Ministry of Health
Sri Lanka

NATIONAL GUIDELINES

Guidelines on Management of Dengue Fever & Dengue Haemorrhagic Fever in Adults

In collaboration with the
Ceylon College of Physicians

Revised and Expanded Edition **September 2024**

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Electronic version available at the websites of:

National Dengue Control Unit *Click here*
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Sri Lanka

Guidelines on Management of Dengue Fever & Dengue Haemorrhagic Fever in Adults

Revised and Expanded Edition September 2024

The guidelines published in September 2024 supersedes the previous guidelines on Clinical Management of Dengue Fever/ Haemorrhagic Fever published by the Epidemiology Unit, Ministry of Health in 2012.

These guidelines were developed based on the best available evidence at the time of writing. It is expected to be used in the clinical management of patients with dengue infection in Sri Lanka. The guidelines will be reviewed periodically when new evidence becomes available.

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CONTENTS

CONTENTS

CONTENTS

MESSAGE FROM THE SECRETARY
Ministry of Health

Dengue fever remains a significant health concern in Sri Lanka. It is observed that cases are steadily rising, particularly among adults, presenting with more severe forms of the illness. The rising incidence of severe cases underscores the critical need for a coordinated national response to reduce morbidity and mortality and ensure that every patient receives the appropriate care promptly.

This updated National Guidelines on the Management of Dengue Fever and Dengue Haemorrhagic Fever in Adults, developed by the Ministry of Health in collaboration with the Ceylon College of Physicians, presents a key part of the response to this most pressing public health problem. By revising this guideline, the aim is to equip healthcare providers with robust, evidence-based knowledge and the skills to manage the complexities of dengue fever, reduce the progression to severe disease, and ultimately decrease dengue-related mortality. The guidelines offer practical insights and clinical recommendations that can be implemented at all levels of healthcare delivery, ensuring consistency and quality of care across the country.

I extend my deepest gratitude to all the dedicated professionals and organizations involved in the development of this important resource. Your commitment to improving public health is invaluable and will continue to play a crucial role in the fight against dengue fever and in saving lives across our nation.

Dr Palitha Mahipala
Secretary
Ministry of Health

MESSAGE FROM
DIRECTOR GENERAL OF HEALTH SERVICES
Ministry of Health

Globally, and in the Southeast Asian region, Sri Lanka is one of the countries most affected by dengue infection. In the absence of a specific treatment or an operationally deployed dengue vaccine, improving clinical care for dengue infection is one of the cornerstones of minimising the morbidity and mortality associated with dengue.

Currently, in Sri Lanka, dengue disease is predominantly seen among adults. The revised "Guidelines on the Management of Dengue Fever and Dengue Haemorrhagic Fever in Adults" is expected to provide updated guidance for managing dengue disease among adults. These guidelines reflect the latest evidence-based practices and lessons learned from frontline clinical experiences across the country.

I appreciate the immense effort expended by all the stakeholders involved in revising the "Guidelines on the Management of Dengue Fever and Dengue Haemorrhagic Fever in Adults", and hope that the effective use of this guideline will save more lives through improved management in both public and private settings in Sri Lanka.

The Ministry of Health remains committed to strengthening clinical governance, capacity-building, and disease surveillance systems to support the implementation of these guidelines. I urge all healthcare professionals to familiarise themselves with the revised recommendations and apply them diligently in their clinical practice.

Together, through collective responsibility and coordinated action, we can further reduce the burden of dengue in our nation and safeguard the health and well-being of our communities.

Dr Asela Gunawardena
Director General of Health Services
Ministry of Health

MESSAGE FROM
DEPUTY DIRECTOR GENERAL (PUBLIC HEALTH SERVICES) I
Ministry of Health

Dengue is now the leading communicable disease-related public health problem in Sri Lanka, with hyper-endemicity in many areas. Approximately two-thirds of dengue infections now occur among adults, with more morbidity among males and more mortality among females, possibly associated with disease exposure and health-seeking behaviour patterns.

In this background, Sri Lanka has achieved notable progress in reducing the case fatality rate due to dengue infection from 0.99% in 2009 to 0.07% in 2023. The National Strategic Plan for the Prevention and Control of Dengue, 2024–2030 aims to reduce the case fatality associated with dengue to zero by 2030.

The revised "Guidelines on the Management of Dengue Fever and Dengue Haemorrhagic Fever in Adults", is thus an effective roadmap for clinicians in both public and private healthcare settings to further strengthen and realign clinical management in accordance with the latest global and local evidence and best practices, to reduce the dengue-related morbidity and mortality among adults in Sri Lanka. I take this opportunity to thank all the experts involved in developing this guideline.

I hope that the implementation of this revised guideline refreshes the skills of the treating physicians and thus further strengthens the clinical management of dengue.

Dr SM Arnold
Deputy Director General (Public Health Services) 1
Ministry of Health

MESSAGE FROM THE DIRECTOR
National Dengue Control Unit

Sri Lanka continues to be among the thirty countries with the highest burden of dengue globally. Dengue remains endemic across all districts in the country, putting significant pressure on our health system, particularly during seasonal outbreaks. Nevertheless, it is encouraging to note that, despite high case reporting, the case fatality rate has sharply and steadily declined over the past 15 years. This positive trend is largely due to improved clinical management, bolstered by user-friendly clinical management guidelines.

We are confident that the revised guidelines will serve as a valuable tool for clinicians in the effective management of dengue. As the focal point in the Ministry of Health for dengue prevention and control, including the enhancement of clinical management facilities, the National Dengue Control Unit extends its heartfelt gratitude to the Ceylon College of Physicians and all contributors for their dedicated efforts in revising the guideline.

Dr Sudath Samaraweera
Director
National Dengue Control Unit
Ministry of Health

MESSAGE FROM THE PRESIDENT
Ceylon College of Physicians

The epidemiology of dengue infection is changing in Sri Lanka. An essentially childhood predominant disease in the 1990s, dengue has now become an infection of adults with a reciprocal reduction in incidence among children.

Our case fatality rate which was 9.8% in 1989, has come down to 0.05% this year. The credit should go to the clinicians, the medical officers and the nursing officers who work tirelessly, look after the patients and follow the current guidelines. The last guideline was published in November 2012 by the Epidemiology Unit of the Ministry of Health Sri Lanka. This was contributed to by many and the enforcement of the guidelines through death reviews was instrumental in bringing down the mortality.

In addition, we have the National Dengue Control Unit and the Epidemiology Unit and their health care personnel in the community who work to the best of their capacity to curb the case load. If we are to bring the mortality rate to a level closer to zero, we need to go beyond the currently available guidelines. We consider that the time is opportune, as we have clinicians who have amassed years of experience in managing difficult cases of dengue.

As the President of the Ceylon College of Physicians, I thank the Guideline Development Committee for compiling the revised guidelines.

Dr Upul Dissanayake
President
Ceylon College of Physicians

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[1] INTRODUCTION

Dengue is endemic in Sri Lanka, with cases reported year-round across the country. The dengue burden demonstrates two distinct peaks corresponding to the southwest and northeast monsoon seasons. Over the years, a notable shift in the demographic pattern of the disease has been observed, with an increasing number of cases reported among adults. This trend has led to higher rates of complications, organ dysfunction and bleeding, often exacerbated by underlying comorbidities in the adult population.

Over the past decade, Sri Lanka has achieved a substantial reduction in dengue case fatality rates through advancements in clinical management and targeted public health interventions. The revised National Dengue Guidelines aim to further enhance patient management protocols, striving to reduce mortality even further and lessen morbidity associated with dengue infections.

This revised guideline includes new evidence-based concepts and expert recommendations for the management of Dengue Fever (DF) and Dengue Haemorrhagic Fever (DHF). It highlights the importance of early detection, identifying the estimated time of the onset of plasma leakage, preventing shock and ensuring early detection and management of shock.

Updated and revised monitoring charts are provided to support clinical decision-making. The guidelines also include detailed discussions on complications such as liver failure, the role of adjunctive therapies in dengue management and approaches to manage special situations, including dengue in patients with comorbid conditions.

Dengue during pregnancy is addressed separately in the National Guideline on Dengue in Pregnancy.

Link for National Guideline on Dengue in Pregnancy:

(https://www.epid.gov.lk/storage/post/pdfs/clinicalmanagementofdengueinfectioninpregnancy.pdf)

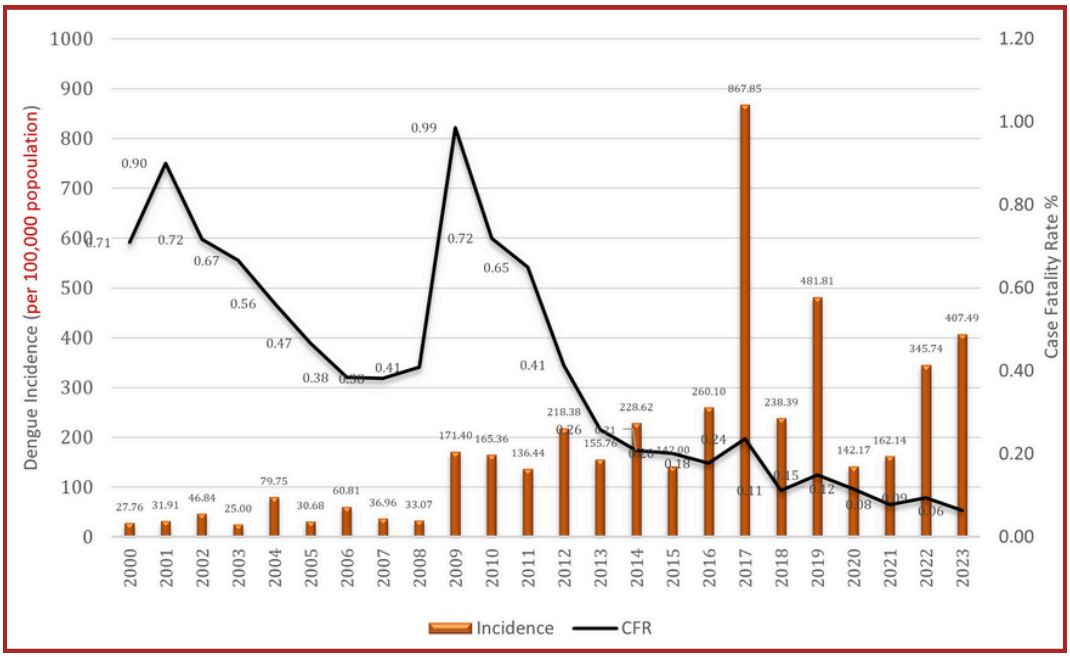


Figure 1.1: Dengue incidence and case fatality rate

[Source: Dengue Disease Surveillance Data (DenSys), Epidemiology Unit & National Dengue Surveillance System of National Dengue Control Unit, Sri Lanka]

[2] PATHOGENESIS AND PATHOPHYSIOLOGY

Dengue is a mosquito-borne infection caused by a single-stranded RNA virus belonging to the family *Flaviviridae*, genus *Flavivirus*. Four antigenically distinct serotypes of DENV, DENV-1, DENV-2, DENV-3, and DENV-4 are known to cause infections. There is considerable genetic variation within each serotype, with distinct subtypes.

Dengue virus (DENV) is transmitted by the *Aedes aegypti* and *Aedes albopictus* mosquito species. Viraemia in humans is usually detected two days prior to the onset of fever (non-febrile phase) and can last for 5–7 days after the onset of fever (febrile phase). This period facilitates the spread of the infection.

Dengue pathogenesis involves several intricate mechanisms including antibody-dependent enhancement (ADE), NS1 antigen-related mechanisms, cross-reactive T cell responses, anti-DENV NS1 antibody-driven responses and viral genomic virulent factors among others. Infection with one serotype confers lifelong immunity to that serotype in most patients. However, secondary infection with another serotype or multiple infections with different serotypes may lead to a severe form of dengue. This is postulated to be due to non-neutralising pre-existing antibodies in a previously immune individual forming virion-antibody immune complexes after secondary infection, facilitating Fcg receptor-mediated entry of these complexes to phagocytes. This process leads to enhanced viral replication, activating an immunopathogenic cascade causing transient vascular leakage and severe manifestations. However, there is no capillary destruction. In addition, activation of DENV-specific cross-reactive T cells produces higher levels of cytokines and chemokines contributing to disease pathogenesis. DENV NS1 is implicated in disrupting endothelial monolayer by activating immune cells through Toll-like Receptor 4 (TLR 4) and activating the complement cascade. In addition to the NS1 protein, antibodies against NS1 are also thought to be initiating inflammatory responses leading to severe disease manifestations. Apart from all host factors, the virulence of DENV serotypes and strains has contributed to severe manifestations and large outbreaks.

[3] NATURAL COURSE OF THE ILLNESS

The clinical presentation of dengue infection varies significantly depending on factors such as the viral strain and host factors, including age, immune status and previous exposure to dengue virus. A notable proportion of individuals infected with dengue remain asymptomatic, while others may present with a spectrum of clinical symptoms.

The incubation period for dengue is typically between 4 to 7 days, with a range of 3 to 14 days. Symptomatic patients may present with one of the following clinical conditions:*

- Undifferentiated fever
- Classical dengue fever (DF)
- Dengue haemorrhagic fever (DHF)
- Expanded dengue syndrome (rare)

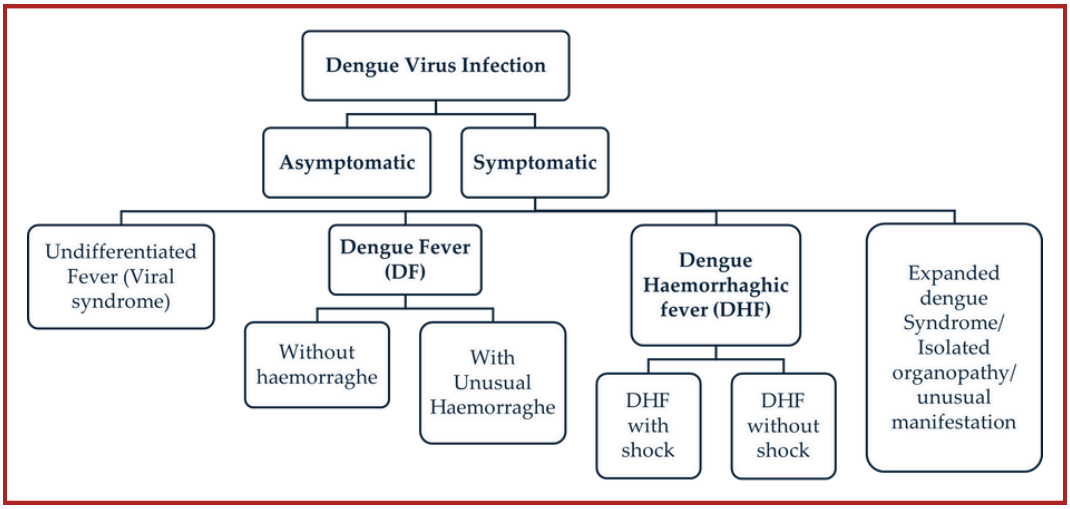


Figure 3.1: Manifestations of dengue virus infection

[Adapted from Comprehensive Guidelines for Prevention and Control of Dengue and Dengue Haemorrhagic Fever, Revised and expanded edition. (SEARO Technical Publication Series No. 60) 2011]

* The guideline development committee decided to adhere to the above classification instead of the classification used in the "DENGUE GUIDELINES FOR DIAGNOSIS, TREATMENT, PREVENTION AND CONTROL" published jointly by the World Health Organization (WHO) and the Special Programme for Research and Training in Tropical Diseases (TDR). The committee believes that the above SEARO classification is based on the pathophysiology of the disease and is more management-friendly than the WHO/TDR classification.

3.1 UNDIFFERENTIATED FEVER

Some of the patients infected with dengue virus, especially for the first time (i.e. primary dengue infection), may develop a nonspecific febrile illness with mild symptoms which are indistinguishable from other viral infections.

3.2 CLASSICAL DENGUE FEVER (DF)

A proportion of patients infected with dengue virus develop classical dengue fever characterised by high fever, severe headache, retro-orbital pain, myalgia, arthralgia and rashes. Leucopenia and thrombocytopenia are usually observed. Fever may be biphasic and lasts for 3-7 days in the majority of patients.

The natural course of the illness has two phases:

- Febrile phase
- Convalescent phase

Although DF is usually benign, it could be an incapacitating disease due to severe headache and musculoskeletal pains (break-bone fever). Occasionally, unusual haemorrhage such as gastrointestinal bleeding, hypermenorrhoea and massive epistaxis may occur.

In patients with DF, FBC is usually normal at the onset of fever. Then leucopenia with a decrease in neutrophils is observed. Most of the DF patients have mild thrombocytopenia (platelet count below 150,000 /mm^3).

However, severe thrombocytopenia (platelet count below 50,000 /mm^3) is noted in some patients. A mild haematocrit rise may be observed due to vomiting and poor oral intake. In DF a mild elevation of ALT/AST is expected.

Both undifferentiated fever and dengue fever need only symptomatic treatment (unless a DF patient gets an unusual haemorrhage). However, during the initial period of fever, it is difficult to differentiate the above from DHF. Therefore, close monitoring is essential.

3.3 DENGUE HAEMORRHAGIC FEVER (DHF)

DHF occurs in a small proportion of patients with dengue infection. Most DHF patients present with acute onset of high fever and associated symptoms similar to DF in the early febrile phase. Plasma leakage and abnormal haemostasis are the hallmarks of DHF which usually occur around defervescence (settling of fever). There is a possibility of developing shock (dengue shock syndrome) if the leakage is severe or due to significant bleeding in addition to leakage.

Therefore, patients with probable dengue illness should be closely monitored to identify DHF.

For efficient management of DHF, it is important to understand its natural history and its dynamic nature. The clinical course of DHF is stereotypic and consists of three phases:

- Febrile phase
- Critical phase (leakage phase)
- Convalescent phase

3.3.1 Febrile phase

The febrile phase is characterised by continuing high fever lasting for 3-7 days. Other features seen in the febrile phase include facial flushing/diffuse blanching erythema of the skin, myalgia, arthralgia, headache, nausea and vomiting. Some patients may have a sore throat, diarrhoea, injected pharynx, conjunctival injection and tender posterior cervical lymphadenopathy. Mild haemorrhagic manifestations can occur. Leucopenia (WBC <5,000/ mm^3) and mild thrombocytopenia (<150,000 /mm^3) are common in the late febrile phase. Tender hepatomegaly and significant (moderate to severe) elevated transaminases in the febrile phase favour the possibility of developing DHF.

Note:

- **A smaller rise in HCT/PCV which may be seen in the febrile phase of the disease is due to dehydration.**

3.3.2 Critical phase (leakage phase)

The critical phase is heralded by the onset of plasma leakage. This usually starts after the 3rd day of fever (usually around the 4th or 5th day of illness) with defervescence (settling of fever). However, some patients may enter the critical phase while having a high fever.

Plasma leakage is due to increased capillary permeability. It is transient and usually lasts for 24-48 hours. Though the disease is systemic, plasma leakage occurs selectively into the peritoneal and pleural spaces. Fluid in pericardial space is rare and if present, the volume is often minimal. The reason for selective plasma leakage to pleural and peritoneal spaces is unexplained but liver involvement in dengue infection may have a role in this.

With the leakage of plasma, there will be haemoconcentration which will manifest as an increase in HCT/PCV. A gradual rise of HCT from the baseline is suggestive of plasma leakage while a 20% rise of HCT from the baseline is

indicative of significant plasma leakage. However, coexisting bleeding in addition to plasma leakage will obscure the expected rise in HCT/PCV. The point-of-care ultrasonography of the abdomen and the chest is a useful method for detecting plasma leakage.

Other evidence which may be suggestive of plasma leakage is a decrease in serum albumin (<3.5 g/dl) and non-fasting serum cholesterol (<100 mg/dl). However, these may vary depending on the baseline of individuals.

The degree and the rate of plasma leakage in DHF can vary. It can be minimal in some patients while in others it can be very significant. The leak usually starts slowly, increases gradually, slows down and then ceases altogether at the end of the critical phase (usually within 48 hours from the onset). In patients who have gone into shock status, the leakage may continue for a period longer than 48 hours.

Those who have severe leakage can develop shock when a critical volume of plasma is lost. If the shock is prolonged, consequent organ hypoperfusion will result in progressive organ impairment, especially liver impairment, metabolic acidosis and disseminated intravascular coagulation (DIC) which will often lead to massive bleeding.

Haemorrhagic manifestations are not essential for the diagnosis of DHF in the presence of objective evidence of plasma leakage. However, the term "DHF" is retained because these patients have abnormal haemostasis and the possibility of developing overt or concealed bleeding during the illness.

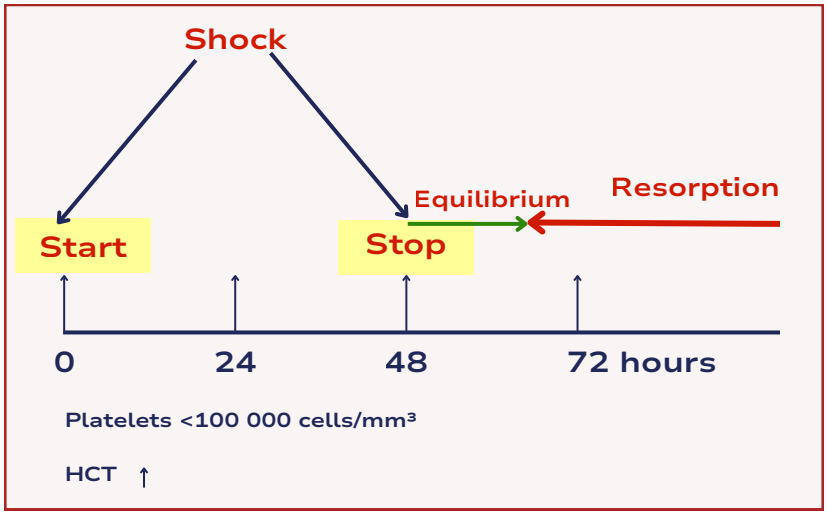


Figure 3.2: Fluid leakage in the critical phase

3.3.3 Convalescent phase (recovery phase)

The convalescent phase begins at the end of the critical phase and usually lasts for 2-5 days. There will be reabsorption of extravasated fluid, during this period.

Table 3.1 - Features of convalescence

- Improved general wellbeing and improved appetite
- Appearance of convalescent rash ('white islands in red sea' appearance)
- Generalised itching (more intense in palms and soles)
- Haemodynamic stability
- Bradycardia (seen in some patients)
- Diuresis
- Stabilisation of HCT (may be lower than baseline due to reabsorption of extravasated fluid)
- Rise in the platelet count.

However, if excessive amounts of intravenous (IV) fluids have been used in the critical phase there could be signs of fluid overload, such as respiratory distress due to pulmonary oedema or large pleural effusions.

3.3.4. Equilibrium phase

In some patients, before they go into the Convalescent phase, a period of equilibrium may be seen where plasma leakage and reabsorption both occur in equal state. A slight rise in HCT may be seen in this period. However, patients will remain stable and will not need any intervention.

3.4 EXPANDED DENGUE SYNDROME/ ISOLATED ORGANOPATHY (UNUSUAL MANIFESTATIONS)

Patients with dengue illness can sometimes develop unusual manifestations such as severe involvement of the liver, kidneys, brain or heart without evidence of fluid leakage and therefore do not necessarily fall into the category of DHF (refer to section 10.5). These conditions are very uncommon and need to be managed according to the involved organ. However, these manifestations, if seen in DHF patients, are mostly a result of prolonged shock leading to organ failure. Therefore, the Guideline Development Committee is of the opinion that such patients should not be categorised as patients with expanded dengue syndrome (EDS).

[4] OUTPATIENT ASSESSMENT AND MANAGEMENT OF A PATIENT WITH DENGUE INFECTION (OPD/ PRIMARY CARE)

In the present hyperendemic setting in Sri Lanka, dengue illness (DF and DHF) should be considered in any patient presenting with an acute febrile illness. Clinical evaluation of dengue is based on symptoms and signs. Basic investigations (FBC ± NS1 Ag) will support the diagnosis.

All patients should be assessed in a stepwise manner to arrive at the diagnosis and determine the severity and place of management.

At the end of the evaluation, a primary care physician should be able to answer the following:

- Could this patient have dengue?
- Are there warning signs?
- Is the patient having plasma leakage?
- Is the patient in shock?
- What is the haemodynamic and hydration status of the patient?
- Are there any comorbidities or high-risk conditions?
- Is hospitalisation required immediately/early?

4.1 FEATURES SUGGESTIVE OF DENGUE ON INITIAL PRESENTATION

Fever and two or more of the following features would suggest dengue infection:

- Headache
- Retro-orbital pain
- Myalgia/arthralgia
- Flushed appearance of skin/rash / haemorrhagic manifestations
- Nausea/vomiting
- Leucopenia (WBC <5,000/mm^3)
- Thrombocytopenia (Platelet count ≤150,000/mm^3)
- Rising haematocrit

Note:

- **Some patients may present with respiratory or gastrointestinal symptoms with or without typical symptoms.**
- **Having a normal full blood count or a count suggestive of bacterial infection on the first day of illness does not exclude dengue illness. Therefore, follow-up FBCs are essential.**
- **A mild to moderate elevation of CRP may be observed in dengue, especially in moderate to severe illness.**

4.1.1 Dengue NS1 antigen test

- This could be useful in the early diagnosis of dengue infection
- Positivity is highest in the first three days of fever
- This test is more likely to be positive for the primary infection than the secondary infection
- Sensitivity rate can vary between 40% – 90%
- Negative NS1 test does not exclude dengue infection (refer to section: 17.1.1)

4.2 CASE CLASSIFICATION

4.2.1 Probable case

Acute febrile illness with two or more of the following:

- Headache
- Retro-orbital pain
- Myalgia
- Arthralgia/bone pain
- Rash
- Haemorrhagic manifestations
- Leucopenia (WBC ≤5,000/mm^3)
- Thrombocytopenia (platelet count <150,000 /mm^3)

And at least one of the following:

- High titre of IgG in a single serum sample tested by haemagglutination inhibition assay or ELISA (≥1280)
- Positive IgM antibody in a single serum sample
- Occurrence at the same location and time as confirmed cases of dengue illness

4.2.2 Confirmed case

A probable case with at least one of the following:

- Isolation of dengue virus from serum, CSF or autopsy samples
- Demonstration of a fourfold or greater rise in serum IgG titre (by haemagglutination inhibition assay) or increase in IgM antibody specific to dengue virus
- Detection of dengue virus or antigen - in tissue, serum or CSF by immunohistochemistry, immunofluorescence or ELISA
- Detection of dengue virus genomic sequences by RT-PCR

4.3 SEVERITY ASSESSMENT

At the time of initial presentation, the patient may be in the critical phase, impending shock, shock or having bleeding manifestations. Early detection and stabilisation of these patients should be done immediately in the OPD/primary care setting.

4.3.1 Early identification of critical phase (DHF)

Clinically significant plasma leakage occurs around defervescence and the patient's general condition may deteriorate with the settling of fever.

Suspect leaking in patients with:
- Platelet counts below 100,000 /mm³ and in patients with a rapid drop of platelet count.
- Progressive rising of PCV towards 20% above the baseline
- Gradual reduction of urine output (UOP)

4.3.2 Early identification of bleeding (DF/DHF)

Bleeding is a common complication in dengue illness and is multifactorial. It can occur in both DF and DHF patients. In paediatric age groups, bleeding usually occurs after prolonged shock. However, in adults, bleeding can occur without shock. In some patients, bleeding can be overt in the form of haematemesis, melaena, and menorrhagia. However, in most patients bleeding is occult.

Suspect bleeding in patients with the following features:
- Unexplained tachycardia
- Normal or low PCV with unstable vital signs and/or reduction of urine output

4.3.3 Early identification of dengue shock syndrome (DSS)

Dengue shock syndrome can occur due to significant plasma leakage and /or bleeding. Patients may present with impending shock /shock where early identification and immediate resuscitation are crucial. Inadequate fluid resuscitation can lead to prolonged shock and organ failure.

Features suggestive of dengue shock syndrome:
- Sweating
- Dizziness
- Severe abdominal pain and vomiting
- Restlessness and altered level of consciousness
- Oliguria/ anuria
- Cold clammy extremities
- Tachycardia and low-volume pulse

- Prolonged CRFT
- Narrow pulse pressure of <30 mmHg
- Postural drop of systolic blood pressure >20 mmHg
- PCV rise of >30%

Impending shock period

It is important to detect the above clinical features before the patient goes into DSS. The above features together with a rising trend in the heart/pulse rate, trend in the blood pressure, especially diastolic pressure to rise and narrowing of pulse pressure may indicate intravascular volume depletion and impending DSS. Therefore, close monitoring, proper assessment and appropriate timely action are essential.

DSS

Circulatory shock is a life-threatening condition of circulatory failure, causing inadequate oxygen delivery to meet cellular metabolic needs and oxygen consumption requirements, producing cellular and tissue hypoxia. In DSS inadequate tissue perfusion is mainly due to reduction in the intravascular volume due to plasma leak or haemorrhage.

Shock can be classified as **compensated shock** and **decompensated shock/ profound shock** in DSS to align with the management protocol (Table 4.1).

Note:

- **Narrow pulse pressure is defined as pulse pressure ≤20 mmHg.**
- **Hypotension is defined as systolic blood pressure <90 mmHg, or a 20 mmHg fall in baseline blood pressure, especially in a hypertensive patient.**

Table 4.1 - Detection of compensated and decompensated/profound shock in dengue

Stable circulation	Compensated shock	Decompensated shock/ profound shock
Clear consciousness	Change of mental status (could still be normal)	Change of mental status (confusion)
Capillary refill time <2 sec	Prolonged capillary refill time (>2 sec)	Prolonged capillary refill time (>2 sec)/ mottled skin
Warm and pink peripheries	Cold	Cold clammy extremities
Good volume peripheral pulse	Weak, thready	Feeble/ absent peripheral pulse
Normal heart rate for age	Tachycardia	Severe tachycardia
Normal BP for age	Trend of dropping BP	Hypotension / unrecordable
Normal pulse pressure for age	Narrow pulse pressure	Narrow/ unrecordable
Normal respiratory rate	Tachypnoea/ hyperpnoea	Tachypnoea/ hyperpnoea (Kussmaul respiration)
Normal urine output	Reducing trend	Oliguria/anuria

[Adapted from: Clinical practice guidelines MOH/P/PAK/309.15 (GU) management of dengue infection in adults (Revised 3rd edition). 2015.]

Note:

- **All above features may not be present in all patients.**

4.4 CRITERIA FOR ADMISSION

- All patients with a platelet count of ≤130,000 cells/mm³ (done within the last 4 hours) should be admitted.
- Irrespective of the platelet count, patients with the following warning signs should be admitted.

Warning signs

- Lethargy or restlessness
- Persistent vomiting
- Severe abdominal pain or tenderness
- Clinical signs of plasma leakage; pleural effusion, ascites
- Tender hepatomegaly
- Increase in HCT of 10% or more, concurrent with a rapid decrease in platelet count
- Mucosal bleeding such as haematemesis, melaena, haematuria, menorrhagia etc.
- No urine output for 6 hours

- Patients with one or more of the following symptoms should be admitted based on clinical judgment:
    - Inability to tolerate oral fluids
    - Postural dizziness/ postural hypotension
    - Reduced urine output for 4–6 hours
    - Seizures
    - Worsening of general condition with defervescence

- Patients at high risk for more severe disease and its complications may need admission even without the above criteria:
    - Pregnant women
    - Older adults (>65 years)
    - Patients on anticoagulants
    - Patients on steroids or NSAIDs
    - Patients with comorbid conditions
        - Obesity
        - Diabetes mellitus
        - Hypertension
        - Chronic renal failure
        - Established liver disease
        - Ischaemic heart disease
        - Active malignancies
        - Haemolytic diseases and other haemoglobinopathies
        - Peptic ulcer disease
    - Patients who have undergone solid organ/ bone marrow transplant

- Patients with adverse social circumstances, e.g., living alone, living far from a health facility without reliable means of transport

4.5 HOME-BASED CARE FOR PATIENTS WITHOUT ANY INDICATION FOR ADMISSION

Fever patients with a platelet count of more than 130,000/ mm^3 (done within the last 4 hours) who are clinically stable (normal vital signs without any warning features) can be managed as outpatients.

4.5.1 Recommended measures in home-based care

- Adequate physical rest in comfortable clothing, preferably under a mosquito net

- Control of temperature
  - Tepid sponging for fever
  - Paracetamol not exceeding 2 tablets (1g) six hourly (reduce dose for patients with low body weights and patients with liver disease). Warn the patient that the fever may not fully settle with paracetamol and advise not to exceed the recommended dose.

- Adequate hydration
  - Ensure adequate oral fluid intake of around 2400 ml for 24 hours. (If the body weight is less than 50 kg, give fluids at 2 ml/kg/hour for 24 hours.) It is better to spread this amount of fluid across the day. This should consist of fluids such as oral rehydration fluid, king coconut water, other fruit juices, kanji or soup which have electrolytes rather than plain water.

- If the appetite is good, patients can take light and nutritious food. If the patient's appetite is poor, forced feeding should not be done as taking adequate amounts of liquid is sufficient.
- It is advisable to avoid red/ brown (i.e. dark) coloured food/ beverages (to avoid confusion with blood-stained vomitus/ melaena).
- Anti-emetics and PPI/ H2-receptor blockers if necessary
- Avoid all NSAIDS (including COX-2 inhibitors) and steroids.
- Temporally withhold warfarin, aspirin, clopidogrel and dipyridamole in patients who take these on a long-term basis and refer early for specialist opinion.
- Ensure adequate urine output (encourage to pass urine every 3-4 hours).
- It is useful to measure the urine output, if possible, and document with time, as any reduction in urine output can be easily identified.
- Review daily with FBC. First FBC should be done at least at the beginning of the third day of fever/ illness (preferably with AST [SGOT] and ALT [SGPT]) and daily thereafter if the platelet count is >150,000 /mm^3. FBC should be done twice daily if the platelet count is <150,000 /mm^3.

- These patients should be followed up until the patient becomes afebrile for 24-48 hours with stable clinical parameters. Usually, by seven days, most patients recover.

Note:

- **A FBC should be done on the first day of fever in pregnant women and patients with comorbidities.**
- **It is important to understand that vital signs and other parameters may be influenced by comorbidities and high-risk conditions (e.g., urine output in diabetes).**
- **Settling of fever is not a sign of recovery. Some patients will start plasma leakage around defervescence.**

4.6 INDICATIONS FOR AN IMMEDIATE RETURN TO THE HOSPITAL FOR REVIEW

Advise patients to return to the hospital immediately, if they develop any of the following conditions:

- Clinical deterioration with settling of fever
- Inability to tolerate oral fluids
- Severe abdominal pain
- Lethargy or irritability/ restlessness
- Bleeding tendencies including inter-menstrual bleeding or menorrhagia
- Reduced urine output for the last 4-6 hours (<150-200 ml/ 4-6 hours if weight is 50 kg or more)
- Cold and clammy extremities

4.7 ADMITTING A PATIENT TO A WARD/ SPECIALISED UNIT OR TRANSFERRING TO ANOTHER INSTITUTION AFTER INITIAL EVALUATION

- The patient should be stabilised before transferring to the ward/ specialised centre.
- All clinical findings, investigation results and treatment given should be clearly documented and sent with the patient.
- When transferring a patient to another institution, reasons for transfer should be clearly documented in the transfer form.
- Before transferring, the patient's condition should be discussed with the relevant management team of the institution to which the patient is transferred.

4.8 STABILISATION OF A PATIENT WITH DSS BEFORE ADMISSION/ TRANSFER

- Secure an IV line and administer a fluid bolus. Initiate IV fluids as per the clinical guidelines (refer to guidelines on fluid therapy in shock).
- If facilities are available, take blood for FBC and PCV before starting the fluid bolus.
- Check for hypoglycaemia and correct if required.
- Give oxygen to maintain a target saturation of >95%.
- If the transfer is delayed, reassess and give fluid according to the advice of the Consultant Physician/ Senior Registrar of the team at the transferring unit.
- Obtain advice from the Consultant Physician/ Senior Registrar of the receiving unit to which the patient is going to be transferred.

STEPWISE APPROACH TO OUTPATIENT MANAGEMENT ON DENGUE

Overall assessment

History
- Date of onset of fever/ illness
- Date and time of last episode of fever
- Oral intake
- Warning signs (refer to section: 4.4)
- Diarrhoea
- Bleeding, including menstrual bleeding
- Change in mental status/ seizure/ dizziness
- Urine output (frequency, volume and time of last voiding)
- Other important relevant histories: drug history, comorbidities

Physical examination
- Mental status
- Hydration status
- Haemodynamic status
- Tachypnoea/ acidotic breathing/ pleural effusion
- Abdominal tenderness/ hepatomegaly/ ascites
- Bleeding manifestations

Investigations
- FBC and HCT
- NS-1 (if available)
- ALT (SGPT)/ AST (SGOT)
- CRP

Figure 4.1: Stepwise approach to OPD management on Dengue

STEPWISE APPROACH TO OUTPATIENT MANAGEMENT ON DENGUE

CONTINUED...

Diagnosis, disease staging and severity assessment

- Dengue diagnosis (provisional)
- Phase of dengue illness if dengue is suspected (febrile/critical/recovery)
- Hydration and haemodynamic status of the patient (in shock or not)
- Whether the patient requires admission

Plan of management

- Notify the relevant medical officer of health (MOH) of the area via the web based National Dengue Surveillance System (NaDSys) followed by disease notification system.
- If admission is not indicated ;
  - Daily or more frequent follow up is necessary especially from day 3 of illness onwards until the patient becomes afebrile for at least 48 hours without antipyretics.
- If admission is indicated;
  - Stabilise the patient at primary care before transfer (refer to intravenous fluid regime)
- Communicate with the receiving hospital/ emergency & trauma department before transfer.

Figure 4.1: Stepwise approach to OPD management on Dengue

[Adapted from: 2. Clinical practice guidelines MOH/P/PAK/302.15 (GU): Management of dengue infection in adults (Revised 3rd edition) 2015 (MaHTAS)]

[5] IN-WARD ASSESSMENT AND MANAGEMENT OF A PATIENT WITH DENGUE INFECTION

5.1 INTRODUCTION

In-ward patients include patients with DF and DHF. Differentiation between these two conditions is difficult during the initial few days of illness (first three to four days of fever).

There is no plasma leakage in DF. Hallmarks of DHF are plasma leakage and haemorrhagic manifestations.

If the plasma leakage is insignificant, the patient will compensate, and changes in the vital parameters or urine output may not be obvious. However, if the leaking is significant, the patient may not be able to compensate. Significant plasma leakage or plasma leakage with bleeding are the main causes of shock in dengue. Persistent shock will result in further bleeding, organ failure and death.

Note:

- **Bleeding can occur without shock in adult DHF patients. Although uncommon, bleeding can occur in DF patients as well (i.e., without plasma leakage).**

The only way of diagnosing a patient with DHF is the detection of plasma leakage.

Therefore, the mainstays of in-ward care are:

- Close monitoring of patients enabling early detection of plasma leakage (onset of critical phase) and/or bleeding
- Judicious fluid management to prevent shock and fluid overload

Indicators of plasma leakage/ onset of plasma leakage (critical phase)

- A white cell count of 5,000 /mm³ or less with a predominance of lymphocytes and a platelet count of less than 100,000 /mm³ indicate that the patient may enter the critical phase soon, therefore close monitoring for the next 48 hours is crucial.

- Plasma leakage begins around the transition from the febrile to the afebrile phase (defervescence). However, some patients may continue to have fever even during the critical phase.

[5] IN-WARD ASSESSMENT AND MANAGEMENT

- A progressively rising HCT, even before reaching a rise of 20% from baseline, may indicate that the patient is entering the critical period. A 20% rise from baseline indicates that there is a significant amount of plasma leakage.

- A 30% rise in the HCT from baseline indicates that the patient is already in critical phase and is indicative of impending shock/ shock.

- Expected HCT rise will not be seen in a patient with plasma leakage if there is coexisting bleeding.

- Other features which may indicate that the patient is entering the critical phase are a gradual reduction of urine output and new onset tender hepatomegaly.

- A rising pulse rate (disproportionate to the degree of fever) and prolongation of capillary refill time may indicate that the patient is already in the critical phase.

In the presence of one or two of the above features, one should actively look for leakage. An urgent focused ultrasound scan is useful when plasma leakage is suspected.

The presence of pleural effusion and ascites indicates that the patient is already in the critical phase. Pleural effusion may not be obvious in a postero-anterior CXR but may only be seen in a right lateral decubitus CXR film. The use of a focused ultrasound scan (USS) will help to identify clinically undetectable pleural effusion and ascites.

If appropriate interventions are not adopted early, patients with plasma leakage may progress to shock due to plasma leakage and/ or bleeding.

Note:

- **Gall bladder wall oedema may be seen by USS in both DF and DHF. It may be the earliest sign of leaking in DHF. However, if pericholecystic oedema is not progressing in subsequent USS, such patients are likely to have only DF.**

5.2 DETERMINING THE ONSET OF THE CRITICAL PHASE

When the plasma leakage is detected clinically, radiologically or with a 20% rise in PCV, the leakage has progressed at least for several hours. It is not possible to ascertain the onset of the critical phase accurately in a DHF patient. However, making a reasonable assumption of the beginning of the leaking is important as it helps the fluid management of the patient, i.e., to decide how much fluid and what fluid to be given.

The following factors should be considered in determining the onset of the critical phase:

- Duration of the illness
  - Usually, the leaking occurs during the 4th and 5th day of the illness (i.e., from the beginning of the fever). Therefore, if a patient admitted on day 3 of fever is found to have leaking, the patient is likely to be in the early part of the critical phase. On the other hand, if a patient is admitted on the 6th day of the illness and is found to be leaking, the patient is likely to be in the second half of the critical phase.

- Platelet count
  - Plasma leakage almost always occurs when the platelet count is less than 100,000. Therefore the time at which the platelet count dropped below 100,000 is useful in determining the onset of plasma leakage.

Note:

- **In pregnant mothers, plasma leakage can occur with higher platelet counts.**

- Defervescence
  - Plasma leakage starts around the time of defervescence. However, some patients leak while having a fever.

- Degree of plasma leakage as shown by USS (further reading: section 5.3)

- Gradual rise of PCV
  - Unless there is coexistent bleeding, PCV rises with plasma leakage. This starts gradually and can rise above 20% from the baseline depending on the degree of plasma leakage. Therefore, when a 20% rise is detected, the leaking has progressed for several hours (more than 12 hours).

- Reduction of urine output
  - With continuing plasma leakage, urine output tends to reduce gradually. However, some patients may have a significant plasma leakage while having an adequate amount of urine output. The urine output can be misleading, especially in patients with poor glycaemic control.

- Patient in shock
  - If the patient is in shock, the patient is likely to have been in the critical phase at least for 18-24 hours.

Once the plasma leakage and the approximate timing of the onset are determined, it is important to start the critical phase monitoring chart. This enables the clinician to manage the patient better.

5.3 POINT OF CARE SONOGRAPHY IN DENGUE

5.3.1 Role of point of care ultrasound (POCUS) in dengue

POCUS has now evolved into an important and reliable method of diagnosing plasma leakage objectively in clinically suspected DHF patients.

There are many advantages of POC ultrasound. It can be done at the bedside on unprepared patients and can be repeated frequently if needed. POCUS can also be used to predict the probable duration of the critical phase.

5.3.2 Areas of interest in POCUS in dengue

Main areas
- Gallbladder - gallbladder wall thickening and appearance of para cholecystic fluid
- Fluid in the hepato-renal pouch
- Fluid in the right pleural cavity
- Fluid in the pelvis (recto vesical pouch)

Additional areas
- Fluid in the left pleural cavity
- Fluid in pericardial space
- Fluid in splenorenal angle

5.3.3 When should you perform POCUS in dengue

- When there is a suspicion of DHF (based on clinical, haematological or rarely biochemical findings)
- Despite the negative initial scan, if there is a clinical suspicion, the POC ultrasound scan should be repeated at frequent intervals.

Once the fluid leakage is detected and the time of onset is defined, there is no need to repeat the scan unless there is a clinical deterioration.

5.3.4 Findings on POCUS in DHF

- The presence of gall bladder wall oedema with no fluid around it is not a feature of plasma leakage. However, this generally precedes plasma leakage. Therefore, if gall bladder wall oedema is detected, a repeat scan is warranted in 3-6 hours to identify possible plasma leakage.

- Gall bladder wall oedema with a thin rim of fluid around it (PCF- peri cholecystic fluid) could be the earliest sonographic finding of plasma leakage. To see the progress of leaking, repeat the scan in 3-6 hours.

Note:

- **When taken together with the duration of illness, drop in the platelet count, changes in haemodynamic parameters and urine output and the ultrasound findings enable the clinicians to estimate the duration of the critical phase.**

- A thin rim of fluid in the hepato-renal recess indicates that a minimum of six hours have elapsed since the beginning of plasma leakage.

- Fluid in the peritoneal cavity, among bowel loops and in the pelvis, indicates that a minimum of twelve hours have elapsed since the beginning of plasma leakage.

- Fluid in the pleural space is commonly seen on the right side and indicates that a minimum of twelve hours have elapsed since the beginning of plasma leakage.

- In a patient where bilateral pleural effusions and ascites are seen, it implies that the patient is in the latter part of the critical phase and more than 24 hours have lapsed from the onset.

You may measure the thickness of fluid in each area for subsequent comparison, especially if there is a clinical deterioration.

Table 5.1 - Ultrasound scan findings and timing of leakage in DHF

Point of care sonographic interest	Expected finding	Presumed time of onset of leaking	Special notes
Gallbladder	Wall thickening (normal 3 mm)	Not started	May be seen in DF (without DHF), hepatitis, gall bladder or colonic infections
Gallbladder	Pericholecystic fluid	May herald leaking, repeat in 3 hours	May be seen in acute cholecystitis
Morrison's pouch (MP)	Fluid	More than 6 hours	
Morrison's pouch + right pleural cavity	Fluid	More than 12 hours	
Morrison's pouch + right pleural cavity+ left pleural cavity	Fluid	More than 24 hours	

Note:

- **USS findings are subjective. Therefore, timing of plasma leakage and detection of critical phase should not solely depend on USS findings.**
- **Leaking may not be detected ultrasonically if the patient is dehydrated or if the leaking is minimal.**

5.4 MONITORING DF/DHF PATIENTS DURING HOSPITAL STAY

Every in-ward patient with suspected DF/DHF should be assessed thoroughly, using the same stepwise approach as for the outpatient assessment (Figure 4.1). The plan of monitoring should be based on the phase of the disease and the haemodynamic status of the patient.

If the patient is clinically stable on admission and DF/DHF is suspected;

- Measure body weight
- Assess vital signs
- Chart temperature 4 hourly
- Observe for evidence of bleeding, especially melaena or bleeding per vagina and quantify
- Maintain an intake and output chart
- Calculate the urine output in ml/kg/hour, using the same weight used for fluid calculation
- Do an urgent FBC on admission and review early
- Repeat FBC daily
- Do AST/ALT on admission

5.4.1 Febrile phase monitoring

- Febrile phase monitoring should be commenced when the platelet count drops below 130,000 /mm³ using the observation chart for the management of dengue in adult patients without evidence of fluid leakage (Annexure II).
- The purpose of this monitoring is to detect entry into the critical phase.

Table 5.2 - Parameters and frequency of pre-critical monitoring

- General condition, appetite, vomiting, loose motion
- Observe for bleeding
- Temperature four hourly
- Vital parameters: pulse, blood pressure (both systolic and diastolic), pulse pressure, respiratory rate, pulse volume and capillary refill time - three hourly

- Detailed fluid balance (Annexure II):
  - Intake with type of fluid and route of administration
  - Urine output – measure three hourly
  - Other fluid losses - vomitus/ diarrhoea/ bleeding

- FBC daily
- In-ward HCT six hourly (refer to section: 18.2)
- AST/ ALT daily (if initial values >200, history of NSAIDs/ steroid intake, patients with chronic liver cell disease, presence of right hypochondrial (RHC) tenderness)

Note:

- **We advocate doing a spun haematocrit during in-ward monitoring. Refer to section 18.2 on 'Measuring Haematocrit'.**

5.4.2 Critical phase monitoring

Use the 'Observation Chart for Management of dengue in Adult Patients with Fluid Leakage' for patients with evidence of plasma leakage (Annexure-I). The purpose of maintaining this monitoring chart is to ensure accurate fluid management and early detection of shock.

Table 5.3 - Parameters and frequency of critical phase monitoring

- Vital parameters (including CRFT) – assess hourly
- Fluid balance - assess two to three hourly
- HCT – assess three hourly or more frequently
- AST/ALT daily; may need to be done more frequently in critically ill patients. (ALT/AST at a given time represents liver dysfunction within the last 12-24 hours.)
- FBC daily; may need to be done more frequently in critically ill patients.
- INR in selected patients
- VBG in selected patients (do not do ABG)

5.4.3 Monitoring of a patient with evidence of compensated shock/ decompensated shock

Vital parameters and CRFT should be checked every 15 minutes until the patient becomes haemodynamically stable. During intense fluid resuscitation, HCT should be checked immediately before and 10-15 minutes after each fluid bolus and then at least two to three hourly.

If the shock is prolonged (not responding to initial fluid bolus) an indwelling urinary catheter should be inserted, and urine output should be measured hourly. Due to fluid extravasation leading to a relative reduction in intravascular volume, the urine output (UOP) is likely to be less than normal. Hence, a UOP of 0.5 ml to 1 ml/kg body weight/hour is adequate during this period. Overenthusiastic fluid replacement to achieve a higher UOP may lead to fluid overload.

Liver profile, blood sugar, serum calcium, serum electrolytes, serum creatinine, clotting profile, venous blood gases and lactate levels should be done in complicated cases such as prolonged shock not responding to adequate fluid resuscitation, liver failure and renal failure.

Once the patient is stabilised, monitoring can be spaced out. Monitoring of vital parameters 1-2 hourly and UOP every 2 hourly would be adequate depending on the patient's haemodynamic status.

5.4.4 Equilibrium phase monitoring

In some patients, after the 48 hours of critical phase, symptoms and signs of recovery may not be seen for several hours. Their UOP may be marginal and HCT/PCV may fluctuate slightly. In such patients, critical phase monitoring should be continued unless they show features of convalescence.

5.4.5 Convalescent phase monitoring

Look for features of improvement (Table 3.1). Bradycardia is an expected finding in the convalescent period, which is usually asymptomatic and transient. High urine output is observed in most patients. However, some patients may develop fluid overload during the convalescent phase. Therefore, it is important to observe for symptoms and signs of fluid overload (refer to section: 8.1). Rising respiratory rate is the most important sign for early detection of fluid overload. Continuous monitoring of vital signs and maintenance of input and output charts are necessary for patients with fluid overload.

However, the frequency of vital sign monitoring can be reduced if the patient is stable (initially 3-4 hours, later 6-12 hours). PCV monitoring can be reduced to every 6 hours. When the platelet count is rising, PCV monitoring can be stopped in stable patients.

[6] FLUID REPLACEMENT IN DENGUE

Fluid replacement is the most important measure in the management of DF/DHF. Adequate fluid replacement is essential to avoid dehydration during the febrile phase, and to avoid shock due to significant volume loss in the critical phase. Careful fluid replacement during the latter part of the critical phase, equilibrium phase and recovery phase in a DHF patient is important to avoid fluid overload.

6.1 FEBRILE PHASE

During the febrile phase, intake of an adequate amount of fluid is important to avoid dehydration. The fluid intake should be adequate to replace the urine output and insensible loss. Approximately this amount is about 2400 ml per day for an average adult. Additional losses such as vomiting and diarrhoea should be replaced according to the volume loss. If the patient is dehydrated on admission, it should be corrected accordingly.

For all inward patients, it is important to have an IV access by inserting preferably a large bore (18 G - Green) cannula. However, IV fluid is not indicated for all inward patients. Consider IV fluids for patients who are unable to take an adequate volume of oral fluid, patients with diarrhoea or vomiting and for patients whose fluid intake is not reliable.

Oral fluids should consist of electrolyte solutions such as king coconut water, other fruit juices, oral rehydration fluid and kanji. Drinking plain water should be discouraged. The recommended solutions for IV fluid therapy are 0.9% saline (normal saline) or Hartmann's solution. The total amount of fluid (both IV and oral) should be approximately 2500 ml for 24 hours for an average adult (2 ml/kg/hour up to a maximum of 50 kg of weight).

However, if there is vomiting or diarrhoea, this amount should be increased, and dehydration should be corrected.

Note:

- **It should be emphasised that over-hydration during the febrile phase will not prevent patients from going into shock in the critical phase. It may cause fluid overload during the critical phase.**

6.2 CRITICAL PHASE

It is extremely important to replace fluid accurately during the critical phase. With plasma leakage, there is an additional loss of fluid from the intravascular compartment (in addition to urine and insensible loss). If the plasma leakage is little, the body mechanism will compensate for the fluid loss. However, if the loss is significant and is not replaced appropriately, resultant volume depletion can lead to acute liver injury and shock.

6.2.1 Calculation of the fluid requirement during the critical phase

The total volume given during the critical phase is calculated using the formula M + 5% of the deficit. M (maintenance fluid) is calculated as shown below:

For the 1st 10 kg	-	100 ml/kg
For the 2nd 10 kg	-	50 ml/kg
From 20 kg and above up to 50 kg	-	20 ml/kg

5% deficit is calculated as 50 ml/kg up to 50 kg

Example of fluid calculation for a 65 kg person (maximum body weight for fluid calculation is 50 kg)

For the 1st 10 kg - 100 ml/kg	=	1000 ml
For the 2nd 10 kg - 50 ml/kg	=	500 ml
From 20 kg and above up to 50 kg -20 ml/kg	=	600 ml
5% deficit is calculated as 50 ml/kg up to 50 kg	=	2500 ml
Total	=	4600 ml

If the body weight is less than 50 kg, the calculation should be done according to the ideal body weight or actual body weight whichever is less.

Note:

- **The maximum usual fluid requirement for an average adult for the entire critical phase (48 hours) is 4600 ml. This is only a guide, and this volume is calculated considering a patient with fluid leakage resulting in moderate dehydration. Some patients might need a higher amount of fluid, especially if they develop shock.**

The fluid quota is aimed at giving just the adequate amount of fluid to maintain perfusion to vital organs without causing fluid overload. Once the fluid quota is exceeded the chances of fluid overload are high.

6.2.2. Indications for IV fluid:

- When the patient cannot have an adequate oral fluid intake or is vomiting
- When HCT continues to rise despite oral rehydration
- When the patient is in impending shock or is in shock

If the patient needs IV fluid, isotonic crystalloids should be used in the initial period of the critical phase. Hyper-oncotic colloid solutions (osmolarity of >300 mOsm/L) such as dextran 40 or starch solutions may be used in the latter part of the critical phase if the patient is unstable and needs more fluid. i.e., patients with massive plasma leakage, and those not responding to the minimum volume of crystalloid (as recommended below).

6.2.3 Types of IV fluid for resuscitation

a) Crystalloids:

0.9 % saline (Normal saline) or Hartmann's solution, should be used for initial fluid resuscitation.

b) Colloids:

Only hyper-oncotic colloids are effective. They are used only as boluses of 10 ml/kg/hour. It is recommended to use dextran 40 as the first choice. If dextran 40 is not available or the maximum quota of dextran 40 is used, tetrastarch (6% starch solution) can be used. Other colloids such as 20% albumin may be used, but these are not as effective as dextran 40.

Colloids should be used:

- In patients whose shock does not respond to two boluses of crystalloids with rising HCT or still high HCT
- In patients who are being treated for shock, have high HCT and whose fluid quota (M+5%) is nearing completion
- In patients who present with shock and fluid overload
- In patients who need more fluids in the latter part of the critical phase, and when their fluid quota is nearly exceeding

As dextran can sometimes interfere with cross-matching, blood should be drawn for grouping and cross-matching before starting on dextran. The maximum amount of dextran for 24 hours is 3 boluses of 500 ml/hour (10 ml/kg/hour). The maximum of tetrastarch is 3 boluses of 500 ml/hour (10 ml/kg/hour) in 24 hours.

6.3 FLUID REPLACEMENT IN DHF

6.3.1 Fluid replacement in DHF - haemodynamically stable patients

For patients who are haemodynamically stable and have no vomiting or diarrhoea, increased oral fluid intake may be sufficient during the critical phase. However, IV fluid is indicated in patients with rising HCT (indicating on-going plasma leakage) despite increased oral intake. IV fluid therapy should also be considered in patients who are vomiting and not tolerating oral intake.

Considering the dynamic nature of plasma leakage, fluids should not be given at a flat rate. In the early stages of the critical phase, the degree of leakage is not predictable. Therefore, after detecting the critical phase, the fluid rate should be increased to 2.5 to 3 ml/kg/ hour (maximum 50 kg) for patients in the first half of the critical phase. After 3-4 hours, fluid rate should be adjusted according to the UOP, haemodynamics and the HCT.

Similarly, when plasma leakage becomes less (second half of the critical phase) it is necessary to reduce the rate of fluid intake in a step-wise pattern. Urine output should be maintained at 0.5-1 ml/kg/hour (Calculate the urine output in ml/kg/hour, using the same weight used for fluid calculation.) and pulse pressure above 30 mmHg during the entire critical period.

Note:

- **It is important to note that there are individual variations in leakage. In rapid leakers, the peak of the leakage will be reached much earlier (before 24 hours). In slow leakers, the peak of the leakage will be reached much later (after 24hours).**
- **When the plasma leakage is detected, the fluid intake should be increased more than the maintenance fluid as there is an additional fluid loss (in addition to the UOP and insensible loss). This increased fluid rate should be maintained until the peak leakage is over.**
- **It should be emphasised that the HCT is a guide for fluid management. Trying to normalise the HCT will generally result in fluid overload.**
- **Expected HCT change following a fluid bolus/blood**
  - **Crystalloid 10 ml/kg over one hour – a drop by around 3**
  - **Dextran 10 ml/kg over one hour – a drop by around 8-10**
  - **Packed RBC one unit (300-350 ml) - a rise by around 7**

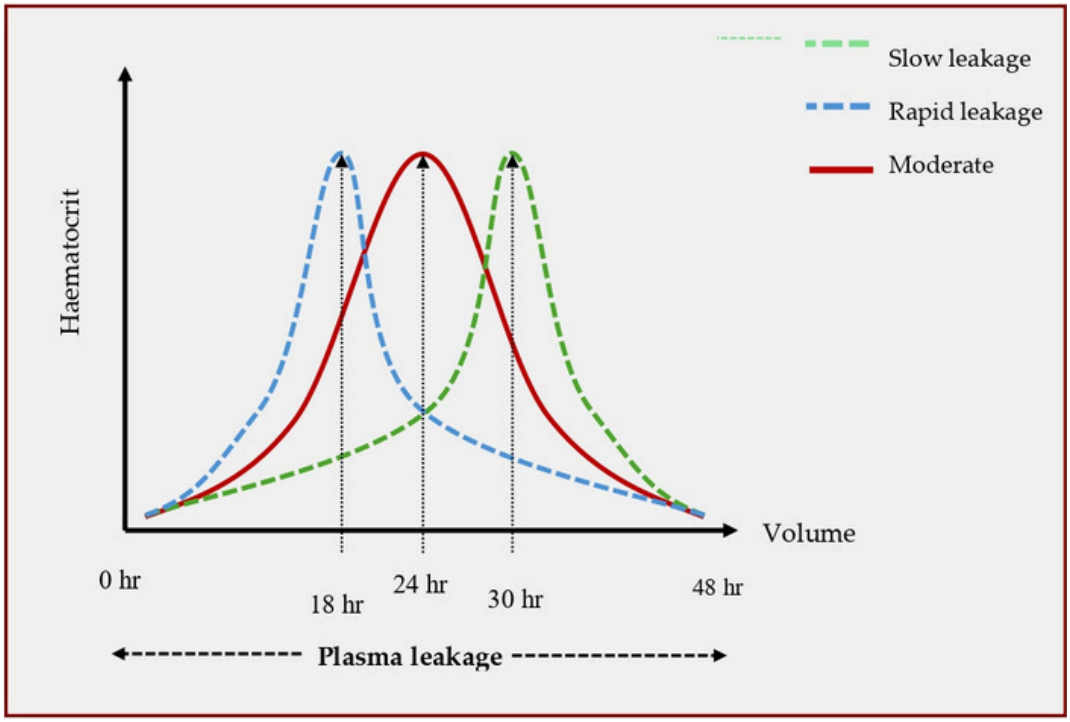


Figure 6.1: Individual variations in plasma leakage

6.3.2 Fluid replacement in DHF - hemodynamically unstable patients

DSS is a medical emergency that needs early recognition and immediate intervention. Failure to recognise impending shock in a patient may lead to shock and other complications. A patient with dengue shock should be managed in a high-dependency area.

If the patient has signs of impending shock (Table 4.1 - Detection of compensated/ decompensated and profound shock in dengue) rate of fluid should be increased to 5-7 ml/kg/hour to keep the vital parameters stable. However, a rate as high as 5-7 ml/kg/hour is only occasionally needed and will be necessary only for a few hours. If the patient improves, fluid can be gradually tailed off. If the patient does not improve, consider giving more fluid, blood or dextran depending on the HCT and the available fluid quota.

If the patient is in shock, IV fluid should be started as a bolus. The volume of initial and subsequent fluid resuscitation depends on the degree of shock and can vary from 10-20 ml/kg body weight (maximum 50 kg).

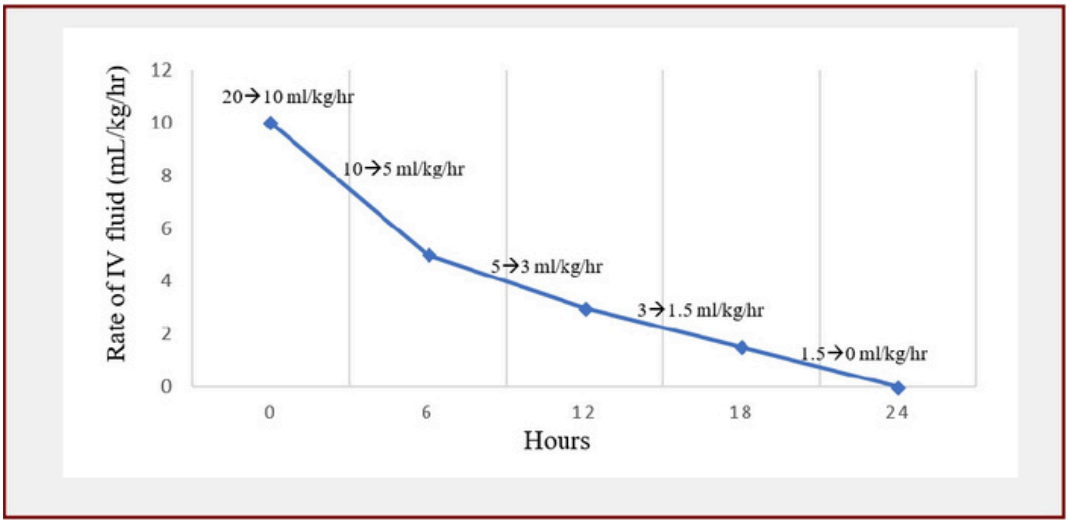


Figure 6.2: Rate of IV fluid in dengue patients with shock (ml/kg/hour)

[Reproduced from Sivakorn C, Schultz MJ, Mabey D, Clark S, Wongsa A, Srisawat N. Treatment of adults with severe dengue in Thailand. Clinical Critical Care. 2022;30: e0005 (doi:10.54205/ccc.v30.255725)]

With fluid boluses, the patient can either;

1. Improve with gradual reduction of HCT
As the fluid leakage continues at a high rate during this period, it should be matched by a high infusion rate of intravenous fluids. Therefore, when the patient is clinically improving, the fluid bolus should be followed by a gradual reduction of fluid in a stepwise manner (Figure 6.2).

2. Remain unstable with static or rising HCT
After two crystalloid boluses, if the patient remains haemodynamically unstable with a high HCT, colloids should be considered for the third cycle.

3. Remain unstable with dropping HCT
After two cycles of resuscitation despite the dropping of HCT, if a patient remains in shock, there is likely significant bleeding. Blood transfusion should be initiated promptly for these patients (bleeding is often concealed).

Note:

- **If the initial HCT is low or normal the shock is due to significant concealed haemorrhage with or without plasma leakage. Therefore, such patients need urgent blood transfusion.**

[6] FLUID REPLACEMENT IN DENGUE

The amount of fluid given during and after shock depends on how much the patient has received before the onset of shock in the critical phase. If the patient has been managed in the hospital and the onset of the critical phase has been identified, the volume of fluid already given would be known. In a patient who comes from home or transferred from another institution and is found to be in shock on admission, every effort should be taken to find out how much fluid was given during the preceding 18-24 hours, because the critical phase would have started 18-24 hours prior to the detection of shock in such a patient. The amount of fluid given during this initial 18-24 hours should be subtracted from M+5% and only the balance amount of fluid should be given for the next 24-36 hours. Judicious control of fluid therapy is important in avoiding fluid overload. However, it is important to give an adequate amount of fluid to avoid prolonged shock in unstable patients, despite the risk of being fluid overloaded. Some patients may need fluid above their calculated fluid quota. If the patient gets fluid overload, that should be managed subsequently.

There may be a haemodynamically unstable patient who is dehydrated (due to persistent vomiting, diarrhoea or reduced oral intake) in addition to plasma leakage at the time of admission. In the resuscitation of such a patient, the degree of dehydration should be considered, and more crystalloids should be given initially to replace the deficit.

Adequate fluid resuscitation is indicated by the following parameters

Clinical parameters

- Improvement of general well-being/ mental status
- Warm peripheries
- Capillary refill time <2sec
- Stable blood pressure
- Improving pulse pressure
- Resolving tachycardia and tachypnoea
- Increase in urine output

Other parameters

- Decrease in HCT
- Improvement in metabolic acidosis
- Reduction of lactate levels

6.4 PATIENTS NOT RESPONDING TO FLUID RESUSCITATION (OR WITH REFRACTORY SHOCK)

6.4.1 ABCS

If the patient is not responding to two boluses of crystalloid, contributory causes for shock other than plasma leakage should be considered.

These are,

- **A**cidosis - Check venous blood gas (VBG) including serum lactate
- **B**leeding - Check HCT
- **C**alcium - Check serum calcium and electrolytes (sodium and potassium)
- **S**ugar - Check random capillary blood sugar

Note:

- **Liver and renal profiles should be checked along with ABCS.**

a. Correction of acidosis

If the VBG is checked, 50 ml of 4.2% sodium bicarbonate (IV) should be given where the pH <7.35 and the HCO3 <15 mmol/l.

If the patient is clinically acidotic, one dose of 50 ml of 4.2% sodium bicarbonate (IV) may be given empirically where blood gas cannot be assessed.

b. Bleeding

Bleeding is a common contributing factor to shock. For identification and treatment, refer to section 7.

c. Calcium replacement

Hypocalcaemia has been demonstrated in dengue infection and is often under-recognised. Hypocalcaemia maybe more pronounced in severe/ critically ill dengue.

IV calcium gluconate may be used empirically, in the following situations:

- Patients with DHF where blood pressure is not responding to two boluses of crystalloids
- Any patient with shock

- DHF/ DF patients receiving >2 units of packed red cells
- Patients with dengue myocarditis
- Other clinical conditions - as decided by the treating clinician (e.g., inadequate clinical improvement despite adequate fluid resuscitations)

Treatment is with 10% calcium gluconate 10 ml over 10 minutes. This may be continued six hourly for 24 hours.

d. Correction of hypoglycaemia

If the blood glucose level is less than 70 mg/dl correct it by giving 25% dextrose 25 ml intravenously as a bolus.

Recheck capillary blood sugar in 15 minutes and if it is less than 70 mg/dl repeat 25% dextrose intravenously. It should be followed by continuous infusion of 5-10% dextrose if necessary.

6.4.2 Other causes for refractory shock

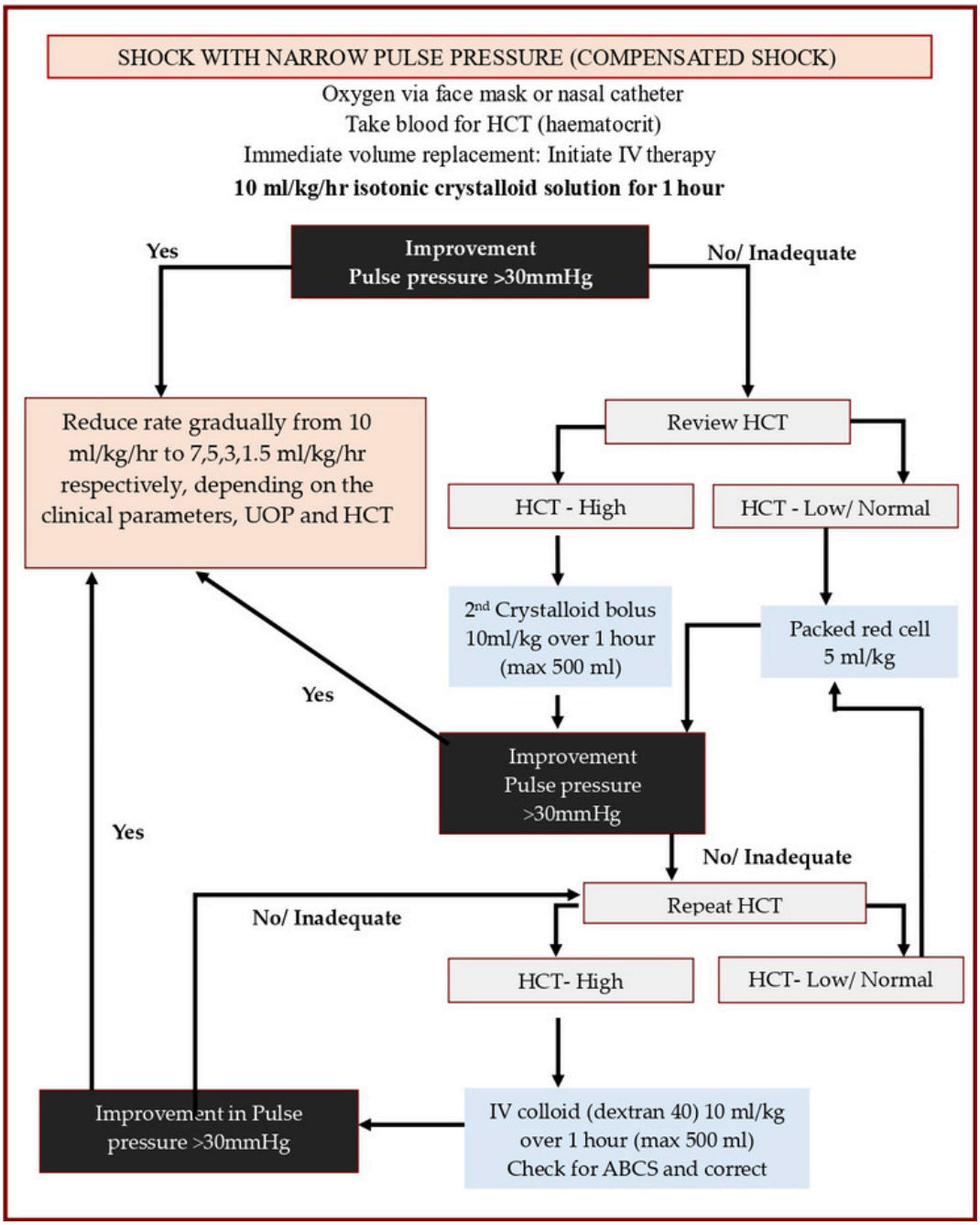
In patients who are in shock after three cycles of fluid resuscitation, other causes for persistent shock should be considered. i.e., sepsis, diabetic ketoacidosis, severe dehydration due to ongoing fluid loss.

6.4.3 Indications for haemodynamic support

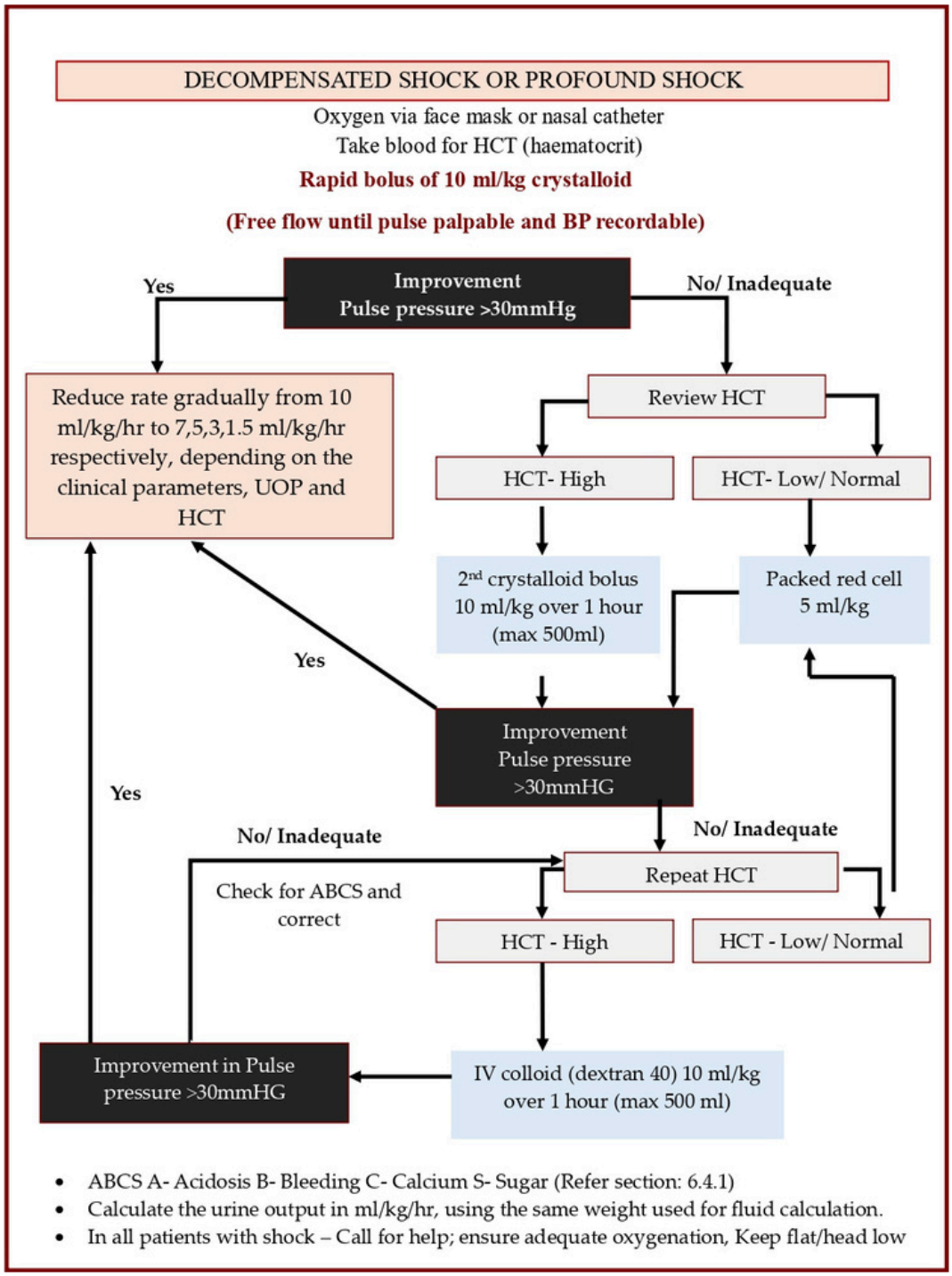
In dengue, hypotension is usually due to plasma leakage or internal bleeding. Fluid resuscitation is crucial and should be initiated first. However, vasopressors (e.g., dopamine and noradrenaline) may be considered when the mean arterial pressure is persistently <60 mmHg despite adequate fluid resuscitation (40-60 ml/kg) with crystalloids, colloids and blood. Intra-arterial blood pressure monitoring or at least central venous pressure monitoring (if possible) would be very useful in this situation. However, insertion of arterial or central venous monitoring lines should be done by an experienced person.

Note:

- **While vasopressors increase blood pressure, tissue hypoxia may be further compromised by vasoconstriction. Therefore, vasopressors should not be started without adequate fluid resuscitation.**


SHOCK WITH NARROW PULSE PRESSURE (COMPENSATED SHOCK)
Oxygen via face mask or nasal catheter
Take blood for HCT (haematocrit)
Immediate volume replacement: Initiate IV therapy
10 ml/kg/hr isotonic crystalloid solution for 1 hour
Improvement Pulse pressure >30mmHg
Yes
No/ Inadequate
Reduce rate gradually from 10 ml/kg/hr to 7,5,3,1.5 ml/kg/hr respectively, depending on the clinical parameters, UOP and HCT
Review HCT
HCT - High
HCT - Low/ Normal
2nd Crystalloid bolus 10ml/kg over 1 hour (max 500 ml)
Packed red cell 5 ml/kg
Yes
Improvement Pulse pressure >30mmHg
Yes
No/ Inadequate
No/ Inadequate
Repeat HCT
HCT- High
HCT- Low/ Normal
Improvement in Pulse pressure >30mmHg
IV colloid (dextran 40) 10 ml/kg over 1 hour (max 500 ml) Check for ABCS and correct

Algorithm 1


DECOMPENSATED SHOCK OR PROFOUND SHOCK
Oxygen via face mask or nasal catheter
Take blood for HCT (haematocrit)
Rapid bolus of 10 ml/kg crystalloid
(Free flow until pulse palpable and BP recordable)
Improvement Pulse pressure >30mmHg
Yes
No/ Inadequate
Reduce rate gradually from 10 ml/kg/hr to 7,5,3,1.5 ml/kg/hr respectively, depending on the clinical parameters, UOP and HCT
Review HCT
HCT- High
HCT- Low/ Normal
2nd crystalloid bolus 10 ml/kg over 1 hour (max 500ml)
Packed red cell 5 ml/kg
Yes
Improvement Pulse pressure >30mmHG
Yes
No/ Inadequate
No/ Inadequate
Repeat HCT
Check for ABCS and correct
HCT - High
HCT - Low/ Normal
Improvement in Pulse pressure >30mmHG
IV colloid (dextran 40) 10 ml/kg over 1 hour (max 500 ml)
ABCS A- Acidosis B- Bleeding C- Calcium S- Sugar (Refer section: 6.4.1)
Calculate the urine output in ml/kg/hr, using the same weight used for fluid calculation.
In all patients with shock – Call for help; ensure adequate oxygenation, Keep flat/head low

Algorithm 2

[7] BLEEDING AND BLOOD TRANSFUSION

7.1 BLEEDING IN DENGUE

Bleeding is a common complication in dengue illness and bleeding can occur in both DF and DHF patients. The severity of bleeding can vary from petechial bleeding to significant bleeding and to massive intractable haemorrhage which may cause shock. Often bleeding is concealed initially. Therefore, bleeding should always be looked for and suspected in dengue patients, especially in an unstable patient.

One of the two hallmarks of DHF is increased bleeding diathesis. In paediatric age groups, significant bleeding usually occurs after prolonged shock due to plasma leakage. However, in adults, significant bleeding can occur in patients with DHF even without the patient going into shock. Even minor bleeding may contribute to shock in a patient who is having plasma leakage.

Many deaths have been attributed to a failure to identify concealed bleeding and/or not transfusing blood at the correct time.

7.2. CAUSES OF BLEEDING

The pathophysiological basis of haemorrhage in dengue infections remains poorly understood and very likely to be multifactorial. The following are likely contributory factors:

- Consumptive coagulopathy
- Vasculopathy
- Platelet dysfunction and thrombocytopenia
- DIC and liver failure which occur as a consequence of prolonged shock, cause multi-organ dysfunction

Possible precipitating causes of bleeding during the dengue infection and its management are:

- Use of NSAIDs
- Use of steroids
- IM injections
- Recent use or continuation of anticoagulants/ antiplatelets
- Physical exertion
- Trauma

7.3 MANIFESTATIONS/ WHEN TO SUSPECT BLEEDING

Bleeding in dengue is commonly occult (can occur in muscles, peritoneal cavity or pleural cavity). However, petechial haemorrhages and microscopic haematuria are seen commonly. Menstrual bleeding can be excessive and intermenstrual bleeding is not uncommon. Haematamesis, melaena, and gross haematuria are uncommon overt bleeds. Therefore, when seeing a patient;

- Always ask about the history of treatment with NSAIDs and steroids. If such history is present, be alert.
- Ask about the history of taking aspirin, clopidogrel, warfarin and other anticoagulants and consider stopping those. If the patient had been on an anticoagulant, do a clotting profile.
- Ask about the presence of bleeding per vagina. This could be menstrual bleeding, intermenstrual bleeding or even post-menopausal bleeding. Young girls who have not attained menarche may develop their first bleeding while having dengue. If bleeding is not present on admission, advise the patient to inform the health staff if bleeding develops. Even normal menstrual bleeding may contribute to shock in a DHF patient.
- Ask the patient about bleeding manifestations such as melaena, haematuria etc. and advise to inform the health staff if such manifestations develop.
- Examine the patient to check for cold and clammy extremities, tachycardia, and low-volume pulse. If present, these may suggest bleeding.
- Suspect bleeding if the patient is having tachycardia without fever or disproportionate to fever.
- Suspect bleeding if the patient is complaining of profuse sweating. (Sweating can occur even when fever is settling.)

Blood grouping and DT are essential in patients with the above features.

7.4. INVESTIGATIONS

- Bedside HCT measurement is the most important investigation. When correlated with the haemodynamic parameters, this gives a reasonably accurate diagnosis of significant bleeding.
- Do PT/INR, LFT and VBG when bleeding is suspected

Note:

- **Thromboelastometry impairment is highly prevalent in dengue patients with thrombocytopenia, particularly in INTEM and EXTEM analyses, while standard coagulation tests are normal. Therefore, thromboelastometry is not useful in detecting bleeding or in the treatment of bleeding.**

7.5. WHEN TO TRANSFUSE BLOOD

Early blood transfusion is essential in the following situations where significant bleeding is overt or suspected:

- If significant overt bleeding (e.g., haematemesis, melaena, bleeding per vagina etc.) of more than 6-8 ml/kg body weight is present, a blood transfusion is necessary.

- Suspect significant concealed bleeding in the following situations:
  - When haematocrit is not high enough to explain the degree of shock by plasma leakage alone (Hypotensive shock with low or normal HCT)
  - A drop in HCT without clinical improvement despite fluid replacement
  - Hypotension not responding to fluids, 40-60 ml/kg given over 4-6 hours
  - Worsening metabolic acidosis despite adequate fluid replacement (refer to section 10)
  - A drop of HCT by more than 10 points or below the baseline HCT after a bolus of dextran (10 ml/kg)
  - A patient who has been unstable for > 6-8 hours

A patient with the following conditions may require blood transfusions:

- If the patient is in shock with a small amount of fluid leakage (small PCV rise, USS showing little fluid)

- Low or normal PCV with unstable haemodynamic parameters such as
  - Cold clammy extremities
  - Prolonged CRFT
  - Tachycardia
  - Narrow pulse pressure
  - Reduced UOP

- Increased INR with low or normal PCV in a patient with plasma leakage

Note:

- **Haemoglobin level may remain normal initially despite significant blood loss.**
- **5-7 ml/kg of packed red cells can be given at a time. HCT is expected to rise by 5-7 points (e.g., from 30 to 35-37) with this amount of blood.**

7.6. HOW TO REDUCE THE RISK OF BLEEDING:

- Avoid all NSAIDS and steroids during illness
- Avoid physical exertion
- Avoid IM injections
- Prevent patients from going into shock and even if they go into shock, detect and treat them as soon as possible.

7.7. OTHER TREATMENTS FOR BLEEDING - (REFER TO SECTION 9)

[8] FLUID OVERLOADED PATIENT

A patient may become fluid overloaded due to over-enthusiastic treatment with IV fluids. (Too much of oral fluid could also contribute to this.) Continuation of IV fluids beyond the critical phase and higher amounts of crystalloids (without changing to colloids/ blood in unstable patients or to oral fluids in stable patients) towards the end of the critical phase are other contributing factors.

8.1 FEATURES OF FLUID OVERLOAD

Early signs and symptoms include puffy eyelids, distended abdomen (ascites), tachypnoea and mild dyspnoea.

Late signs and symptoms include all of the above, along with moderate to severe respiratory distress, shortness of breath, wheezing, crepitus and low oxygen saturation. Restlessness/agitation and confusion are signs of hypoxia and impending respiratory failure.

8.2 TREATMENT OF A FLUID OVERLOADED PATIENT

A fluid-overloaded patient should be treated according to the haemodynamic status and the HCT.

- Oxygen should be administered if the saturation is less than 94%.
- If the patient is in shock or has features of fluid overload (haemodynamically unstable) and has high HCT, a bolus of colloid (dextran 40 or tetrastarch) should be given 10 ml/ kg (500 ml for an average adult) over an hour. In the midway of the bolus, frusemide 5-10 mg should be given. Furosemide can be repeated if necessary.
- If the patient is in shock (haemodynamically unstable) and has a normal or low HCT, immediate blood transfusion is necessary. Until blood is available, a bolus of colloid (500 ml of dextran 40 or tetrastarch) could be administered.
- If the patient is haemodynamically stable and has a normal or low HCT, fluid should be restricted and the patient should be monitored carefully, as the patient is likely to improve within hours. The most probable reason for low haematocrit is haemodilution. However, consider the possibility of concealed bleeding and reserve blood to transfuse if the patient becomes unstable. If the patient develops features of pulmonary oedema, furosemide 5-10 mg should be given intravenously. This dose can be repeated after half an hour.

- If the patient is haemodynamically stable and has high HCT, the fluid should be restricted, and the patient should be monitored carefully. The patient will likely go into polyuric phase and the HCT will settle within several hours.

- In a patient with evidence of fluid overload and poor peripheral circulation consider therapeutic aspiration if there is a massive pleural effusion interfering with ventilation. (Therapeutic pleural aspiration may be considered in patients who are on mechanical ventilation, preferably under ultrasound guidance after assessing the bleeding risk.)

- Rarely, severe ascites can cause abdominal compartment syndrome. (This should be suspected if the abdomen is very tense even without distension.) Drainage of ascitic fluid, in addition to transfusion of colloids, may be indicated if this causes impairment of venous return or interference with renal function. This can be assessed by measuring the bladder pressure. Consider ascitic fluid aspiration if the bladder pressure is more than 20 mm of water.

Table 8.1 - Management of patients with fluid overload

	Haemodynamically stable	**Haemodynamically unstable**
Low/ Normal PCV	• Restrict fluids, and monitor closely • If no spontaneous diuresis, give IV furosemide 5-10 mg and monitor • You may repeat furosemide if needed	• Transfuse blood with furosemide 5-10 mg given mid-way • This can be repeated
High PCV (Equilibrium phase)	• Restrict fluid • Patient will progress into polyuric phase and PCV will drop with fluid resorption	• Give IV dextran 500 ml bolus with furosemide 5-10 mg mid-way

[9] PLACE OF ADJUNCTIVE THERAPY

9.1 PLATELET TRANSFUSION

Prophylactic transfusion with platelets does not produce sustained changes in platelet count or coagulation status in patients with DHF. It does not change or reduce the bleeding outcome in DHF either. On the other hand, platelet transfusions can lead to fluid overload resulting in pulmonary oedema causing respiratory embarrassment. Therefore, prophylactic transfusion of platelets is not recommended.

However, platelet transfusions may be required in a patient with thrombocytopenia who is to undergo an urgent surgery and has active bleeding which continues despite repeated blood transfusions, DIC or in patients with intracranial haemorrhage.

9.2 FRESH FROZEN PLASMA TRANSFUSION

Like platelet transfusions, prophylactic FFP transfusions do not produce sustained changes in the coagulation status and therefore, do not change or reduce the bleeding outcome in patients with DHF/DSS. FFP transfusions can also lead to fluid overload. In addition, transfusion of blood products may cause anaphylaxis and transmission of blood-borne diseases like HIV, Hepatitis B etc. Therefore, prophylactic transfusion of FFP is not recommended. However, FFP could be useful in a dengue patient with hepatic encephalopathy or with active bleeding despite blood transfusion.

9.3 PROTHROMBIN COMPLEX CONCENTRATE (PCC)

PCC can be used to replace factors II, VII, IX and X. It has the added advantage that it will not contribute to fluid overload, unlike FFP. PCC should only be used in patients with liver failure and active bleeding.

9.4 RECOMBINANT FACTOR VII

There is no evidence to support the use of recombinant factor VII in DHF patients with bleeding due to prolonged shock, DIC or multi-organ failure. Therefore, the use of factor VII as a treatment for bleeding in DHF is not recommended. Recombinant factor VII is useful only in patients who have massive bleeding due to a specific cause such as bleeding peptic ulcer or bleeding from a specific place (e.g., bleeding from the nose) before surgical intervention. This helps to buy time for specific surgical treatments like banding, cauterisation etc. It should be used only if definite plans are there for surgical intervention as the arrest of bleeding with recombinant factor VII is only temporary due to its short half-life.

9.5 STEROIDS AND IV IMMUNOGLOBULIN

There is no evidence to support the use of intravenous immunoglobulin or steroids in the management of dengue patients unless complicated by haemophagocytic lymphocytic syndrome (HLH). Steroid use in the early part of the dengue infection can lead to bleeding.

Therefore, the use of steroids (hydrocortisone, dexamethasone, prednisolone and methylprednisolone) and/or immunoglobulin is not recommended.

9.6 TRANEXAMIC ACID

Bleeding per vagina, either menstrual, intermenstrual or premenopausal can be excessive in DHF. Hence those who have such bleeding may be started on tranexamic acid 500 mg - 1 g eight hourly. Tranexamic acid can also be used together with proton pump inhibitors in gastric bleeding in DHF.

9.7 NORETHISTERONE

Norethisterone may be started together with tranexamic acid or later if the response to tranexamic acid is inadequate. The starting dose is 5 mg TDS and can be increased to 10 mg TDS if needed.

9.8 FUROSEMIDE

Intravenous furosemide 5-10 mg could be used in the following circumstances:

- In fluid-overloaded patients who are haemodynamically stable
- In fluid-overloaded patients who are haemodynamically unstable, the midway point of a colloid bolus or a blood transfusion during the critical phase

Adult dengue patients are very sensitive to furosemide and respond well to small doses. The dose may be repeated if necessary.

Note:

- **Furosemide should not be used in oliguric patients during the critical phase to increase the output.**

9.9 ANTIBIOTICS

There is no evidence to support the prophylactic use of antibiotics in DF or DHF patients with low white blood cell count (WBC). It is also known that low WBC is a very transient phenomenon. By the time the WBC is at its lowest, the marrow is already hyperplastic.

Therefore, there is no place for the use of prophylactic antibiotics during the first 4-5 days of fever if dengue is suspected, even in the presence of pleural effusion or ascites.

Antibiotics should be started in patients with suspected co-infection or with secondary bacterial infections. Cultures should be obtained before antibiotic use whenever possible.

Commonly encountered secondary infections are thrombophlebitis and intra-abdominal gram-negative infections. Therefore, starting flucloxacillin and broad-spectrum antibiotics with gram-negative cover (i.e., cefotaxime) is appropriate in the above conditions respectively.

Empiric use of antibiotics is appropriate for patients with hepatic failure.

[10] HEPATIC INVOLVEMENT IN DENGUE

Liver involvement is common and usually self-limiting in dengue. However, it is also the most significant organ involvement which can lead to a fatal outcome in dengue. Significant liver injury is usually due to prolonged shock or repeated episodes of shock. However, it could occur in the absence of shock at times due to persistent intravascular hypovolaemia (without causing shock) for several hours or rarely due to severe dengue hepatitis.

10.1 CLINICAL FEATURES OF ONGOING LIVER DAMAGE IN DENGUE FEVER

It is well known that irreversible liver damage in dengue could result following liver ischaemia within a few hours without a warning. In the absence of a reliable marker, a high degree of clinical suspicion is needed to detect impending severe liver damage. Features such as rapid clinical deterioration, RHC or epigastric pain (especially new onset), tender hepatomegaly, severe vomiting, tachycardia and tachypnoea are suggestive of impending severe liver damage. The worsening clinical condition of the patient despite adequate fluid resuscitation should alert the physician of the possibility of ongoing liver ischaemia.

10.2 LIVER PROFILE IN DENGUE

- Mild to moderate liver transaminase elevation is seen in most patients with dengue. It is well-recognised that AST(SGOT) is higher than ALT(SGPT) in dengue. There is no need for interventions in these patients especially if they are clinically stable. However, liver function tests should be regularly monitored especially if the fever is persisting or the patient is deteriorating clinically.

- Significant and rapid elevations of transaminases and rising bilirubin are usually due to significant liver damage.

- Very high levels of AST (>1000 U/L) and/or greater elevations of AST compared to ALT (AST >3xALT) in the critical phase of DHF are likely to be due to ischaemic liver damage.

- Early detection of liver ischaemia is challenging as significant transaminase elevations become evident only after several hours of ischaemic liver injury.

10.3 LACTATE LEVELS AS A MARKER OF LIVER ISCHAEMIA

- Raised lactate level is a more reliable marker of liver ischaemia than liver transaminases in dengue.

- Lactate levels preferably should be monitored periodically in all patients with clinical deterioration and haemodynamic instability with or without significantly deranged liver function tests in the leaking phase.

- Raised levels of lactate, above >2 mmol/l should alert the physician of the possibility of significant liver ischaemia which needs urgent attention.

- Clinical deterioration and rising serum lactate levels could be useful in detecting significant liver damage early.

- Lactate levels which remain elevated despite adequate resuscitation is indicative of liver ischaemia.

10.4 HOW TO MINIMISE LIVER DAMAGE DURING THE LEAKING PHASE OF DENGUE

Liver ischaemia though uncommon is also encountered without significant systemic hypotension at times. The objective should be to maintain adequate liver perfusion and oxygenation during the period of leakage.

If liver ischaemia is identified, early and simple interventions like adequate oxygen delivery, adequate volume resuscitation and preventing significant elevations of PCV (e.g., levels above 20%) could prevent serious liver damage.

- Adequate liver perfusion should be a priority in the management of patients with DHF as it is the most significant organ involved that could lead to fatal outcomes.

- Early detection of liver ischaemia during the leaking phase, and maintaining good oxygenation and perfusion could help to minimise liver damage during the leaking phase of dengue.

- In high-risk patients, ALT(SGPT)/ AST(SGOT) and INR should be carried out more frequently (twice a day) during the leaking phase and the results should be followed up without a delay in addition to more careful monitoring to detect significant liver involvement early.

High-risk patients

- Patients with pre-existing CLCD, NAFLD, diabetes mellitus, hypertension, obesity and patients who consume alcohol frequently

- Patients with pre-existing systemic illnesses like COPD, heart failure & CKD

10.5 MANAGEMENT OF LIVER FAILURE IN SEVERE DENGUE ILLNESS

Acute liver failure (ALF) is rare in dengue illness (0.35%) but can be fatal. Acute liver failure is diagnosed when the INR is raised beyond 1.5 in the presence of any grade of hepatic encephalopathy (elevated bilirubin is not essential for diagnosis). Elevated serum lactate levels and acidosis predict mortality in ALF due to dengue. If ALF is allowed to progress this will lead to multi-organ failure. Elevated lactate, ammonia and acidosis will lead to cerebral oedema. General principles of management (see below for details) will include transferring the patient to an intensive care unit and initiating general measures and specific therapies.

10.5.1 General measures in the management of ALF

(A) Circulatory support

- Fluids
  - With ongoing leaking of plasma in DHF, it is important to identify the intravascular volume status and fluid responsiveness. By this time most of the patients would have received a significant volume of crystalloids and/or dextran. If the HCT is high and the recommended dextran volume is not completed, dextran should be given. If the recommended dextran volume is exceeded, 4-5% albumin could be used as the resuscitative fluid especially when serum albumin <3 g/L.

  - As the coagulation is deranged in these patients, FFP and cryoprecipitate may be beneficial.

  - There should be a low threshold for packed cell transfusion, especially if the HCT/PCV is low and if there is a significant drop in HCT/PCV following dextran or if the ***acidosis is not improving with adequate fluid resuscitation***.

  - Avoid hydroxyethyl starch as resuscitative fluid which may worsen coagulopathy and acute kidney injury (AKI) in the presence of ALF.

- Vasopressors and Inotropes
  - Vasopressor support should be considered if the mean arterial pressure (MAP) is <65 mmHg or if the SBP is <90mmHg despite adequate fluid resuscitation. In the setting of severe ALF with worsening encephalopathy higher MAP may be beneficial to target higher cerebral perfusion pressures (CPP).

  - Norepinephrine is the vasopressor of choice. Vasopressin may be added for shock refractory to norepinephrine. Addition of dobutamine is recommended if there is evidence of cardiac dysfunction with a low cardiac output.

(B) Prevention and management of cerebral oedema

The objective should be to prevent cerebral oedema as the prognosis worsens if cerebral oedema sets in.

- All patients with liver failure should be positioned at a 30° inclination by elevating the head end of the bed, and the neck should be kept without rotating (in anatomical neck position) to promote venous drainage of the brain.

- Consider early intubation in patients with hepatic encephalopathy as deterioration may be rapid and also in patients with refractory shock with or without fluid overload.

- Adequate sedation and analgesia with muscle paralysis are needed in patients who are intubated to prevent the rise in intracranial pressure.

- Maintain normoxia (PaO2 >90 mmHg) and normocapnia (PaCO2 should be 35-40 mmHg)

- Use of low PEEP over high PEEP is recommended except in moderate to severe ARDS considering the risks vs benefits of increasing the ICP and preventing the collapse of alveoli.

- Standard drugs used in cirrhosis for hyperammonaemia, such as lactulose and nonabsorbable antibiotics (e.g., rifaximin), can be used in patients with acute liver failure. Ammonia-scavenging agents such as L-ornithine L-aspartate (LOLA) have not been shown to improve survival in ALF.

- Hyponatraemia promotes water entry into astrocytes and should be corrected. When the patient shows deterioration in neurological condition (often pupillary changes), a bolus of mannitol (0·5–1·0 g/kg body weight) or hypertonic (3%) saline 3 ml/kg over 10 min should be administered intravenously. Serum sodium should be preferably maintained around 145-155 mEq/L.

- Hypernatraemia (>155 mEq/L) should be treated with intra-nasal desmopressin.

- Patients should not be warmed, as spontaneous hypothermia to 33–35°C might decrease the incidence of intracranial hypertension. However, fever should be treated actively (tepid sponging etc.).

10.5.2 Acute kidney injury (AKI)

- Renal failure may set in especially due to acute tubular necrosis and functional renal failure similar to hepato-renal syndrome seen in patients with cirrhosis. High bilirubin leading to bilirubin cast nephropathy is also an important cause of AKI.

- Management includes the maintenance of SBP >90 mmHg, pulse pressure >20 mmHg, restoration of mean arterial pressure and renal replacement therapy (RRT).

- Renal replacement therapy should be considered early in these patients as they tend to deteriorate rapidly and also helps in the removal of inflammatory mediators.

- The modality of renal replacement therapy (CRRT, SLED or Intermittent HD) is decided according to the clinical parameters of the patient. CRRT is the preferred choice of RRT in the presence of cerebral oedema as it enables fine-tuning of fluid and electrolyte balance.

- CRRT is considered beneficial in ALF, especially in patients with unstable blood pressure.

- For patients with AKI, in the absence of facilities for HD/ CRRT or if the patient is having persistently low BP, acute peritoneal dialysis (PD) preferably using a flexible coil peritoneal dialysis catheter (which enables smooth functioning of the PD catheter) should be considered. If the patient is in lactataemia, a bicarbonate-based PD fluid should be used instead of the lactate buffer. PD will have the additional benefit of removal of fluid accumulated in the peritoneal cavity during the leaking phase which will improve renal haemodynamics in return. It also has the added benefit of not requiring anticoagulants unlike in CRRT or SLED.

10.5.3 Management of coagulopathy

A low threshold for blood product transfusion in DHF patients with ALF would be appropriate. ROTEM if readily available, may be useful in these patients.

10.5.4 Infections

- Infections are common among patients with ALF and are associated with poor outcomes. Hospital-acquired infections such as pneumonia, urinary tract infections, catheter-associated bloodstream infections and spontaneous bacteraemia should be considered early.

- Empirical broad-spectrum antibiotics (e.g., piperacillin/tazobactam) should be considered in these patients to cover a wide range of organisms. Blood, urine and sputum cultures should be done before starting antibiotics on admission and regularly after admission to the intensive care unit.

10.5.5 Glucose control

Target glucose levels should be 110 mg/dl to 180 mg/dl. Oral hypoglycaemics should be discontinued and short-acting insulin should be used.

10.5.6 Nutrition

Ensure optimal nutrition with a protein target of 1.2-2 g/kg/day (use ideal body weight to calculate). Nasogastric feeding is preferred.

10.5.7 Specific therapies

(A) N-acetyl cysteine (NAC)

NAC has anti-inflammatory, antioxidant, inotropic and vasodilatory properties. NAC is considered to be beneficial only in patients with established acute liver failure with early grades of encephalopathy (grades 1&2).

Dose	150 mg/kg in 250 ml of 5% dextrose	over 1 hour
	50 mg/kg in 500 ml of 5% dextrose	over 4 hours
	150 mg/kg in 1000 ml of 5% dextrose	over 24 hours for a total of 72 hours

Low volumes of the diluent may be considered to avoid fluid overload.

Note:

- **There is no evidence for the use of NAC prophylactically in preventing liver failure in patients with liver dysfunction.**

(B) Therapeutic plasma exchange (TPE)

- DHF patients in ALF, who do not respond to the above therapeutic measures may be considered for TPE.

- This is suitable for patients with preserved renal functions. Both high-volume (3-4 times the patient's plasma) and low-volume (1.5 times the patient's plasma) therapeutic plasma exchange can be used in patients with ALF.

- The procedure may be repeated depending on the improvement of INR and bilirubin after 2-4 cycles.

- Plasma exchange in combination with CRRT may be beneficial in liver failure secondary to dengue.

(C) Continuous renal replacement therapy (CRRT)

CRRT is considered beneficial in ALF, especially in patients with unstable blood pressure and a degree of kidney injury. Early initiation of CRRT could be beneficial in liver impairment associated with dengue as these patients tend to deteriorate rapidly. Indications for CRRT in dengue are different from traditional indications of AKI. CRRT is beneficial in the removal of toxic products of metabolism like ammonia and lactic acid, and helps to correct disturbances of the sodium level. Consequently, this will delay the onset of cerebral oedema which is one of the main causes of death in ALF.

Indications for CRRT in acute liver failure, irrespective of serum creatinine;

- Arterial serum ammonia >150 µmol/L (Arterial puncture is not generally recommended in dengue. If essential, should be done by an experienced medical officer.)
- Established cerebral oedema
- Volume overload
- Oliguria despite adequate volume replacement

[11] HAEMOPHAGOCYTIC SYNDROME (HAEMOPHAGOCYTIC LYMPHOHISTIOCYTOSIS - HLH)

HLH is a rare, aggressive, and life-threatening syndrome induced by aberrantly activated macrophages and cytotoxic T cells, which can occur rarely in dengue patients.

11.1 WHEN TO SUSPECT HLH IN DENGUE

- Persistent fever after 7 days
- Worsening cytopenia after 7 days of fever (thrombocytopenia/ leucopenia/ anaemia) together with clinical deterioration of the patient

In addition, such patients can have;

- Organomegaly (splenomegaly is very common. May also have hepatomegaly.)
- Lymphadenopathy
- Neurologic dysfunction (such as encephalitis, seizures, or coma), oedema, dermatologic manifestations and stigmata of liver dysfunction or coagulopathy (such as jaundice or bruising)

Diagnostic criteria to be fulfilled for HLH (5 of the 8 criteria below)

1. Fever
2. Splenomegaly
3. Cytopenias (affecting at least 2 of 3 lineages in the peripheral blood)
    a. Haemoglobin <90 g/L
    b. Platelets <100 × 10^9/L
    c. Neutrophils <1.0 × 10^9/L
4. Hypertriglyceridaemia and/or hypofibrinogenaemia
    a. Fasting triglycerides ≥3.0 mmol/L (i.e., ≥265 mg/dl)
    b. Fibrinogen ≤1.5 g/L
5. Haemophagocytosis in bone marrow or spleen or lymph nodes without evidence of malignancy
6. Low or no NK cell activity (according to local laboratory reference)
7. Ferritin ≥500 µg/L
8. CD25 (i.e., soluble IL-2 receptor) ≥2400 U/ml

[Source: Henter JI et al. Pediatr Blood Cancer. 2007;48(2):124–31. "HLH2004: Diagnostic and therapeutic guidelines for hemophagocytic lymphohistiocytosis." (doi:10.1002/pbc.21039)]

[11] HAEMOPHAGOCYTIC SYNDROME

Note:

- **In dengue serum ferritin is high. Therefore this criteria is not applicable. Consider ferritin levels more than 10,000 µg/l.**

Other features supporting an HLH diagnosis that are not part of the above HLH-2004 criteria include hyperbilirubinaemia, hepatomegaly, transaminitis (present in the vast majority of patients with HLH) elevated lactate dehydrogenase and D-dimer levels.

Management

HLH has a high mortality rate, especially if there is a delay in commencing treatment. Therefore, prompt treatment is critical. On occasions, despite all five criteria not being fulfilled, HLH may be strongly considered, and HLH-directed therapy may be initiated. The mainstay of treatment is dexamethasone, which is initially given IV 10 mg/m²/day. Once the patient improves, this can be changed to oral and tailed off. In addition, IV immunoglobulin 0.75 g/kg stat followed by 0.4 g/kg for 3 days can be considered. Etoposide is suggested as a rescue therapy.

Use of broad-spectrum antibiotics and adequate fluid therapy is also important in these patients.

[12] MYOCARDIAL INVOLVEMENT IN DENGUE

Global or patchy dysfunction of myocardial contractility may be seen uncommonly in DHF patients without shock and could be due to the direct effect of the virus on the myocardium. This does not warrant any specific treatment and is usually self-limiting. The presence of myocardial dysfunction should not be a hindrance to fluid management in dengue. Myocardial dysfunction can be seen commonly in patients who are in prolonged shock due to metabolic acidosis. Hypocalcaemia (which is a common finding in DHF patients with moderate to large pleural effusions/ascites) may be a contributory factor.

Therefore, empirical treatment with calcium is justifiable in patients with large pleural effusion/ascites. Myocardial involvement is an uncommon finding in dengue (unless following DSS) and is very unlikely to cause death in a patient with DHF. However, such patients could easily develop pulmonary oedema due to fluid overload.

Note:

- **The presence of myocardial dysfunction should not be a hindrance to fluid management in dengue.**

[13] DENGUE IN COMORBID CONDITIONS

Non-communicable comorbidities have been implicated in the development of severe dengue, DHF, and DSS. Dysregulated immune responses, metabolic derangement, and perturbations at the endothelial layer, which have been linked to these comorbid conditions, are likely to play a role in aggravating the heightened immune response and intractable endothelial hyperpermeability seen in severe dengue. Therefore, dengue infections in patients with comorbid conditions can be severe and may even lead to death if they are not managed properly during the early febrile phase. Making an early diagnosis of dengue illness in such patients can be challenging. Thus, the possibility of dengue should be considered early, and close monitoring is important in such patients.

13.1 DIABETES MELLITUS (DM)

Patients with DM and hyperglycaemia are more prone to develop severe dengue compared to patients with normoglycaemia. In patients with both type 1 and type 2 diabetes mellitus, the risk of plasma leakage is increased, probably due to pro-inflammatory cytokine overload and co-existing fatty liver.

Frequent monitoring of blood sugar is important from the time of admission. Patients who are on oral antidiabetic drugs, pre-mixed insulin, or long-acting insulin should be switched to short-acting insulin. Blood sugar level should be maintained preferably below 180 mg/dl. The patient should be closely observed for the possible development of diabetic ketoacidosis, where the patient will need more IV fluid, insulin as an infusion, and monitoring of central venous pressure if possible.

Patients with diabetes mellitus can be polyuric even during shock due to hyperglycaemia. Hence, urine output may not be a good guide to the volume status of such a patient.

Acidosis could be due to both the shock and the ketones, and may not reflect the severity of the shock.

13.2 LIVER DISEASE

Baseline liver function tests (LFT), including prothrombin time (PT), are of value when dengue is suspected in patients with chronic liver disease. If AST/ALT is very high, the patient is likely to develop neurological involvement (hepatic encephalopathy), especially those with gastrointestinal (GI) bleeding. In such patients, the liver failure regimen should be used early (refer to section 10.5). If the baseline albumin level is low, these patients may have more plasma leakage.

Managing these patients should be done with a minimum but adequate amount of IV fluids to maintain intravascular volume to prevent further liver damage without causing fluid overload. Prolonged PT or INR (>1.3) indicates that the patient has a tendency to bleed and therefore IV vitamin K is recommended. In addition, assessment of the degree of bleeding and transfusing an adequate amount of blood and blood components are important considerations.

13.3 HEART DISEASE

The key consideration in patients with heart disease would be to identify the underlying heart disease and the current medication. These patients should be observed with close and continuous monitoring, especially during the critical phase. Careful adjustment of IV fluids is the key to success and to prevent complications. Those who are on antiplatelet or anticoagulation therapy are recommended to stop these medications for a few days, especially when the platelet count drops below 130,000 /mm^3. If they have been on long-term diuretics, antihypertensives (including beta blockers), and statins, those should be continued.

With the bleeding diathesis and thrombocytopenia in dengue, it would be extremely rare to have a myocardial infarction in a dengue patient due to coronary artery thrombosis.

13.4 RENAL DISEASE

The baseline renal function tests (blood urea, creatinine, glomerular filtration rate, electrolytes, UFR) and acid-base balance should be assessed during the early febrile phase, and regularly monitored during the illness.

Their usual medication, including diuretics, should be continued. Antiplatelets and anticoagulants should be discontinued when the platelet count is <130,000 /mm^3. Close monitoring of fluid intake and urine output is very important.

The recommended usual fluid intake for an anuric or oliguric patient should be taken as the maintenance fluid requirement for these patients during the dengue illness as well. Judicious fluid replacement during critical and convalescent phases is crucial in these patients to prevent fluid overload and related complications while maintaining adequate intravascular volume.

Early consultation with a nephrologist and early planning of renal replacement therapy in those patients who are oliguric with signs and symptoms of fluid overload is important.

13.5 HYPERTENSION

Hypertension is a risk factor for severe dengue. DF patients with pre-existing hypertension are more likely to progress to DHF. Therefore, close monitoring is important from an early phase of the disease.

Hypertension may mask the cardiovascular response in shock. The blood pressure that is perceived to be normal may be low for these patients. Therefore, the patient's baseline blood pressure should be considered when interpreting measured blood pressure in these patients. A drop of 30 mmHg in systolic blood pressure should be considered as shock in patients with high baseline blood pressure.

The patients should continue their antihypertensive medication which they take regularly, unless there is a drop in their blood pressure.

[14] TRANSFERRING A PATIENT TO ANOTHER INSTITUTE

Facilities in some peripheral hospitals may not be adequate to manage a patient with DHF who has entered the critical phase. A patient whose platelet count goes below 100,000 /mm^3 should be managed in a unit under the supervision of a consultant physician. Furthermore, a patient in prolonged shock needs to be managed in an intensive care unit. Hence, such patients may be transferred to an institution with adequate facilities. The decision to transfer should be made by the consultant or the medical officer in charge of the unit.

If the patient has signs of shock (i.e., tachycardia, low blood pressure, pulse pressure < 20 mmHg, and cold extremities, etc.), a normal saline bolus of 10 ml/kg over one hour (for an average adult – 500 ml) is recommended before referral. Check capillary blood sugar (CBS) for hypoglycaemia and correct it with oral or IV dextrose before referral. IV fluids and oxygen inhalation should be continued during the transfer.

Every such transfer should be done after obtaining advice from the consultant physician who will be receiving the patient and after resuscitating per the advice. If a patient in the critical phase is transferred, the patient should be accompanied by a medical officer and a nursing officer and should be monitored continuously.

Proper resuscitation before transferring is especially important if the journey is going to take a long time. Adequate information regarding the patient should be provided in the transfer form, and this should include daily fluid balance, regular HCT results, other investigation results, and treatment given. Also, it is important to send copies of the temperature and monitoring charts.

[15] DISCHARGE

The following criteria should be fulfilled when discharging a patient.

Table 15.1 - Discharge criteria

- No fever for at least 24 hours without the usage of antipyretic drugs
- A minimum of 24 hours after the completion of the critical phase with stable haemodynamic parameters
- At least two days have lapsed after recovery from shock
- Good general condition with improving appetite
- No distress from pleural effusions
- No tense ascites
- Stable HCT around baseline value or around 38-40% when baseline value is not known
- Improving trend of liver enzymes
- Rising trend of platelet count with the latest count preferably above 50,000 /mm^3
- No other complications

15.1 ADVICE ON DISCHARGE

- If fever recurs, or if the patient feels generally unwell, has breathing difficulty or nausea and vomiting, the patient should seek medical attention immediately.
- A follow-up visit is advised with the relevant blood investigations.
- Once discharged, the patient can have a normal diet, usual amounts of liquid, and carry out normal day-to-day activities.
- Complete bed rest is not required. However, strenuous physical activity should be avoided for 1 week in patients who have had uncomplicated dengue fever or uncomplicated DHF, and for 2 weeks in patients who have had complicated DHF.
- Generalised fatigue may be present and continued for a few weeks, but it generally resolves on its own.
- Some people can experience transient hair loss.
- Medications previously taken for long-term illnesses such as diabetes mellitus and hypertension should be continued unless advised otherwise.
- The patient no longer carries the dengue virus and therefore cannot transmit it to another person.
- The patient may have acquired the infection from the household or work environment; therefore, it is important to clean the environment frequently and regularly.
- If the other members of the household develop a fever, the possibility of dengue fever should be considered.

[16] OUTBREAK RESPONSE PLAN FOR HOSPITALS

There have been an increasing number of dengue outbreaks in many parts of the country. Therefore, having a hospital emergency response plan for dengue outbreaks is vital in early diagnosis and appropriate clinical management of cases to minimise complications and deaths.

Such a plan should include the following key elements:

- Outpatient care (with triage and resuscitation areas)
- Assess bed occupancy in each unit (to identify additional beds during outbreaks)
- High-dependency care beds
- Staffing and surge capacity needs
- Stock management of essential medicines and supplies
- Laboratory facilities
- Keeping the hospital premises free of mosquito breeding places

As the first step, with the available resources, hospitals should develop and strengthen their capacity to screen and triage suspected dengue patients in the outpatient departments.

Hospital staff, including doctors, nurses, and other categories, should be trained and assigned specific responsibilities in case of an outbreak. It is essential to conduct regular training for medical staff based on the current guidelines on clinical management of dengue fever and dengue haemorrhagic fever.

Following essential medicines, supplies, equipment, and services should be available in the hospitals providing in-ward care for patients with dengue haemorrhagic fever during an outbreak.

Medicines:

- Paracetamol tablets
- Domperidone tablets
- Oral rehydration solution
- IV fluids– crystalloids: 0.9 % saline
- Colloids: hyper-oncotic (plasma expanders) – 10% dextran 40 and 6% starch
- Dextrose - 25% or 50%
- IV vitamin K
- IV calcium gluconate (10% solution)
- IV KCl (20 or 40 mmol concentrated solution)
- IV sodium bicarbonate (8.4% solution)

Supplies and equipment:

- Thermometers
- Sphygmomanometers
- IV canulae and infusion sets
- Burette sets
- Oxygen delivery systems
- Microhaematocrit machine and capillary tubes (for bedside haematocrit assessment)
- Glucometers (for blood sugar estimation)
- Observation charts
- Ultrasound machines

Laboratory support:

Laboratories should be equipped around the clock for basic tests such as FBC, haematocrit, platelet count, white blood cell count (WBC), and differential counts.

More complicated patients will need blood sugar, liver function tests, renal function tests, serum electrolytes (including serum calcium), blood gases, and coagulation assays.

Blood bank:

Packed red cells and other blood products should be available on demand.

Keeping the hospital premises free of mosquito breeding places:

It is crucial to keep hospital grounds free of mosquito breeding sites, as hospitals treat many patients with dengue. An increase in the density of *Aedes* mosquitoes could lead to a higher risk of virus transmission to these mosquitoes, potentially impacting both staff and other patients. Therefore, hospitals should nominate a responsible person (such as a Medical Officer Public Health/ PHI) to implement regular cleaning and monitoring mechanisms to ensure that the environment remains mosquito-free.

[17] NOTFICATION

- Notification of suspected dengue patients is crucial for dengue prevention and control, as early detection of cases will help prevent further spread in the community.
- Therefore, clinicians must notify suspected dengue cases (Surveillance Case Definitions for Notifiable Diseases in Sri Lanka, 2005) through the notification system using the web-based National Dengue Surveillance System (NaDSys) and the 'Notification of Communicable Diseases' form (document number - H544).
- The notification of dengue patients enables public health officials to take control and take preventive action. Each suspected dengue case is investigated by the Range Public Health Inspector (PHI), who investigates the case and takes immediate control and preventive measures.
- Immediate control and preventive measures include referring fever patients among family members and the community for treatment, inspecting and eliminating potential breeding sites, and taking other vector control measures such as chemical larval control and space spraying (fogging).
- Further, the investigated reports are received by the Medical Officer of Health (MOH)/ Additional Medical Officer of Health (AMOH), Supervising PHI (SPHI), at the district level and central level, who utilise this data for action in prevention and control, as well as disseminate it to relevant stakeholders for information and action. Therefore, the notifications should be complete (notification of all cases), timely, and accurate.
- Notification should be done by all clinicians treating any suspected dengue patient in the public and private sectors.
- Additionally, if a large number of patients from the same area seek treatment within a short period, it may indicate a dengue outbreak. In such instances, the public health officials of the area (MOH/AMOH & PHI) should be promptly informed.
- In over 180 hospitals, including all major government hospitals (National, Teaching, District General, Base Hospitals), major private hospitals, and the military and police hospitals, the notification system is linked to NaDSys.
- NaDSys is a web-based, real-time surveillance systemthat receives notifications and field investigation information for upload. It enables timely action for control and prevention, as well as the timely dissemination of information.

[18] FURTHER READING

18.1 MOLECULAR AND IMMUNOLOGICAL DIAGNOSIS OF DENGUE

The dengue virus (DENV) initially infects the keratinocytes and other immune cells in the dermis at the time of inoculation by an infected mosquito and subsequently results in viraemia that infects many immune cells, such as monocytes, macrophages, and dendritic cells, hepatocytes, keratinocytes, and possibly endothelial cells. The onset of symptoms usually coincides with the peak viraemia, after which the viraemia declines due to the rapid clearance of the virus from the host's immune system. Therefore, the diagnosis of dengue would depend on the days from the onset of illness and whether a person has a primary or secondary dengue infection.

During the viraemic phase, dengue can be diagnosed by detecting the virus or NS1 antigen. Once the viraemia declines, diagnosis of dengue is carried out by detecting DENV-specific antibodies, which can be difficult to interpret in certain circumstances. The different diagnostic tests and their usefulness and interpretation at different stages of the illness are described below.

18.1.1 Detection of dengue NS1 antigen

Dengue NS1 antigen is a secretory protein that circulates independently of the virus during acute infection. The detection of NS1 antigen can be performed using a rapid antigen test, or an NS1 ELISA. The NS1 ELISA has a higher sensitivity to detect the NS1 antigen than the rapid antigen tests, which are point-of-care (POC) tests. The overall sensitivity of the rapid NS1 antigen test varies from 58.4% to 62.4%, while the sensitivity for primary dengue is higher (80.3% to 89.5%), with lower values for secondary dengue (43.4% to 56.3%), due to earlier clearance of the virus (and NS1). Sensitivity has also been shown to be lower for DENV2 (<50%). The sensitivity drops below 50% after day 3 of illness and due to the limited sensitivity of the NS1 antigen test in secondary dengue, and in some serotypes, a negative NS1 even in early illness does not exclude dengue. However, in some patients, the NS1 antigen test can be positive even in later stages of illness (days 7 to 9). False positives are very rare and may occur in acute Zika virus infection or certain haematological malignancies.

As the NS1 antigen levels are highest in early illness, the likelihood of the test becoming positive declines with time. Highest positivity rates occur in the first 24 to 48 hours. The selection of tests at different stages of illness is shown in Table 8.

Table 18.1 - Investigations at different stages of illness

Type of test	Day of illness		
	Day 1 to 3	Day 4 to 7	Day 8 to 10
NS1 Ag test (rapid)	High positivity rate (negative test does not exclude dengue).	Positivity rate declines.	Many are unlikely to be positive.
NS1 Ag test (ELISA)	High positivity rate (negative test does not exclude dengue).	Positivity rate declines, but higher than rapid antigen tests.	Very few patients are likely to be positive. Sensitivity is higher than rapid antigen tests.
Quantitative real-time PCR for dengue	High positivity rate. Sensitivity is higher than NS1 Ag tests (negative test does not exclude dengue).	Although positivity rates decline, higher sensitivity than NS1 Ag tests.	Some patients may still be positive.
Dengue IgM and IgG antibodies (rapid)	Unlikely to be positive. IgG may be positive during early secondary dengue.	Some patients are likely to be positive. IgG is likely to be positive, with a negative IgM, in most patients with secondary dengue. Negative result does not exclude dengue.	Most patients are likely to be positive. IgM may still be negative in patients with acute secondary dengue. A positive IgM alone is most likely to indicate a primary dengue infection, although it is not a confirmatory test.
Dengue IgM and IgG antibodies (ELISA)	Results are similar to rapid antibody tests, but more sensitive.	Results are similar to rapid antibody tests, but more sensitive.	Results are similar to rapid antibody tests, but more sensitive. A ratio of >1.2 indicates a primary dengue infection.

18.1.2 Detection of the dengue virus

The DENV can be detected in early illness, usually in the first 5 days since the onset of symptoms, by PCR. Quantitative real-time PCR is especially sensitive and can be used to simultaneously identify the infecting DENV serotype. Quantitative real-time PCR is far more sensitive than NS1 detection, and tests can be positive sometimes even in late illness. Although the virus can also be detected by virus isolation, this is cumbersome and is usually only used in research settings.

18.1.3 Detection of dengue virus-specific antibodies

DENV-specific IgM and IgG can be detected either by rapid tests or by ELISA. In a primary dengue infection, DENV-specific IgM is usually detectable after day 5 of illness and is followed by an IgG response. In a secondary dengue infection, due to the presence of DENV-specific IgG antibodies to the previous infecting serotype, the IgG antibodies can sometimes be detected as early as day 3 and rise rapidly. However, in a secondary dengue infection, the IgM antibodies usually rise later and due to the lower levels produced, compared to a primary dengue infection, may even be negative. Therefore, a primary and secondary dengue infection is usually identified by the IgM: IgG ratio in an ELISA. In a primary dengue infection, the IgM: IgG ratio is more than 1.2, based on the WHO guidance document, although these ratios would depend on the time of sample collection.

The positivity of dengue-specific IgG alone tested by diagnostics used for acute dengue, indicates a recent infection or an early acute secondary dengue infection and does not indicate a past infection. The threshold of the tests (rapid antibody tests or the ELISAs) that are used to detect dengue antibodies in acute infection has been set at a higher level so that they do not give a positive result for past infection. For the detection of past infections, a different type of ELISA with a lower threshold is used. These tests are used for epidemiological serosurveys.

Unlike the dengue NS1 Ag test and virus detection, detection of DENV-specific IgM or IgG does not confirm an acute dengue infection due to the wide cross-reactivity with other flaviviruses. Acute infection with many other flaviviruses, such as Japanese encephalitis, West Nile virus, and Zika, which have all been reported in Sri Lanka, can give rise to cross-reactive antibodies, which will give a positive result with dengue-IgM and IgG tests (ELISA and rapid tests).

The rapid diagnostic tests for the detection of IgM and IgG have low sensitivity, and a negative test does not exclude a recent dengue infection.

18.2 MEASURING HAEMATOCRIT

Haematocrit can be measured in two ways: either by the spun method or by calculation.

Spun haematocrit (spun HCT)

Spun HCT refers to the direct measurement of haematocrit using centrifugation. Blood is collected in a capillary tube and spun in a centrifuge, separating the blood into its components: red blood cells (RBCs), plasma, and the buffy coat (white blood cells and platelets).

The proportion of the blood volume occupied by RBCs is measured directly as the haematocrit. This method is highly reliable and accurate since it physically separates the components of blood.

Advantages:

- Direct and simple measurement
- Accurate in detecting changes in blood volume and RBC count

Limitations:

- Requires manual handling, which can introduce variability if not performed properly
- Some training is required
- Affected by conditions like dehydration or poor sample collection (e.g., improper anticoagulation)

Calculated haematocrit (calculated HCT)

Calculated HCT is derived using automated analysers, based on the following formula:

$$\text{HCT} = \frac{\text{RBC count} \times \text{Mean Corpuscular Volume (MCV)}}{10}$$

In this method, the RBC count and the MCV (the average volume of individual red blood cells) are determined using advanced laboratory equipment, and the haematocrit is calculated mathematically.

Advantages:

- Quick and automated, minimising human error
- Consistent, as it is integrated into most automated blood analysers in modern laboratories

- Requires less manual handling of blood, reducing risks of contamination or errors

Limitations:

- May be less accurate in cases where RBC morphology is abnormal (e.g., in anaemias or other blood disorders)
- Agglutination of red cells can falsely decrease the calculated HCT
- Time-consuming in our setting as labelling of the sample, transportation, testing and getting the report back takes time
- Spun HCT tends to be more accurate in terms of reflecting the actual packed cell volume (PCV), while calculated HCT relies on the precision of other indices and may introduce minor discrepancies, especially in abnormal blood conditions.

Due to the above reasons, we advocate doing the spun haematocrit in-ward for dengue patients. However, if this cannot be done, calculated haematocrit should be obtained without a delay from a blood sample sent to the laboratory. As there can be differences in readings of the two methods, it is recommended that one method is used as much as possible.

18.2.1 Measuring haematocrit using the spun method (using a microhaematocrit machine)

Equipment and supplies

In the trolley:

Upper tray

- Anticoagulant whole blood in EDTA
- Clay sealer
- PCV reader (card or Hawksley model)
- Microhaematocrit machine
- Pair of clean gloves
- Capillary tubes
- Tissue paper

Lower tray

- Sharps container
- Clinical waste bin
- Refuse bin

Table 18.2 - Procedure of measuring haematocrit using the spun method

Steps of the procedure	Rationale
Wash hands and dry	To minimise contamination due to microorganisms
Wear clean gloves	
Mix the sample thoroughly by inverting it gently, at least five times.	To avoid red cells settling towards the bottom. If red cells settle in the bottom, there is a risk of an incorrect reading.
Open the blood sample and place the capillary tube in it. Tilt the sample to about 30 degrees.	To assist in filling the tube according to the pressure gradients.
Once the tube is about ¾ full, place your index finger over the open end before removing it from the blood sample.	This helps to prevent air bubbles from forming in the other end of the tube and avoid leaking.
Wipe the outside of the capillary tube, with a piece of tissue.	
Seal the end that was placed in the sample by pressing it into the clay sealer.	
Unscrew and open the metal cover of the centrifuge tray of the microhaematocrit machine.	
Fill two tubes and place both tubes in the centrifuge tray grooves directly opposite one another.	That will help to ensure the centrifuge is balanced.
Ensure the clay seals are towards the outside.	
Screw the lid (plate) of the centrifuge tray firmly.	
Close and secure the centrifuge lid.	
Set the time to 3 minutes, then start the centrifuge machine.	
Once the centrifuge has come to a complete stop, open the lid and remove the metal cover.	

[18] FURTHER READING

Reading

- Once the centrifuge tray has completed its spin, remove a capillary tube, and examine it visually.
- Place the capillary tube either onto a reader order or into the tube holder on a Hawksley, haematocrit reader.
- Align the bottom of the RBC column with the 0% line and the top of the plasma column with the 100% line.
- The measurement is taken at the top of the RBC column and is expressed as a percentage %.
- Repeat the second tube for quality control processes, each reading should be within 1% of the average.

Documentation

- Documentation should be done in the relevant chart.

Aftercare of the used instrument

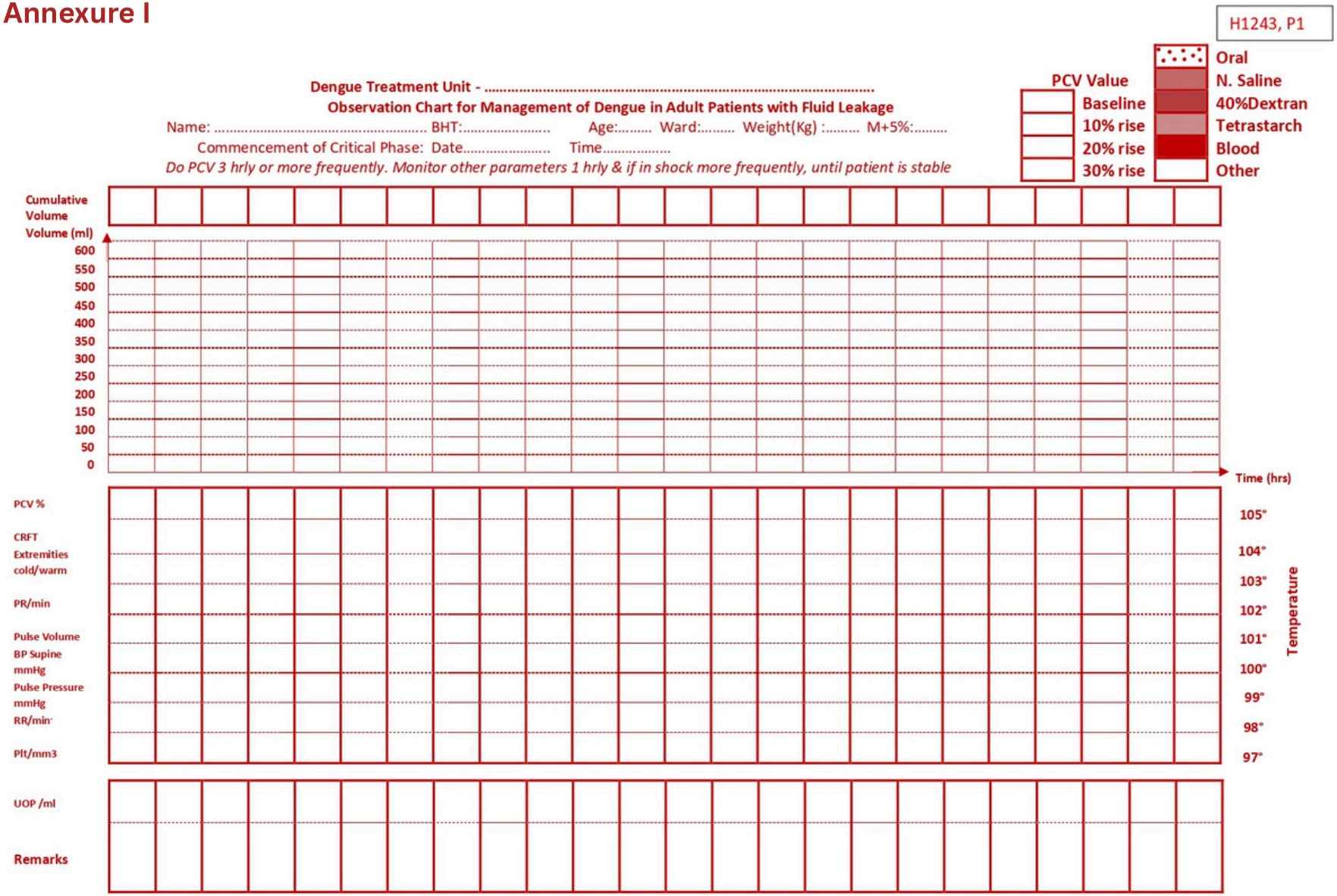
- Dispose of any glass in a sharps bin.
- Clean any equipment contaminated with blood – e.g., disinfectant wipe (H_2O_2 or surgical spirit).
- Clean inside the centrifuge tray with a disinfectant wipe.
- Return all equipment to its storage container.

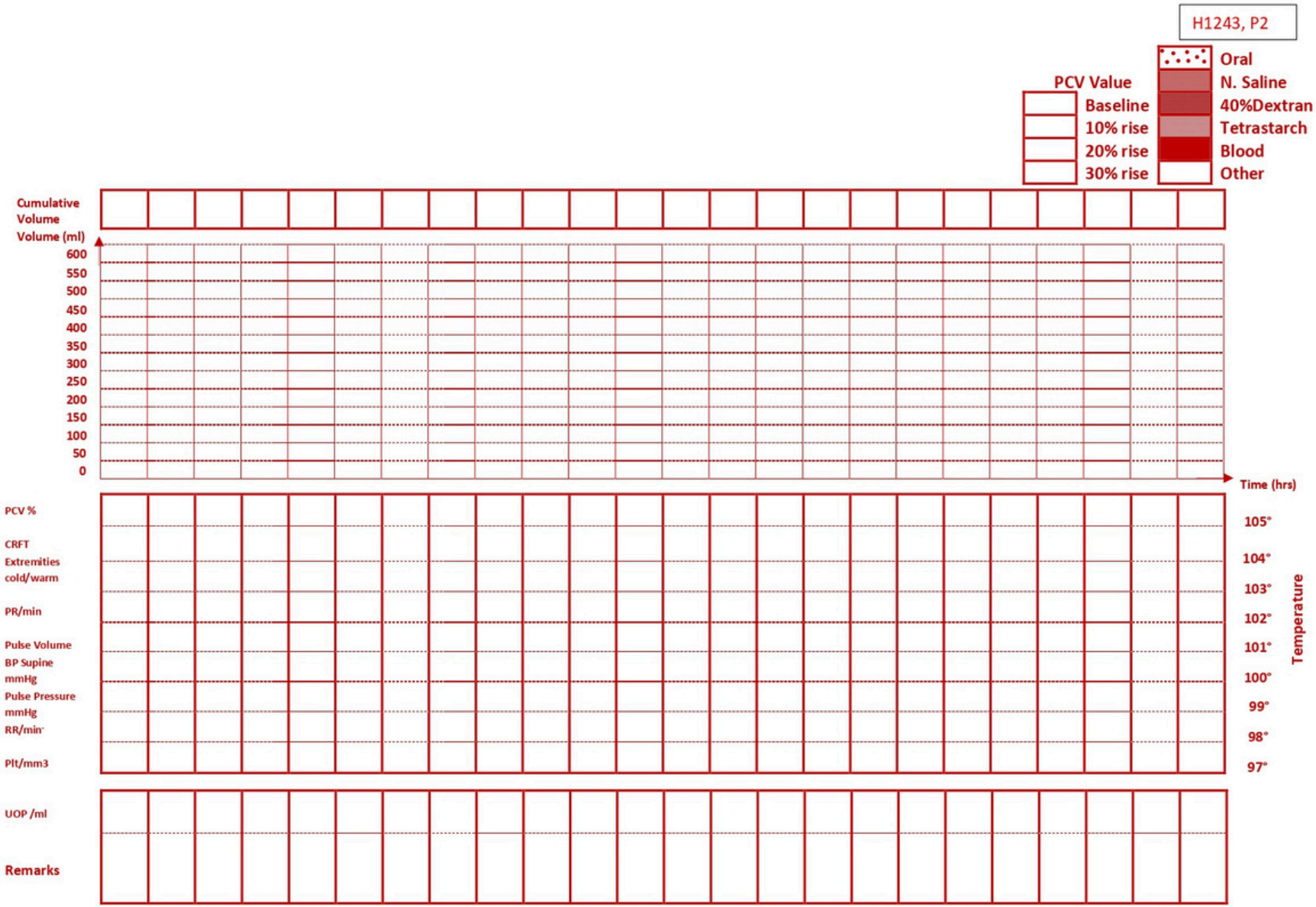
Note:

- **When performing more than one test, the nurse must maintain a chart, including the name of the patient and centrifuge tray number. There are 1 – 24 numbered slots in a centrifuge tray.**

Ensure all the steps in the user manual are followed carefully, to improve operational safety and to prevent erroneous reading.

Annexure I


H1243, P1
Dengue Treatment Unit - .....
Observation Chart for Management of Dengue in Adult Patients with Fluid Leakage
Name: ..... BHT:..... Age:..... Ward:..... Weight(Kg) :..... M+5%:.....
Commencement of Critical Phase: Date..... Time.....
Do PCV 3 hrly or more frequently. Monitor other parameters 1 hrly & if in shock more frequently, until patient is stable
PCV Value
Baseline
10% rise
20% rise
30% rise
Oral
N. Saline
40%Dextran
Tetrastarch
Blood
Other
Cumulative Volume
Volume (ml)
600
550
500
450
400
350
300
250
200
150
100
50
0
Time (hrs)
PCV %
CRFT
Extremities cold/warm
PR/min
Pulse Volume
BP Supine mmHg
Pulse Pressure mmHg
RR/min
Plt/mm3
105°
104°
103°
102°
101°
100°
99°
98°
97°
Temperature
UOP /ml
Remarks


H1243, P2
PCV Value
Baseline
10% rise
20% rise
30% rise
Oral
N. Saline
40%Dextran
Tetrastarch
Blood
Other
Cumulative Volume
Volume (ml)
600
550
500
450
400
350
300
250
200
150
100
50
0
Time (hrs)
PCV %
CRFT
Extremities cold/warm
PR/min
Pulse Volume
BP Supine mmHg
Pulse Pressure mmHg
RR/min
Plt/mm3
105°
104°
103°
102°
101°
100°
99°
98°
97°
Temperature
UOP /ml
Remarks

Annexure II

Dengue Treatment Unit -..... **H,1242, P1**

Observation Chart for Management of Dengue in Adult Patients-Without Evidence of Fluid Leakage

Monitoring should be started at a Platelet Count of <130,000/mm³(and if decided by treating physician even at a higher count)

Instructions-Do FBC daily /bd and PCV 6hrly. Monitor other parameters 3 hourly.

Name of patient : .....
Age .....
Date & Time of admission :.....
Duration of fever :.....
Baseline PCV % :.....

BHT No :.....
Ward :.....
Weight :.....

Indications to call for immediate advice
i) Pulse rate > 120/min with fever or >100/min without fever
ii) Pulse Pressure 25mmHg or less (In supine position)
iii) Postural drop of SBP >20mmHg.
iv)Significant bleeding (Haemetemesis, Malaena, Bleeding PV etc.)
v) UOP <O.5ml /Kg/hr
vi) CRFT > 2 sec
vii)PCV rise of >IO% from the baseline.

Date / Time	PR Min⁻	Bp Supine (mmHg)	Pulse Pressure (mmHg)	Bp Sitting (mmHg)	CRFT Sec⁻	RR Min⁻	PCV%	WBC / PLT	Date & Time	Kind of Fluid	IV *ml*	Oral *ml*	Total	UOP *ml*	Remarks + V/D/B*

* **Vomiting/Diarrhoea/Bleeding**

Date / Time	PR Min⁻	Bp Supine (mmHg)	Pulse Pressure (mmHg)	Bp Sitting (mmHg)	CRFT Sec⁻	RR Min⁻	PCV%	WBC / PLT	Date & Time	Kind of Fluid	IV *ml*	Oral *ml*	Total	UOP *ml*	Remarks + V/D/B*

Annexure III

FEVER CORNER-Out Patient Department

Name..... **Age**..... **OPD No**..... **Weight**.....

Risk factors: DM/HTN/IHD/Stroke/Obesity/Pregnancy/
Use of NSAIDs/Antiplatelet/Anticoagulants/Steroids

Date & Time	Fever Day	Fever	Pulse Rate (min)	Blood Pressure (mmHg)	UOP (ml)	WBC	Plt	PCV	Giddiness	Vomiting	Diarrhoea	Abdominal pain	Bleeding	Severe Headache	Menstrual state	Remarks

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