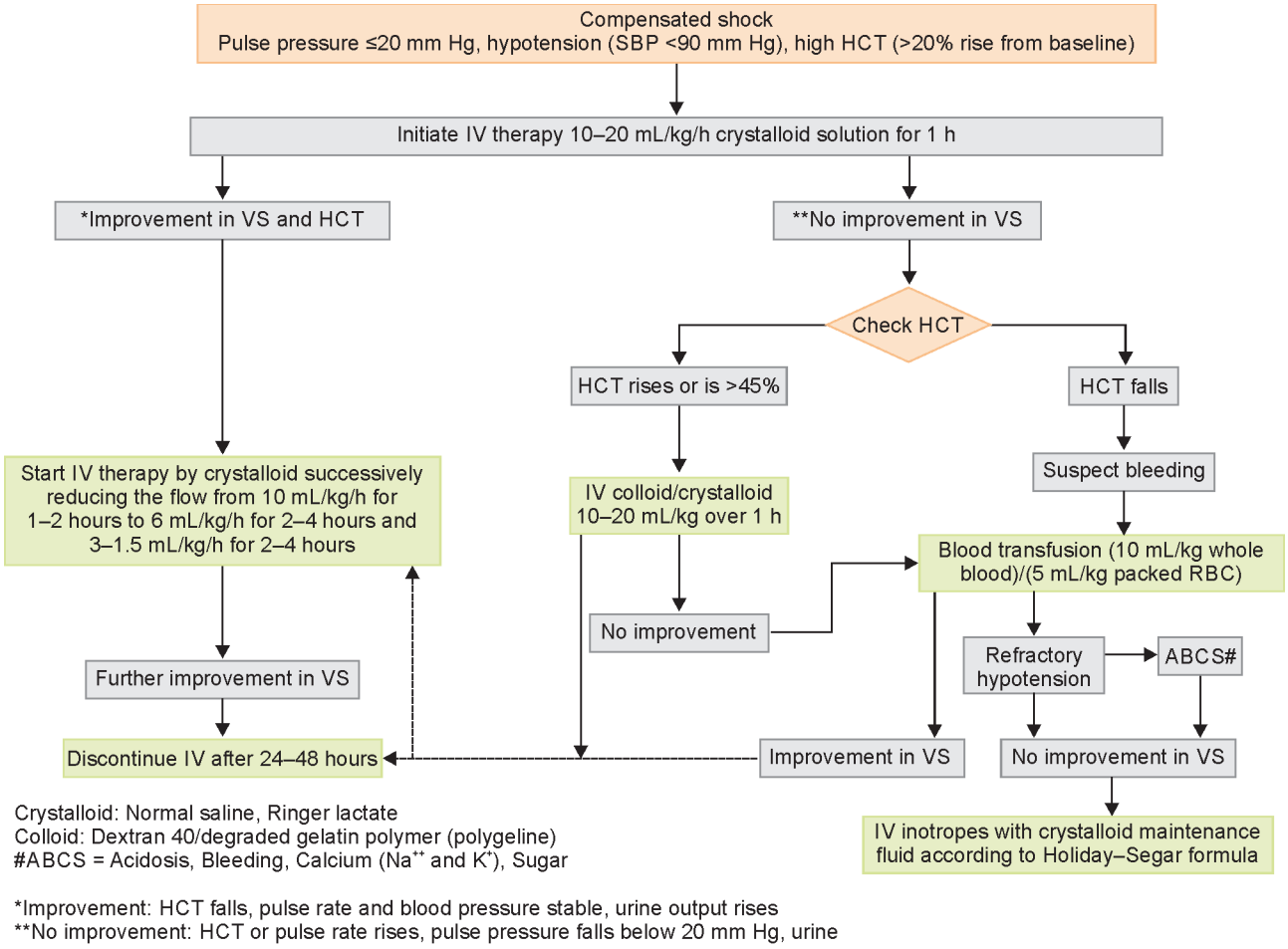
Keywords and Search String for Blood Transfusion Practices and Plasmapheresis

Plasmapheresis
Plasma exchange
Blood platelet transfusion
Blood component transfusion
Fresh frozen plasma
Transfusion trigger



Notes:
*Improvement: HCT falls, pulse rate and blood pressure stable, urine output rises
**No Improvement: HCT or pulse rate rises, pulse pressure falls below 20 mm Hg urine output falls

Annexure 1: Volume replacement algorithm for patients with moderate dengue fever



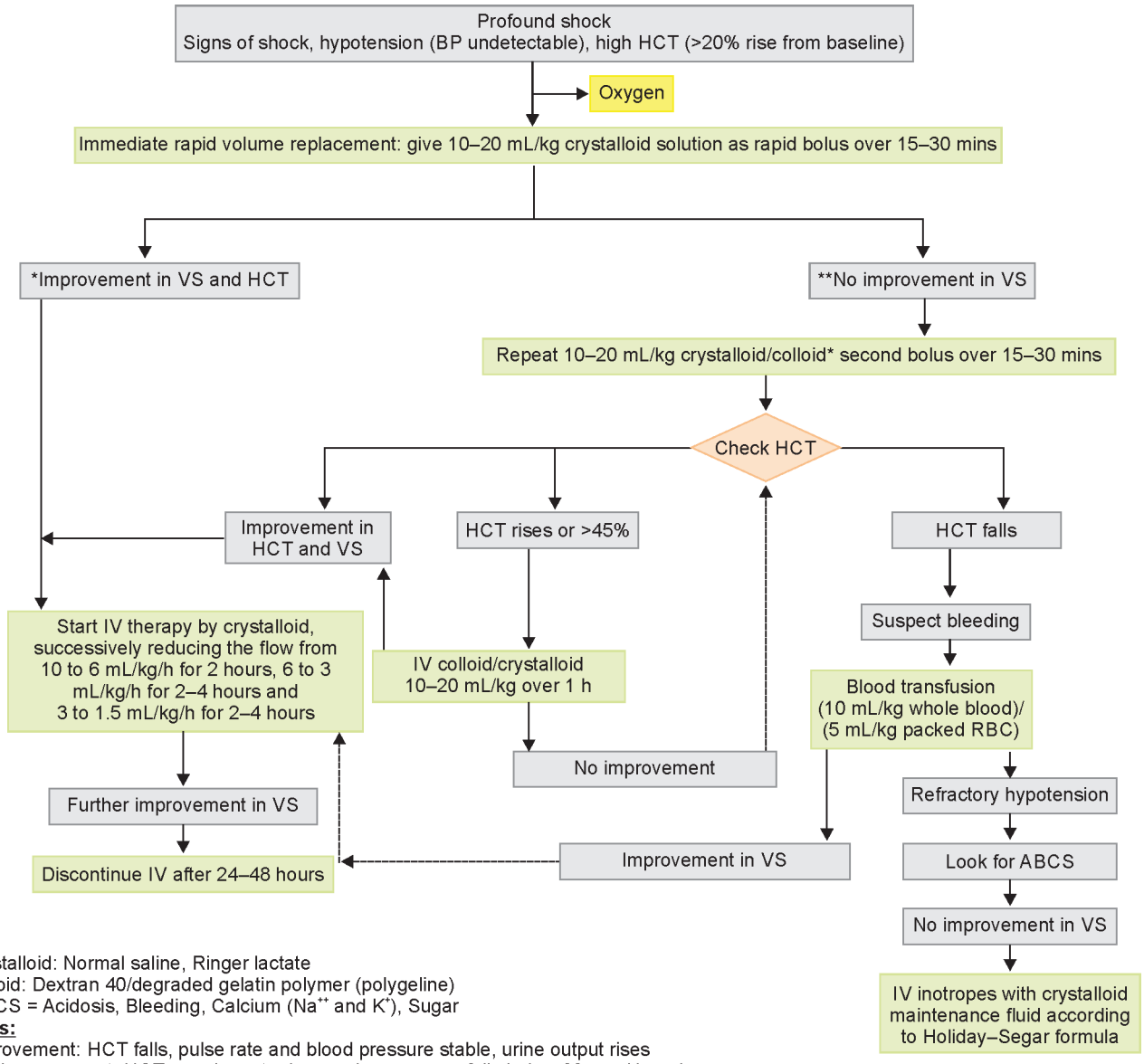
Annexure 2: Volume replacement algorithm for patients with severe dengue fever

Search strings:

- Dengue fever and Thrombocytopenia and Blood platelet transfusion or Transfusion trigger
- Severe dengue and Thrombocytopenia and Blood platelet transfusion or Transfusion trigger
- Dengue shock syndrome and Thrombocytopenia and Blood platelet transfusion or Transfusion trigger
- Dengue hemorrhagic fever and Thrombocytopenia and Blood platelet transfusion Or Transfusion trigger
- Dengue fever and Coagulation protein disorders/virology and Fresh frozen plasma
- Severe dengue and Coagulation protein disorders/virology and Fresh frozen plasma
- Dengue shock syndrome and Coagulation protein disorders/virology and Fresh frozen plasma
- Dengue hemorrhagic fever and Coagulation protein disorders/virology and Fresh frozen plasma
- Dengue fever and Disseminated intravascular coagulation
- Severe Dengue and Disseminated intravascular coagulation
- Dengue Shock syndrome and Disseminated intravascular coagulation
- Dengue hemorrhagic fever and Disseminated intravascular coagulation
- Dengue fever and Hepatitis and Plasmapheresis or Plasma exchange
- Severe Dengue and Hepatitis and Plasmapheresis or Plasma exchange
- Dengue Shock syndrome and Hepatitis and Plasmapheresis or Plasma exchange
- Dengue hemorrhagic fever and Hepatitis and Plasmapheresis or Plasma exchange A. Dengue and respiratory failure

Keywords and Search String for Dengue and Cardiac/Renal/Respiratory/CNS Involvement

Dengue
Severe dengue
Dengue shock syndrome
Heart
Myocardium
Cardiac
Kidney
Renal dysfunction
Acute kidney injury
Dengue AND heart: 14 results



-Crystalloid: Normal saline, Ringer lactate
-Colloid: Dextran 40/degraded gelatin polymer (polygeline)
- ABCS = Acidosis, Bleeding, Calcium (Na^{++} and K^{+}), Sugar

Notes:

*Improvement: HCT falls, pulse rate and blood pressure stable, urine output rises
**No improvement: HCT or pulse rate rises, pulse pressure falls below 20 mm Hg, urine output falls
• Unstable vital signs: Urine output falls, signs of shock
• In cases of acidosis, hyperosmolar or Ringer's lactate solution should not be used
• Serial platelet and HCT determinations: Drop in platelets and rise in HCT are essential for early diagnosis of DHF
• Cases of DHF should be observed every hour for vital signs and urine output

Annexure 3: Volume replacement algorithm for patients with dengue shock syndrome

Severe Dengue AND cardiac: 9 results
Dengue shock syndrome and myocardium: 4 results
Dengue AND myocardium: 11 results
Dengue AND cardiac: 35 results
Dengue AND kidney: 64 results
Severe dengue AND kidney: 8 results
Dengue AND renal dysfunction: 101 results
Dengue AND acute kidney injury: 61 results
(Dengue) AND (respiratory failure) – 115 hits,
Adults only – 46 hits
Filters applied: Clinical study, clinical trial, meta-analysis, observational study, systematic review,
Adult: 19+ years – 4 hits

Dengue and ARDS

1. Dengue AND (acute respiratory distress syndrome) – 75 hits
2. Adults only – 28 hits
3. Filters applied: Case reports, clinical trial, meta-analysis, observational study, randomized
   Controlled Trial, Systematic Review, Adult: 19+ years – 16 hits
4. Excluding case reports – 4 hits

Dengue Encephalitis

(Dengue AND (Encephalitis)/(Dengue) AND (Encephalitis) – 380 hits (only adults)

1. Filters applied: Case Reports, Clinical Trial, Guideline, Meta-Analysis, Observational Study, Practice

2. Guideline, Randomized controlled trial, review, systematic review, humans, adult: 19+ years – 105 hits
3. Removing case reports – 37 hits
4. Removing narrative review – 19 hits
5. Filters applied: Clinical trial, meta-analysis, randomized controlled trial, systematic review, humans, Adult: 19+ years – 14 hits
6. Only RCTs – 9 (all are on dengue vaccines)

Keywords and Search strings for ICU Admission and ICU Discharge

[Dengue (Mesh)] AND [Patient Admission (Mesh) OR Intensive Care Units (Mesh)]] 53 hits

Dengue and *ICU admission*: 40 results
Dengue AND *ICU admission* NOT COVID: 35 results
Severe dengue* AND ICU (Filter English language only): 56 results
Dengue (Mesh) AND Intensive Care Units (Mesh) 39 hits
Dengue'/exp AND 'ICU disscharge'/exp 4 hits.
Dengue AND ICU discharge: 9 results
Dengue AND discharge NOT COVID: 184 results
Discharge criteria AND Dengue: 17 results
Embase search string: 'dengue'/exp AND 'ICU admission'/exp 48 hits