DENGUE CASE MANAGEMENT

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To begin the module press here

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Objectives

- To improve recognition and diagnosis of dengue cases and provide appropriate care to patients.
- To identify severe dengue and carry out more focused close monitoring and prompt appropriate management.
- To provide guidance on appropriate and timely fluid management and the use of blood and blood products.
- To improve on early and accurate notification of dengue cases for prompt public health intervention

MENU

- There is no specific treatment of Dengue Infection.
- The treatment is only supportive and symptomatic and the management aim is not to miss the complications of critical phase if they occur.

- This module is developed in accordance with the regional resources, best practices and with the aim to create uniformity in care by knowing the clinical course of the disease, case definitions, differential diagnosis, identifying complication in each phase of the disease and how to recognize the warning signs, plasma leakage and early shock and to apply correct treatment to dengue patients.
- At the same time tools are provided for the managers to monitor the care of patients in the health care facilities and how to prepare for Dengue outbreaks management in the hospitals.

Acute Febrile Illnesses

- With the addition of other viral infections to the list of causes of acute febrile illness the importance of knowing some basics about each one of these is becoming a constant need for the frontline clinical staff.

Introduction

- Dengue is a viral infection caused by the enveloped ssRNA Dengue Virus from the flaviviridae family of the viral hemorrhagic fevers.
- Dengue virus has 4 serotypes
- Incubation period is 3-14 days
- Dengue infection with its variety of clinical presentations and with the risk of increased morbidity if not managed properly is actually working as a litmus test of the health system of a region, with the increasing awareness in the general public any mismanagement is quickly picked and highlighted with its sequellae.

A CHANGING CLIMATE DRIVES A GRADE 3 EMERGENCY

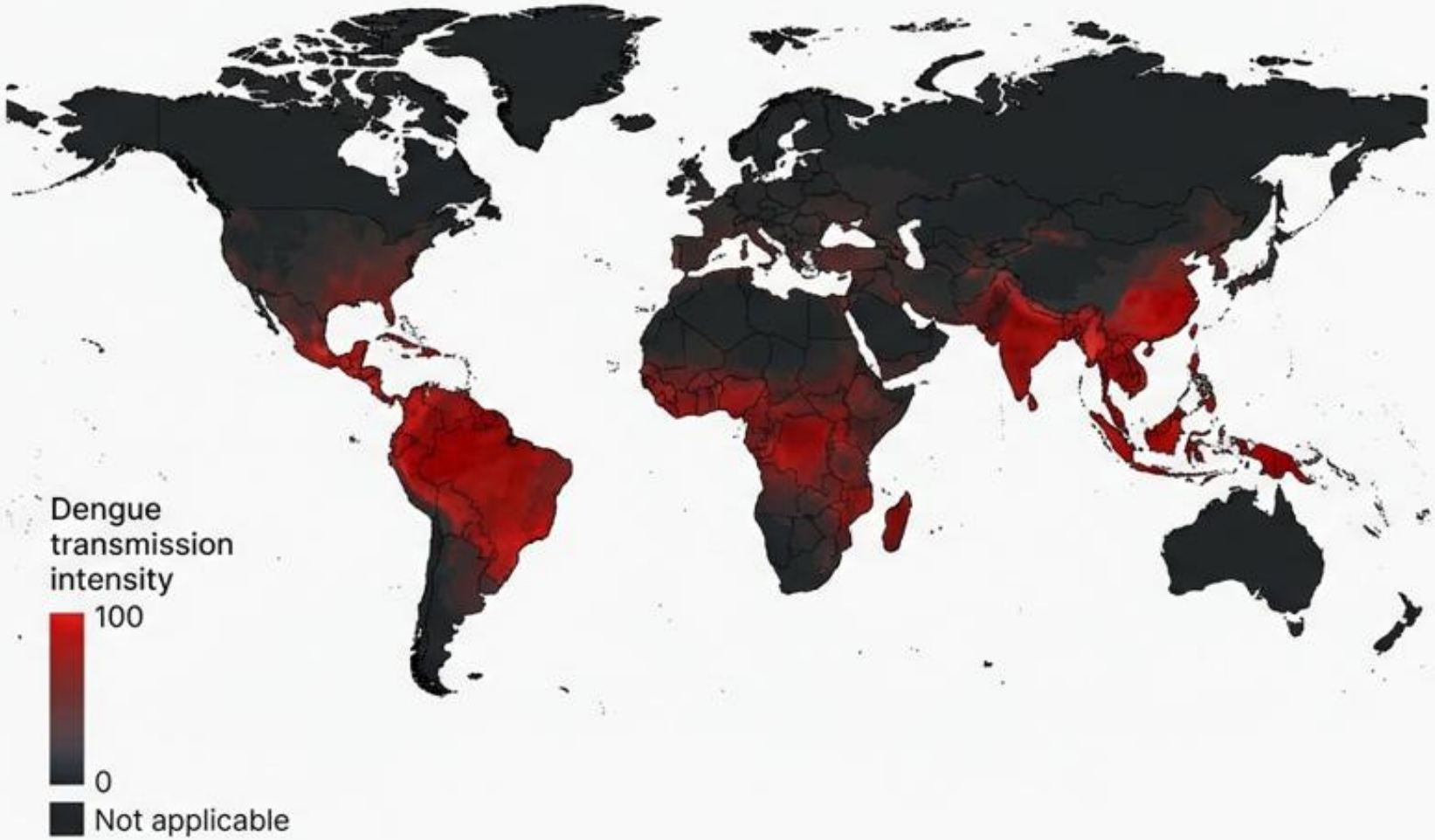
3.6 MILLION+
Infections reported early 2025

2,000+
Deaths recorded

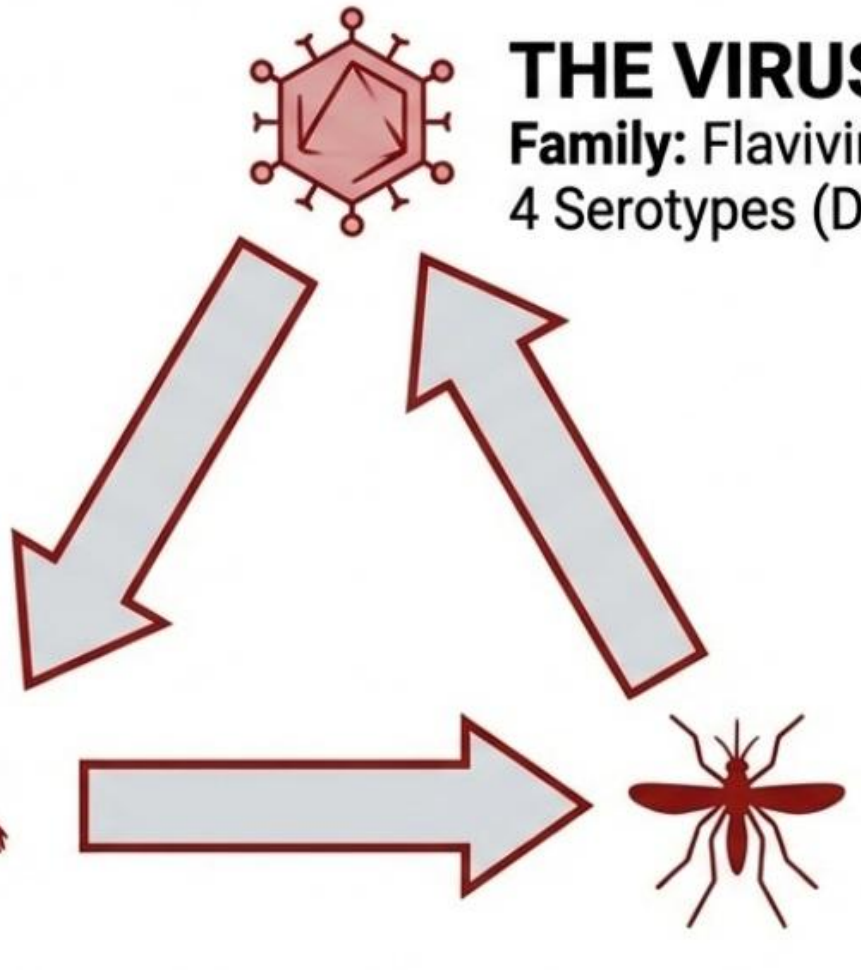
CLIMATE CATALYST
Vectors expanding +6.5m elevation annually

Poleward shift of 4.7km per year

NEW FRONTIERS
Local transmission verified in France, Italy, Spain



THE TRANSMISSION TRIAD



THE VIRUS

Family: Flaviviridae.
4 Serotypes (DEN-1 to DEN-4).

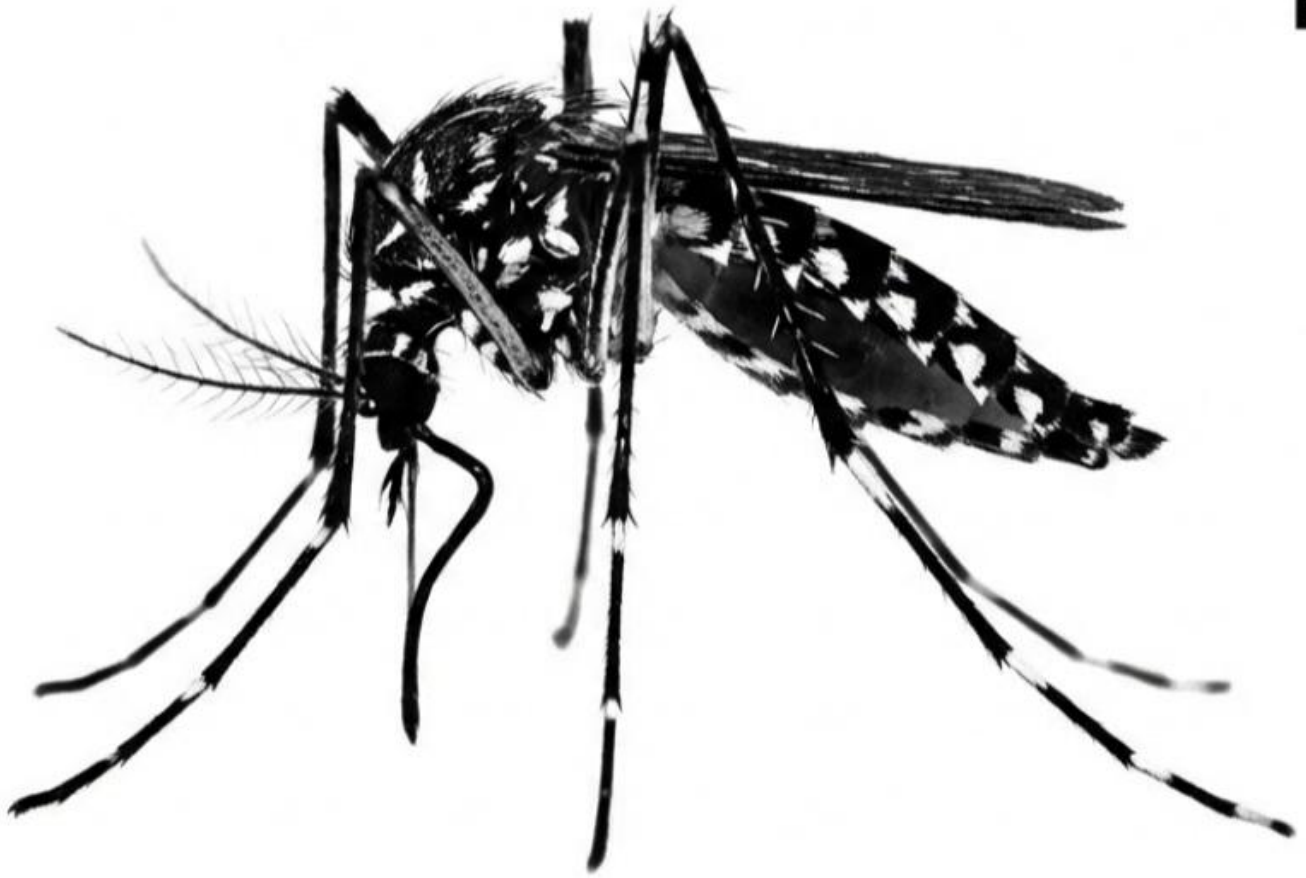
THE HOST

Humans as amplifying hosts. Viraemic travellers as couriers.

THE VECTOR

Primary: *Aedes aegypti* (Urban).
Secondary: *Aedes albopictus* (Cold-tolerant).

THE VECTOR: *AEDES AEGYPTI*



Biological Profile

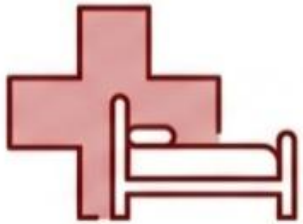
- **HABITAT:** Highly anthropophilic. Lives indoors/urban areas.
- **FEEDING:** Daytime feeder. Multiple bites per meal.
- **BREEDING:** Artificial water containers. Eggs viable for months without water.
- **RANGE:** Limited by 10°C winter isotherm (35°N to 35°S).

The socioeconomic impact

- Studies on the cost of dengue were conducted in eight countries in 2005-2006: five in the Americas and three in Asia. As dengue also affected household members who helped care for the dengue patient, an **average episode represented 14.8 lost days for ambulatory patients and 18.9 lost days for hospitalized patients**. The overall cost of a non-fatal ambulatory case averaged US$ 514, while the cost of a non-fatal hospitalized case averaged US$ 1491, almost three times the cost of an ambulatory case.

- These conservative estimates ignore not only the underreporting of cases but also the substantial costs associated with dengue surveillance and vector control programs.

THE HIDDEN COST OF INFECTION



528 DALYs

lost per million population.

Burden in Latin America equals Malaria + TB + Helminths combined.

High hospitalization rates among children.

3X COST:

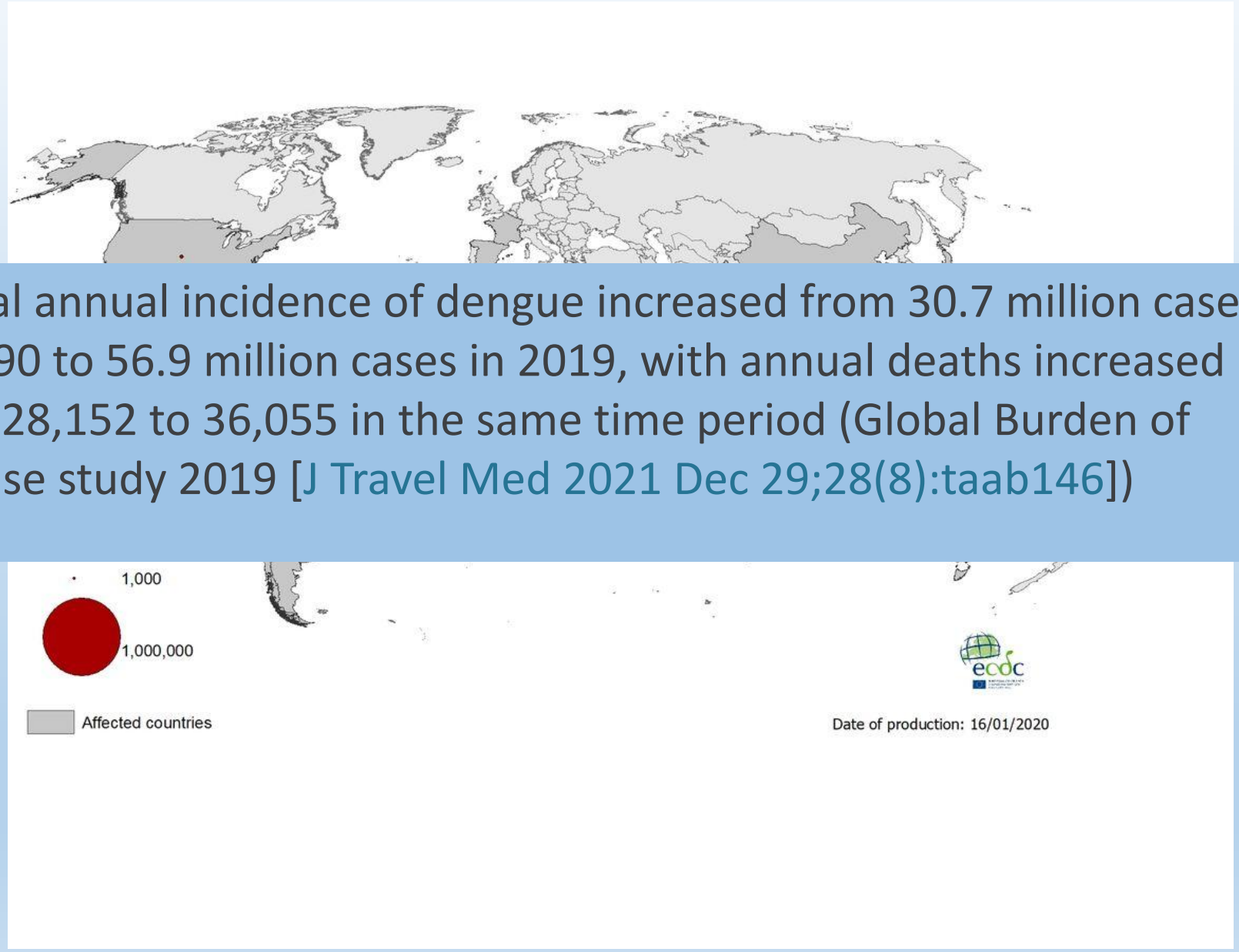
Hospitalized cases cost 300% more than ambulatory cases.

US$ 587 MILLION:

Annual cost across 8 studied endemic countries.

19 Days: Average lost productivity per hospitalized episode.

Geographical distribution of dengue cases reported worldwide, 2019



Global annual incidence of dengue increased from 30.7 million cases in 1990 to 56.9 million cases in 2019, with annual deaths increased from 28,152 to 36,055 in the same time period (Global Burden of Disease study 2019 [J Travel Med 2021 Dec 29;28(8):taab146])

Surveillance Case Definition for Dengue Fever

- **1. Suspected case of Dengue Fever**
- **2. Probable case of Dengue Fever**
- **3. Confirmed case of Dengue Fever**

Suspected case of Dengue Fever

- **Lives in OR travel to endemic area and Presence of 3 or more Clinical Criteria**
  Clinical Criteria:
- Acute high grade Fever of 2 to 5 days duration (essential criterion)
  AND any two of the following:
- Headache
- Retro orbital pain
- Myalgia
- Arthralgia/ severe backache/ bone pains
- Rash
- Bleeding manifestations (epistaxis, hematemesis, bloody stools, menorrhagia, hemoptysis)
- Abdominal pain
- Decreased urinary output despite adequate fluid intake

Probable Case Of Dengue Fever

- **Suspected Case with Supportive Lab Evidence**

- Thrombocytopenia ≤ 100,000/mm3
- Leukopenia ≤ 4000/mm3

Confirmed case of Dengue Fever

- **Suspected or Probable case with any one of the three Confirmatory Evidence**

  Confirmatory evidence of viral infection would therefore, be based on:
- Detection of viral antigen (NS1 antigen in blood)
- **OR**
- Detection of IgM
- **OR**
- Detection of virus by PCR
- **OR**
- Demonstration of ≥ 4 fold rise in IgG antibody titer in paired acute and convalescent serum

Clinical Classification /categorization of Dengue Patients

- A majority of the patients who got infected with dengue virus are never recognized due to asymptomatic infection that could be as high as 80-90%.
- Patients who develop symptomatic disease can be categorised/classified into those with
  - Undifferentiated fever,
  - Classic Dengue Fever (DF)
  - Dengue Haemorrhagic fever (DHF)
  - Dengue shock syndrome (DSS)
  - Those with organ failures based on severity of the disease/Expanded Dengue Syndrome (EDS)

Dengue Fever(DF)

- Dengue fever sometimes called “Break bone fever ” is a severe, flu-like illness that affects infants, young children and adults.
- The clinical features of Dengue fever vary according to the age of the patient. Infants and young children may have a non-specific febrile illness with rash.
- Older children and adults may have either a mild febrile syndrome or the classical incapacitating disease with abrupt onset and high fever, severe headache, pain behind the eyes, muscle and joint pains, and rash.

Dengue Haemorrhagic fever (DHF)

- Dengue haemorrhagic fever is different from Dengue Fever in that the patient has typical pathophysiologic hall marks of selective plasma leakage into the body cavities and other extravascular compartments and a tendency to bleed.
- The term “Dengue haemorrhagic fever” per say does not mean that all these patients will be bleeding, its actually the leaking of plasma from the intravascular compartment to the extravascular compartment due to endothelial dysfunction.
- Actual bleeding is found in a smaller fraction of these patients

Dengue Shock Syndrome (DSS) and Expanded Dengue Syndrome (EDS)

- Dengue Shock Syndrome(DSS) may develop in the Dengue Haemorrhagic fever patients who have massive plasma leakage compromising the hemodynamic status with out proper intervention. In simple terms DSS is the severe form of DHF.
- Expanded Dengue Syndrome (EDS) or Dengue with organ damage/failure usually occurs in patients who have undetected DSS which results in prolonged shock and organ damage, other causes of EDS are dengue infections in hosts with co-morbidities or coinfections with other microbial agents.

Pathophysiology of Vascular permeability in Dengue

- The **pathophysiology of endothelial dysfunction** in dengue hemorrhagic fever involves increased vascular permeability without morphological damage to the capillary endothelium, which is a key feature of the disease. This dysfunction is characterized by extensive plasma leakage in various tissue spaces and serous cavities, leading to profound shock**.**
- **The mechanisms contributing to this dysfunction include immune complex disease, T-cell-mediated responses, antibodies cross-reacting with vascular endothelium, enhancing antibodies, complement activation, cytokine release, and virus virulence**.
- The primary target cells for Dengue virus (DENV) are dendritic cells and monocytes/macrophages, which upon infection release chemokines and cytokines that activate the endothelium, contributing to vascular permeability. Recent studies indicate that DENV can also directly replicate in endothelial cells, further exacerbating vascular permeability and immune targeting of the endothelium

- The changes in vascular permeability in Dengue Hemorrhagic Fever (DHF) involve **compromised endothelial glycocalyx integrity** and the role of Dengue nonstructural protein 1 (NS1) in mediating vascular hyperpermeability. Studies suggest that in DHF, the endothelial glycocalyx layer (EGL) is compromised, leading to increased vascular permeability.
- This disruption of the EGL, composed of proteoglycans and plasma proteins, is associated with damage, degradation, and increased plasma leakage
- Additionally, the **DENV NS1 protein plays a crucial role in vascular hyperpermeability by promoting the breakdown of the EGL independently of inflammatory mediators**. NS1 interacts with Toll-like receptor 4, inducing the production of proinflammatory and vasoactive mediators that contribute to endothelial damage and vascular pathology
- These mechanisms highlight the complex interplay between viral proteins, immune responses, and endothelial dysfunction in Dengue Hemorrhagic Fever.

- **Histamine contributes to increased vascular permeability in Dengue Hemorrhagic Fever (DHF) by inducing the breakdown of the endothelial glycocalyx layer**, allowing plasma to leak from blood vessels into surrounding tissues.
- **In DHF, histamine levels are elevated**, leading to the activation of endothelial cells and the release of pro-inflammatory molecules that disrupt the glycocalyx layer. This disruption compromises the barrier function of the endothelium, allowing plasma to reach the intercellular junctions and leak out into tissues, resulting in increased vascular permeability

Antibody-dependent enhancement (ADE) during secondary infection with a different serotype

- Typically occurs when titer of preexisting antibodies declines into a specific range that is not high enough to neutralize the second infecting serotype
- Instead of binding of cross-reactive antibodies, suboptimal neutralizing antibody concentrations facilitate viral entry into Fc gamma-receptor bearing cells, such as monocytes, dendritic cells, and macrophages
- This leads to increased viral replication and evasion of host immune responses, resulting in reported viremia 10-100 times greater than in primary dengue
- Greater viral burden results in more pro-inflammatory profile
  - excess pro-inflammatory response such as interferon (IFN)-gamma, tumor necrosis factor (TNF)-alpha, and vascular endothelial growth factor (VEGF)-A are produced
  - elevated cytokine concentrations may lead to increased vascular permeability and plasma leakage, potentially leading to shock

- There isn't just "one" antibody type that protects against all dengue serotypes; rather, the immune system produces a complex mix of **serotype-specific** and **cross-reactive** antibodies.

Serotype-Specific Antibodies

- Natural infection by one dengue serotype is considered to induce lifelong, serotype-specific immunity

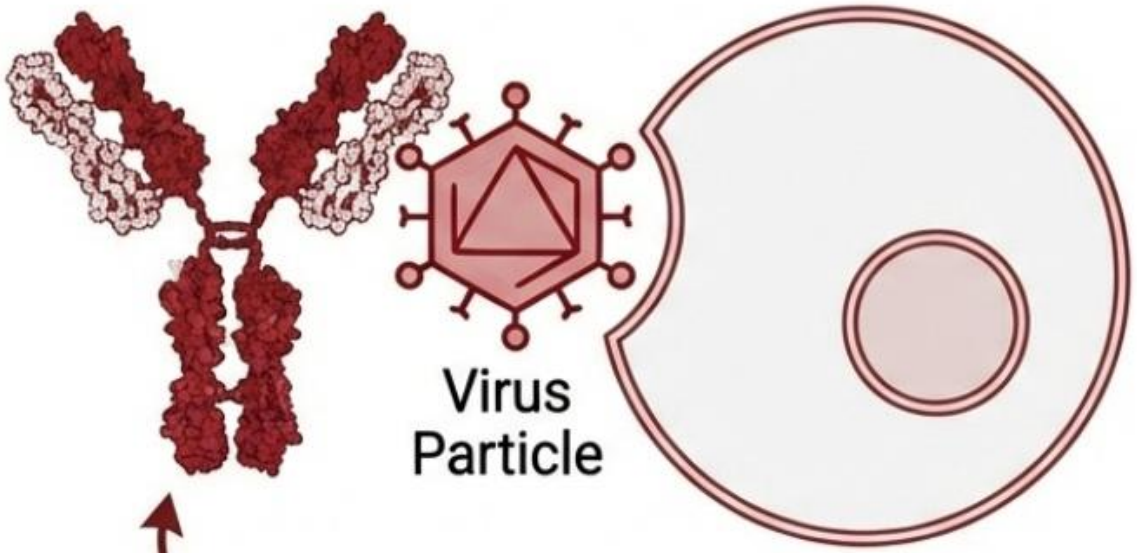
- This means the body produces highly specialized neutralizing antibodies that effectively recognize and inactivate that specific serotype if you are exposed to it again

Cross-Reactive Antibodies

- When infected with one serotype, the body also produces antibodies that are highly cross-reactive, meaning they can bind to the other three serotypes
- However, these cross-reactive antibodies only provide temporary immunity against different serotypes
- Over time, these cross-reactive antibodies can become "sub-neutralizing." Instead of protecting the body, they can facilitate the entry of a different serotype into host cells, a dangerous phenomenon known as antibody-dependent enhancement (ADE)

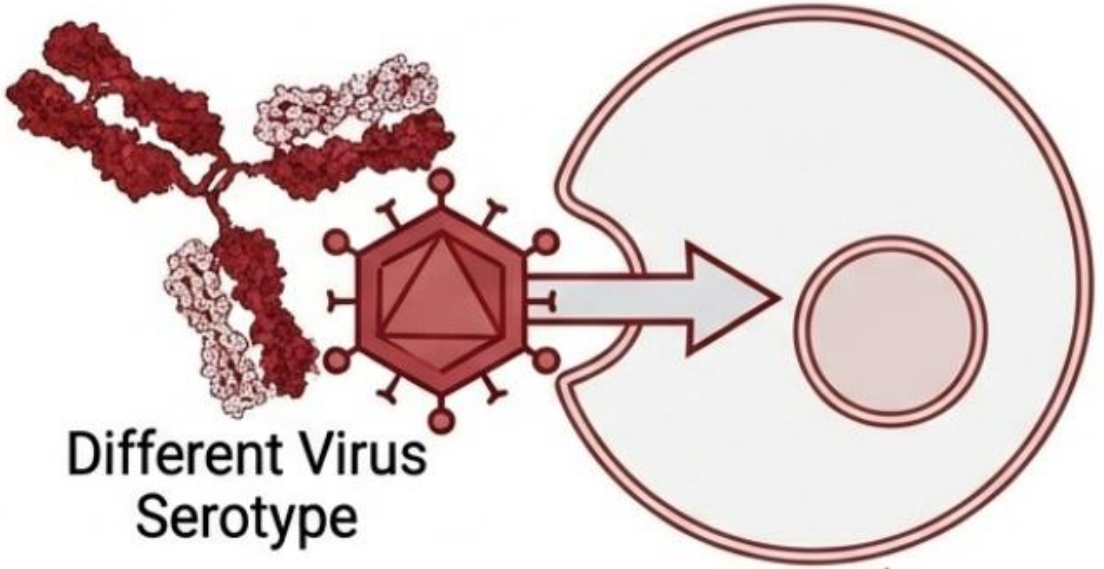
THE IMMUNOLOGICAL PARADOX

Primary Infection



Lifelong immunity to specific serotype.

Secondary Infection (ADE)



Antibody-Dependent Enhancement (ADE).

Cross-reactive antibodies facilitate virus entry rather than neutralizing it.
This is a major risk factor for Severe Dengue.

Host genetic factors

- Certain human leukocyte antigen (HLA) polymorphisms may be associated with protection from or susceptibility to infection
- genetic variation within MICB (MHC class I polypeptide sequence B), PLCE1 (phospholipase C, epsilon 1), MBL2, and IFN-gamma genes reported to be associated with severity of dengue disease

- (BMC Infect Dis 2018 Jun 22;18(1):282, Nat Genet 2011 Oct 16;43(11):1139)

Differential Diagnosis (Infections)

- Malaria
- Chikungunya
- Influenza
- COVID-19
- Measles
- Typhoid
- Other viral haemorrhagic fevers
- Rickettsial fevers
- West Nile virus infection
- Zika virus infection

History checklist

- ✓Patient identification
- ✓Demographics
- ✓Date and time of onset of current fever
- ✓Date and time of last fever documented/noted in the preceding week if the patient is afebrile on presentation or coming on a follow up visit
- ✓Vomiting, oral intake, urine output
- ✓Sick contacts
- ✓Travel history if any in the last two weeks
- ✓High risk factors
- ✓Any medication that patient is already using for other ailments or used for this fever

High risk patients

- Infants
- Pregnancy
- Poor social situation
- Elderly
- Obese
- Renal Failure
- Cardiac Disease
- Diabetes Mellitus
- Liver cirrhosis
- Bleeding Disorder
- Malignancy
- Immunosuppressive therapies

Important Phases of Dengue symptomatic infection based on the history

- **Febrile Phase**
  - Does the patient still have fever? If yes, then the disease is in the febrile phase.
  - How many days has the patient had fever? If fever has been present for at least 3 days, the patient could be nearing defervescence (the day and time when the body temperature drops and remains below 38.0°C). Be prepared as this could be the beginning of the critical phase that occurs in a significant number of patients
- **Critical Phase**
  - If the patient is afebrile at presentation, what was the day and time of the last fever? If the patient is within 24–48 hours of defervescence, then the disease is in the critical phase as the chances of leaks usually occurs during this phase called Dengue Haemorrhagic Fever (DHF) or Dengue Shock Syndrome (DSS).
  - (This is critical phase in term of monitoring for these possible sequellae and not to miss)
- **Recovery Phase**
  - If the patient has been without fever for more than 48 hours, and is hemodynamically stable and diuresing, then the disease is in the recovery phase.

PHASE 1: THE FEBRILE PHASE

Days 1–3

40°C

Clinical Features:

- Sudden onset high-grade fever.

- Facial flushing & skin erythema.

- “Breakbone fever”: Severe myalgia and arthralgia.

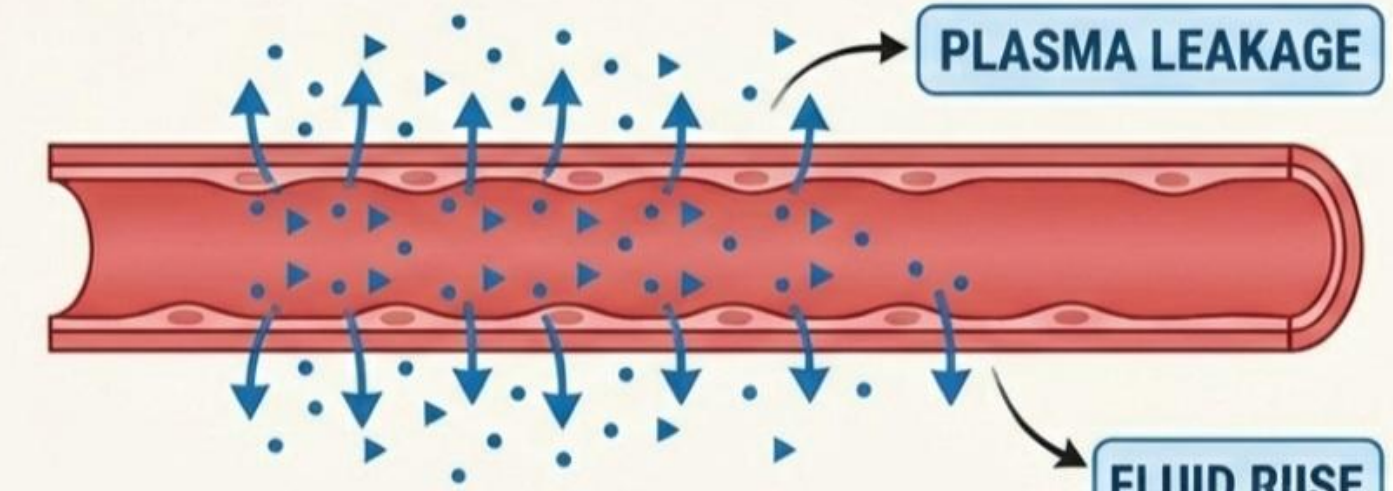
- Positive Tourniquet test.

Lab Alert

EARLY WARNING: Progressive decrease in total white cell count.

PHASE 2: THE CRITICAL PHASE

Days 3–7 (Lasts 24–48 hours)



Platelets Drop

Haematocrit Rises

DANGER ZONE:

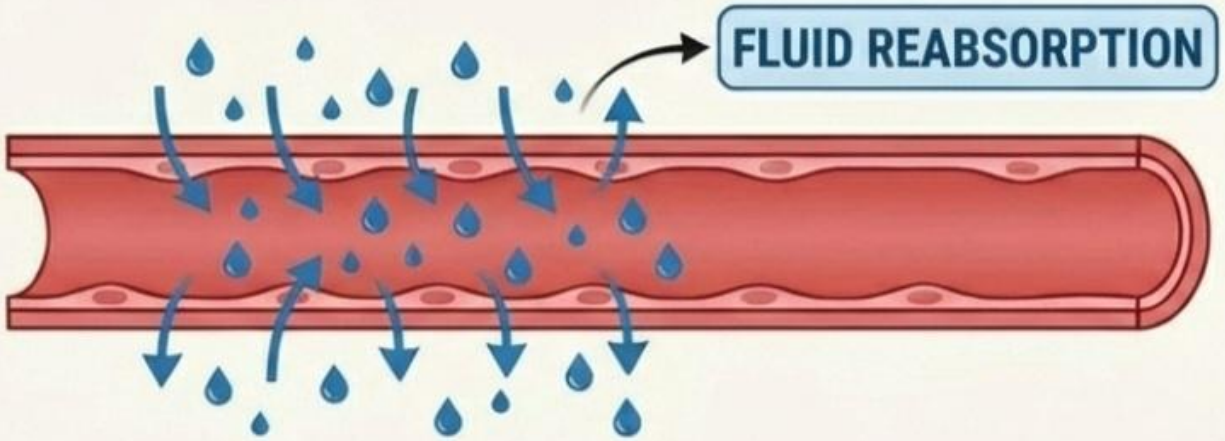
Occurs at Defervescence (fever drop).

Improvement in temperature does NOT mean recovery.

Leakage → Hypovolaemia → Shock

PHASE 3: THE RECOVERY PHASE

Post-Critical (48–72 hours)



Clinical Signs:

- Gradual reabsorption of extravascular fluid.
- Stabilized haemodynamic status.
- Diuresis.
- Appearance of Rash:

MANAGEMENT RISK:

Hypervolaemia (Fluid Overload) if IV therapy is not stopped.

Rash: White Islands in a sea of red

SURVEILLANCE CASE DEFINITIONS & TRIAGE

SUSPECTED DENGUE

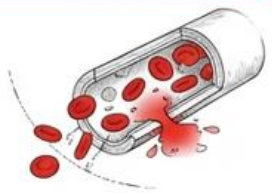
Acute Febrile Illness + 2 Criteria: Nausea, Rash, Aches, Leucopenia, Tourniquet Test +

DENGUE WITHOUT WARNING SIGNS

Action: Home Care (Group A)

DENGUE WITH WARNING SIGNS

- Abdominal Pain
- Persistent Vomiting
- Mucosal Bleed
- Lethargy
- Liver >2cm
- Rising HCT + Dropping Platelets

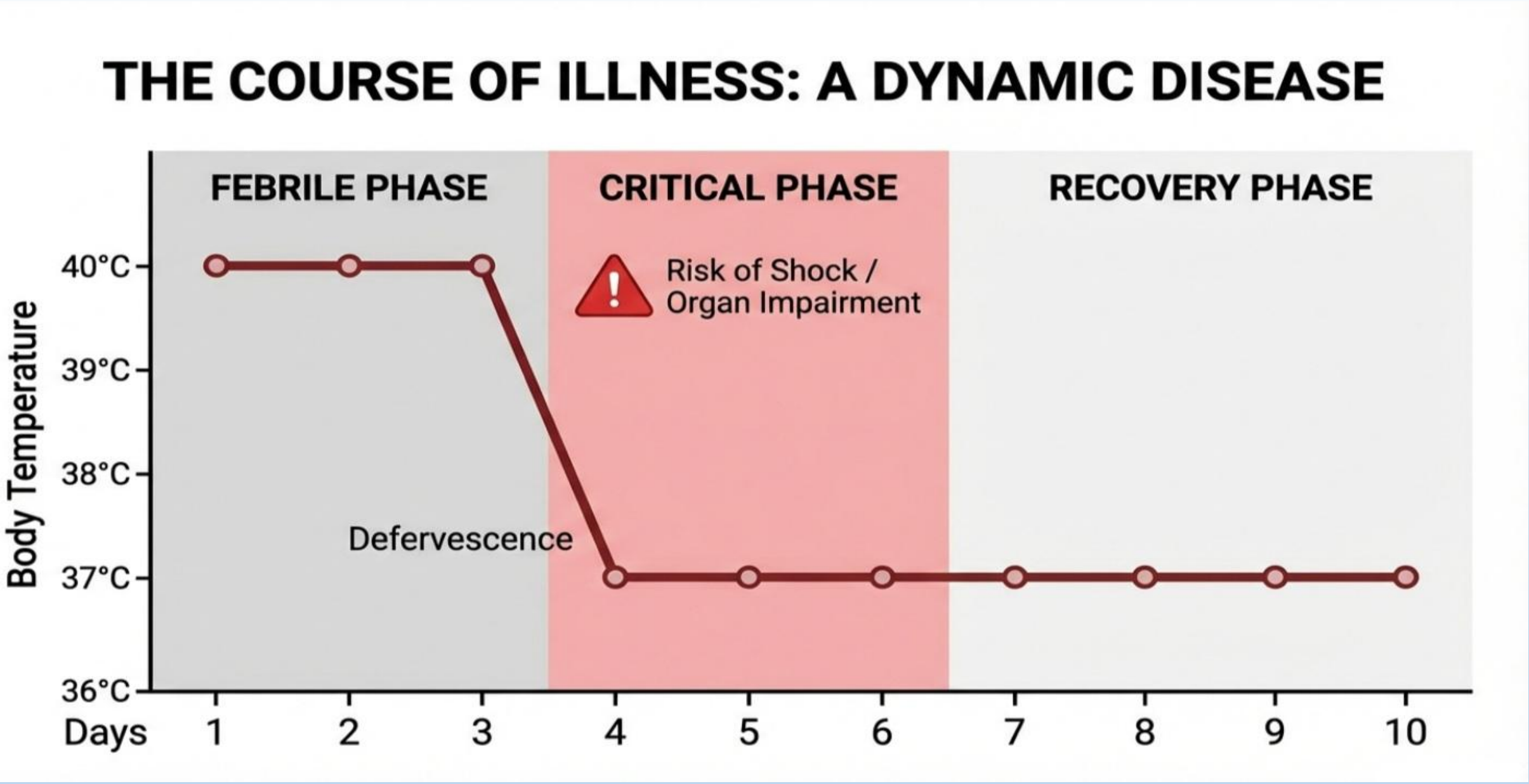


Action: Admit for Observation (Group B)

SEVERE DENGUE

- Severe Plasma Leakage (Shock)
- Severe Bleeding
- Organ Failure (AST/ALT >1000)

Action: Emergency Resuscitation (Group C)



The Febrile Phase lasts for 3 to 7 days

Potential complications associated with the Phase of disease

- **Febrile phase**
  - Dehydration
  - Febrile seizures
  - Neurologic manifestations
- **Critical phase**
  - Prolonged shock
  - Organ/s failure
  - Bleeding
- **Recovery phase**
  - Fluid overload
  - Worsening effusions
  - Acute pulmonary edema

Examination checklist

- ✓ What is the patient's mental status?
- ✓ What is the patient's hemodynamic status?
- ✓ What is the patient's hydration status?
- ✓ Are there any warning signs for severe disease?
- ✓ Are there signs or symptoms of plasma leakage or bleeding?

Assessing Hemodynamic Status

1. Skin color/texture
2. Cold/ warm extremities
3. Pulse rate
4. Pulse volume
5. Capillary refill time (normal <2 seconds)
6. Blood pressure
7. Pulse pressure
8. Postural drop if possible

Clinical Signs of Dehydration

- Fast pulse rate
- Poor skin turgor
- Delayed capillary refill
- Dry mucous membranes
- Sunken fontanelle
- Dry eyes or no tears
- Postural drop
- Low blood pressure

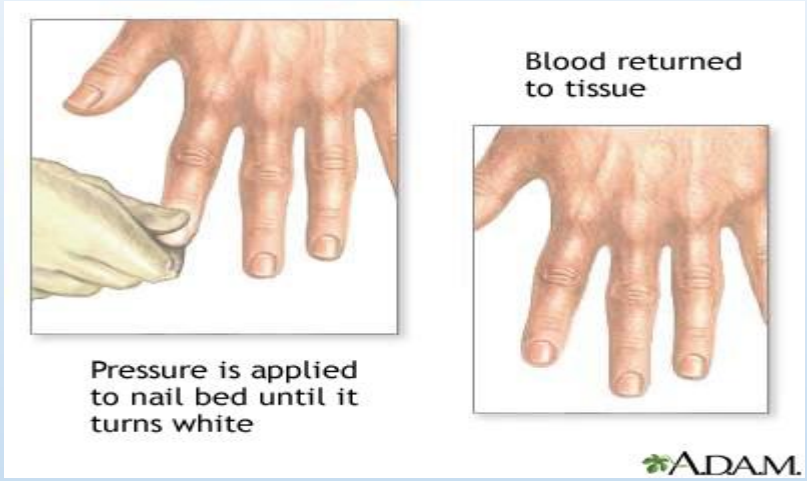
Warning Signs

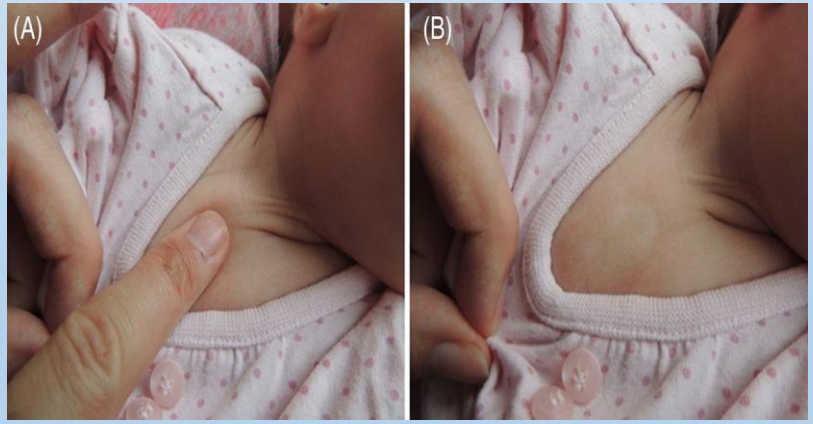
- Severe abdominal pain or tenderness
- Persistent vomiting more than three times in a day
- Bleeding manifestations: petechiae, epistaxis, gum bleeding, coffee ground vomiting , hematemesis, melena, mucosal bleed
- Liver enlargement >2cm
- Clinical fluid accumulation
- Lethargy; restlessness; behavioural changes; Giddiness
- Increase in HCT concurrent with rapid decrease in platelet count
- Pale, cold clammy hands and feet
- Decrease urine output/ anuria

Capillary Refill Time (CRT)

- Press on the finger for five seconds using moderate pressure at an ambient temperature of 20–25 degrees Celsius.
- Normal capillary refill time is usually less than 2 seconds.
- A capillary refill time of two seconds or more should be considered abnormal.

How to check for CRT?
Press here





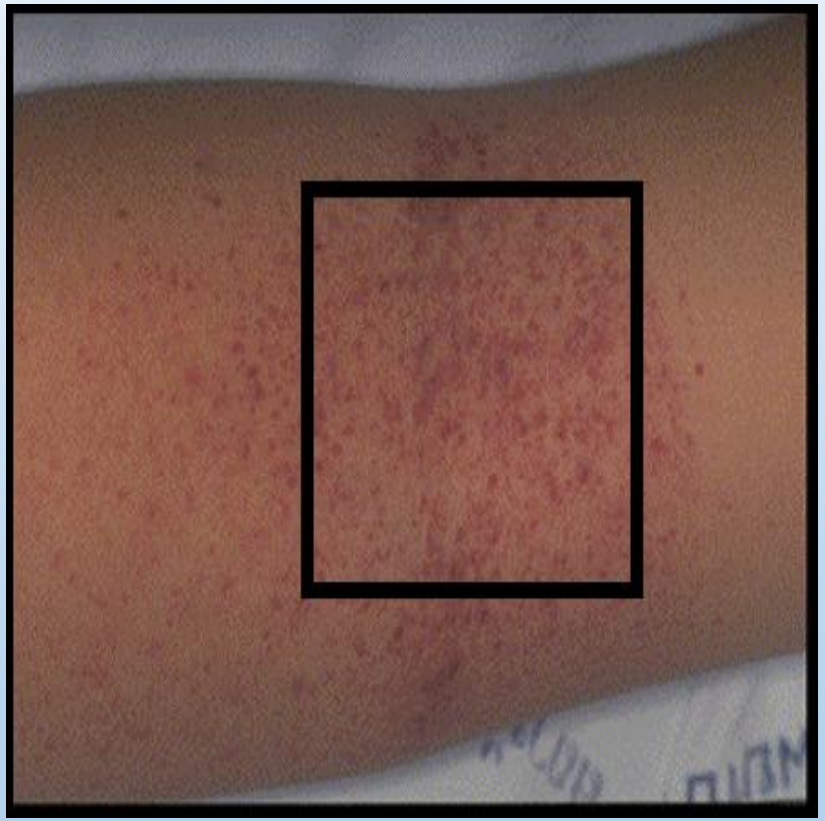
Tourniquet test (TT)

- The tourniquet test is part of the new WHO case definition for dengue. The test is a marker of capillary fragility and it can be used as a triage tool to differentiate patients with acute gastroenteritis, for example, from those with dengue. Even if a tourniquet test was previously done, it should be repeated if
  - It was previously negative
  - There is no bleeding manifestation

How to do a Tourniquet Test?

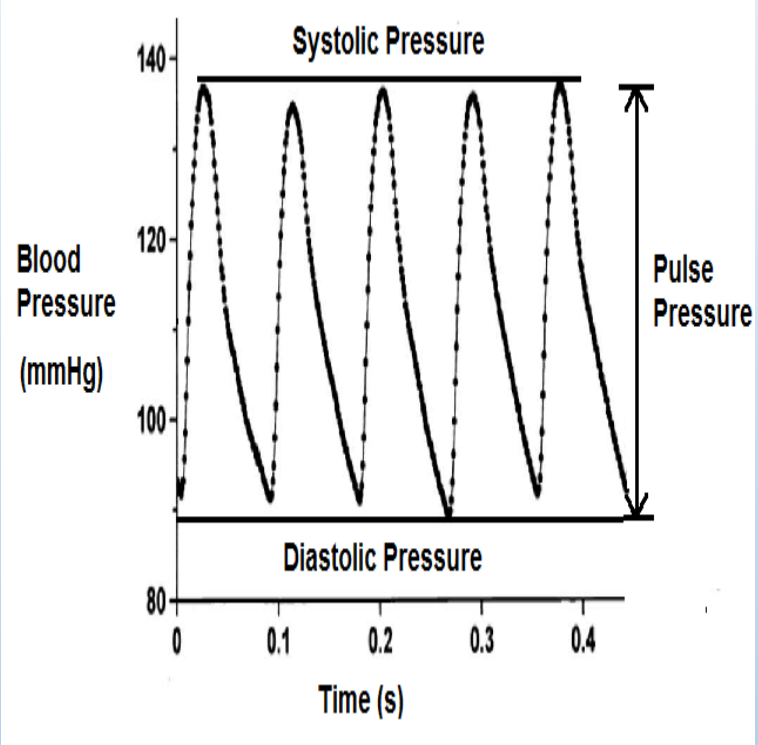
1. Take the patient's blood pressure and record it, for example, 100/70.
2. Inflate the cuff to a point midway between SBP and DBP and maintain for 5 minutes. (100 + 70) ÷ 2 = 85 mm Hg
3. Reduce and wait 2 minutes.
4. Count petechiae below antecubital fossa. See image at right.

A positive test is 10 or more petechiae per 1 square inch.



Pulse Pressure (PP)

- Pulse pressure is the difference between the systolic and diastolic blood pressure. It is measured in millimetres of mercury (mmHg).
- For early detection of compensated shock this is a simple clinical parameter where pulse pressure will become narrower and a pulse pressure of 20mmHg or less is used as a cut off mark to label a patient as having compensated shock during clinical monitoring



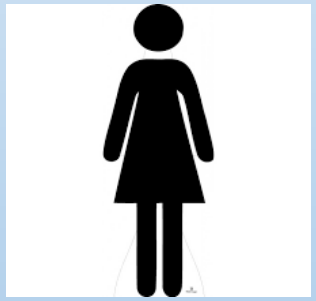
Example:

If resting blood pressure is 120/80 mm Hg, then the pulse pressure is 120 minus 80 that is 40 mmHg. (120-80=40)

Ideal Body Weight(IBW)

- Males: IBW = 50 kg + 2.3 kg for each inch over 5 feet.
  - Example: IBW of a 5.8 feet tall male with actual weight of 92 kg

    = 50+2.3(8)=50+18.4=68.4 kg



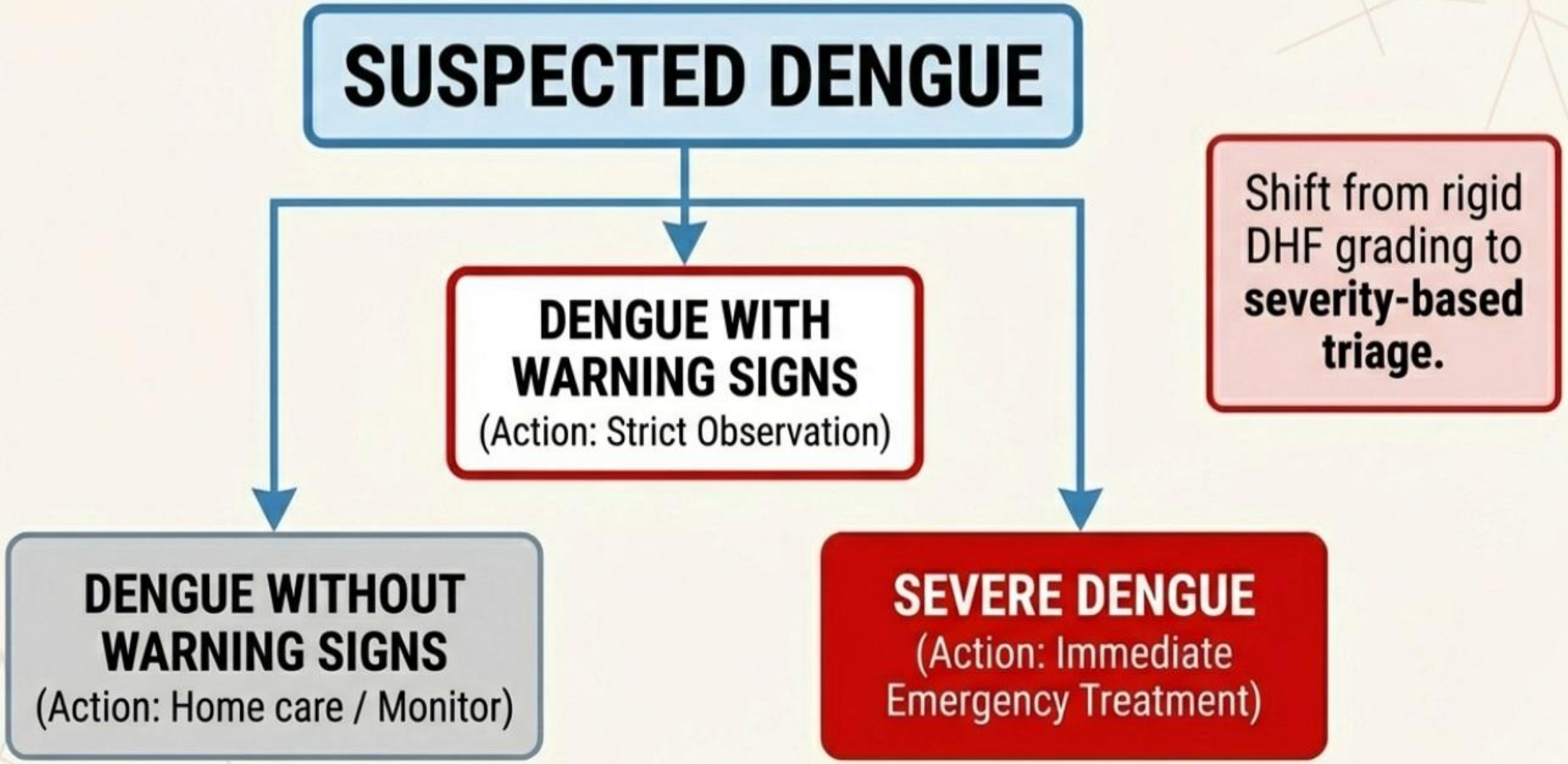
- Females: IBW = 45.5 kg + 2.3 kg for each inch over 5 feet
  - Example: IBW of a 5.8 feet tall female with actual weight of 92 kg

    = 45.5+2.3(8)=45.5+18.4=63.9 kg

Based on evaluations from history, physical examination +/- CBC and HCT, the clinicians should be able to determine:

1. Diagnosis of Dengue Fever (suspected, probable or confirmed)
2. The phase of illness (febrile/critical/convalescent or recovery)
3. The hydration and hemodynamic status of patient
4. Whether the patient requires admission

CLASSIFICATION: A SHIFT IN THINKING



RECOGNIZING THE WARNING SIGNS

Transition from Non-Severe to Severe

- [x] **Abdominal pain or tenderness**
- [x] **Persistent vomiting**
- [x] **Clinical fluid accumulation** (ascites, pleural effusion)
- [x] **Mucosal bleed**
- [x] **Lethargy or restlessness**
- [x] **Liver enlargement >2cm**
- [x] **LAB: Increase in Haematocrit + + Rapid decrease in Platelets**

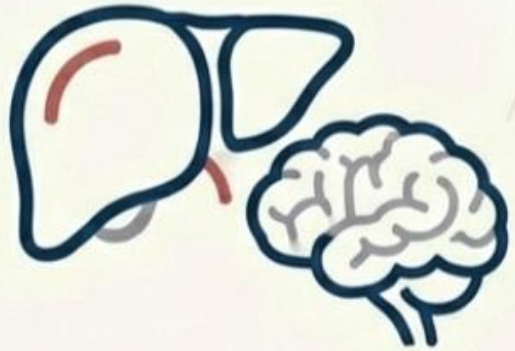
DEFINING SEVERE DENGUE

SEVERE PLASMA LEAKAGE

Leading to Shock (DSS) or fluid accumulation with respiratory distress.

SEVERE BLEEDING

As evaluated by the clinician.



SEVERE ORGAN IMPAIRMENT

- **Liver:** AST or ALT ≥1000.
- **CNS:** Impaired consciousness.
- **Heart:** Cardiomyopathy.

Dengue clinical management groups

- For management purposes Dengue patients are grouped based on the clinical characteristics and laboratory parameters into;
- **Group A**
    - Undifferentiated fever
    - Classic Dengue Fever (DF)
- **Group B**
    - Dengue Haemorrhagic fever (DHF)
- **Group C**
    - Dengue shock syndrome (DSS)
    - Those with organ failures based on severity of the disease also called Extended Dengue Syndrome(EDS)

- Group B and C are actually comprised of DHF patients with different severity as explained by WHO criteria for Grading severity of DHF;
  - DHF Grade I : Fever and plasma leakage without spontaneous bleeding
  - DHF Grade II: Fever and plasma leakage plus spontaneous bleeding
  - DHF Grade III: Grade I or II plus evidence of shock
  - DHF Grade IV : Grade I or II plus evidence of profound shock
- DHF Grade I & II = Group B = DHF
- DHF Grade III & IV =Group C = DSS

Group A (DF)

Suspected, Probable OR **Confirmed** Dengue fever patient as per the Surveillance case definition for Dengue

And **No Warning Signs, No Risk Factors,** tolerate adequate volume of oral fluids, hemodynamically stable and stable/normal haematocrit.

These patients will be sent home on the Out Patient Management protocol

Indications for Dengue tests

Group B (DHF Grade I & II)

Suspected, Probable OR **Confirmed** Dengue fever patient as per the Surveillance case definition for Dengue

Plus Warning Signs OR Risk Factors, has challenging social circumstances such as living alone or living far away without a reliable means of transport .

Patients with co morbidities, pregnancy, extreme of ages should preferably be kept under observation

These patients will be admitted/referred for Inpatient Management

Group C (DHF Grade III & IV OR DSS/EDS)

Suspected, Probable OR **Confirmed** Dengue fever patient as per the Surveillance case definition for Dengue having

- **A: Compensated Shock** (Circulatory failure manifested by narrow pulse pressure)

  OR
- **B: Hypotensive Shock** (Systolic BP less than 90mmHg or more than 20% reduction in SBP)

  OR

  Patients with any of
- Severe Plasma leakage with shock and or fluid accumulation with respiratory distress
- Severe bleeding
- Severe organ impairment

These patients will be admitted /referred for inpatient Management preferably HDU/ICU after resuscitation

Dengue laboratory tests

Diagnostic Tests.

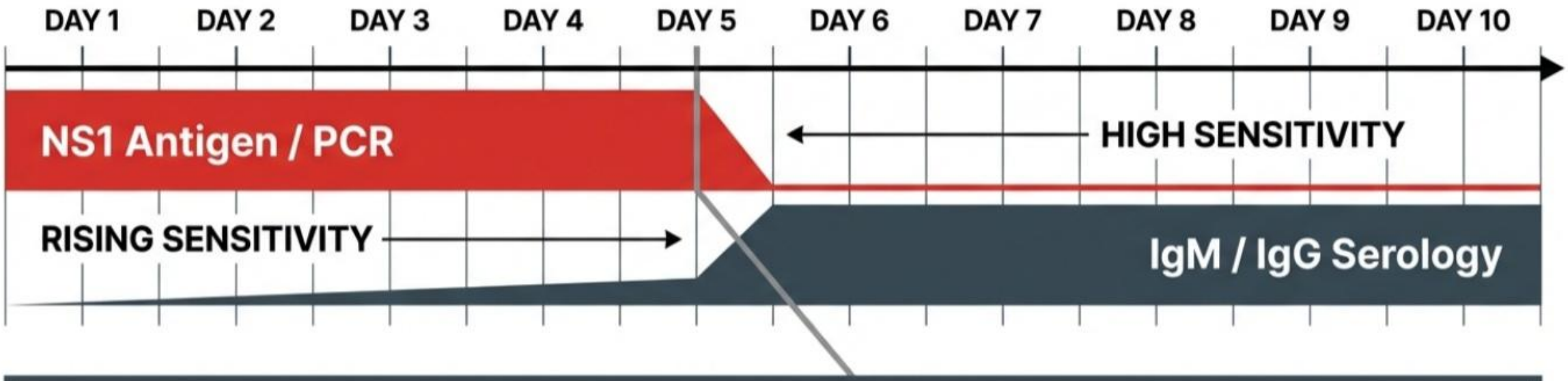
- **NS1 Ag Test:**
- For early confirmation of Dengue this is the quickest option and is reported in 5-10 minutes. It is positive during the febrile phase with a sensitivity of 40-70% depending on the viremia and kit quality. The percentage of positivity decreases rapidly as the days of fever passes on and usually become negative after 5-7days of onset of illness. The positivity is high in primary infection compared to those patients who have a second infection.
- **A negative NS1 does not mean that the patient do not have Dengue due to the low sensitivity and if the patient is fulfilling the criteria for suspected dengue, patient should be managed.**
- **This test does not guide the clinical management, It only confirms dengue infection.**
- False positivity with other flaviviruses is another concern.

Anti-Dengue IgG/IgM:

- Usually become positive on 5th day so it is not used for the early diagnosis, it is used to confirm dengue but can become positive as late as 7-14 days after the initial infection, if only IgM is positive it suggests acute primary infection, if both IgG and IgM positive, this suggest secondary dengue infection or a late testing. The IgM will remain positive upto 1-2 months. If only IgG is positive this suggest past dengue infection because IgG can persist for years.

- **Dengue NS1, Anti Dengue IgM and IgG by Elisa compared to RDT do not add too much to the management of Dengue patients.**
- **For epidemiological investigations and genotype testing blood samples should be submitted to the National/ Provincial reference labs .**

LABORATORY DIAGNOSIS & CRITICAL MONITORING



CLINICAL MARKERS (ACUTE PHASE)

- **HAEMATOCRIT (HCT):** The primary guide for fluid therapy. Rising HCT = Leakage.
- **PLATELETS:** Thrombocytopenia is supportive but HCT is the priority indicator.

- Primary infection - antibody response in patients never exposed to a flavivirus (neither by infection or vaccine)
  - Anti-Dengue IgM
    - detectable in 50% by days 3-5
    - detectable in 80% by day 5
    - detectable in 90% by day 10
    - peak at about 2 weeks
    - decline to undetectable levels over 2-3 months
  - Anti-Dengue IgG
    - usually detectable in low levels by end of first week of illness
    - can still be detected after months and may be detectable for life

- Secondary infection - antibody response in patients who have had previous exposure to dengue or other related flavivirus
  - anti-dengue IgG levels rise rapidly to high levels
  - can be seen early in disease course
  - last for months to life
  - IgM levels are much lower than in primary infection

Indications for Dengue testing

- Dengue specific testing is indicated at all regions in patients presenting with ACUTE FEBRILE ILLNESS having Dengue as a differential diagnosis where the disease activity is not confirmed yet and the samples should be submitted to the national/provincial reference laboratories for further confirmation and genotyping.
- In areas where the disease activity (Dengue cases) is already confirmed and patients are fulfilling the criteria for Group A, B or C Dengue testing is not indicated in routine and should be encouraged only in severe cases, and a negative test should not hinder the clinical case management due to the variable sensitivities.

Out Patient Management (Group A)

- There is no specific treatment of Dengue Infection.
- The treatment is only supportive and symptomatic and the management aim is not to miss the complications of critical phase if it occurs.
- During the febrile phase (may last 2–7 days) and subsequent critical phase (1–2 days) if any, you should:
  - Follow CBCs (Frequency based on baseline)
  - Watch for dehydration
  - Watch for warning signs, including decreasing platelet count and increasing hematocrit
  - Watch for defervescence (Not always but could be the beginning of critical phase)

Out Patient Management (Group A)

Clinical and laboratory monitoring chart for all patients on out patient management

Name _____ **Age** _____**MRNO/OPD NO**_____ **Date**_____

Day of onset of fever	Day 1	Day 2	Day 3	Day 4	Day 5	Day 6	Day 7	Day 8
Date								
Time								
Temp								
Heart Rate								
Capillary refill time (CRT)								
Blood Pressure (BP)								
Pulse Pressure (PP)								
Respiratory Rate (RR)								
Urine Out Put (UOP)								
Bleeding if any								
HB%								
HCT/PCV								
TLC								
Platelet count								
RBS								
ALT/AST								
Dengue NS1 Dengue IgM Dengue IgG								

Instructions regarding monitoring of Out patients

- Beside detailed history and evaluation all the patients who are categorised as Group A patients and are on outpatient plan for management should have this monitoring form with them and all the required data should be documented.
- Every patient should be instructed to bring this form on each follow up visit.
- This monitoring is usually required up to 8 days from the beginning of fever
- If the first RBS,ALT,AST is normal they should be repeated on need basis only
- Dengue NS1,IgG, IgM are not mandatory in endemic situations (check Dengue test in the booklet for details)

Advise for the patient and family who are going to home

- **Control the fever**
- **Prevent dehydration**
- **Prevent spread of dengue within your house and surroundings**
- **Watch for Warning Signs**
- **Schedule for laboratory monitoring and follow up visits**

1) Fever Control

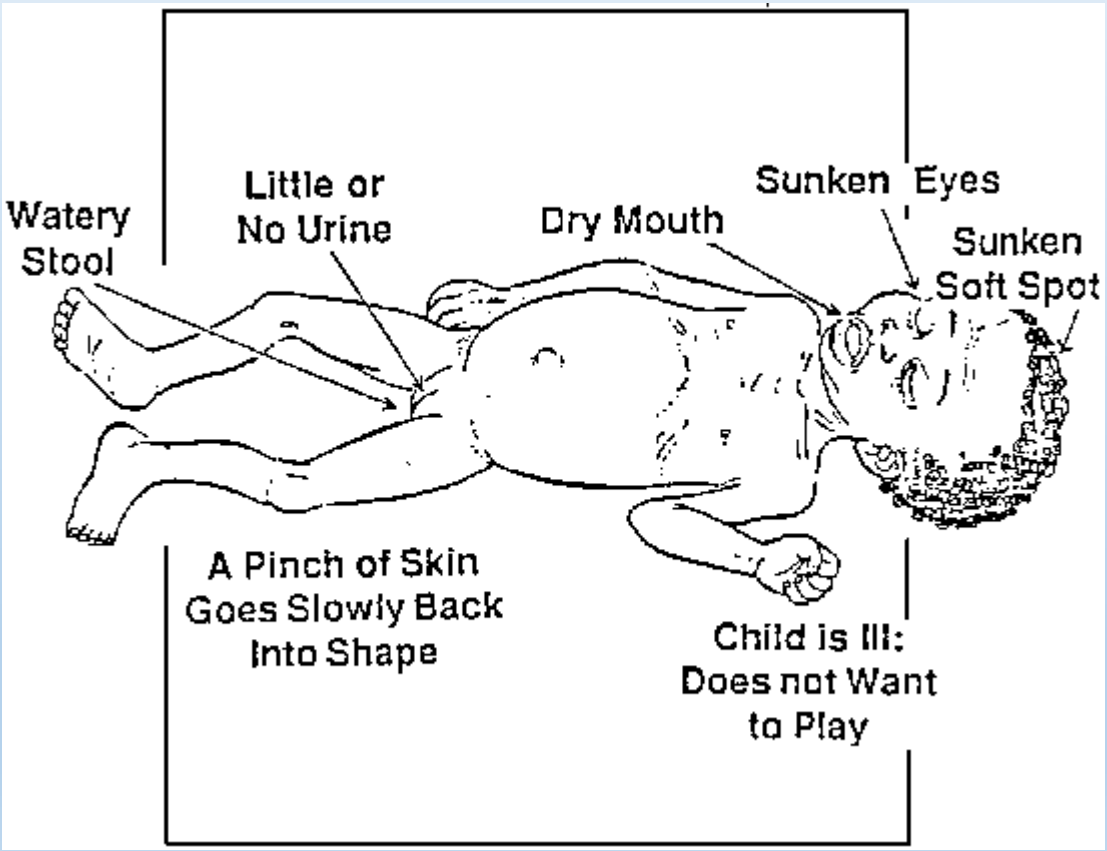
- Give acetaminophen every 6 hours (maximum 4 doses per day).
- Do not give ibuprofen, aspirin, or aspirin- containing drugs.
- Sponge patient’s skin with tepid water when temperature is high.

2) Prevent dehydration

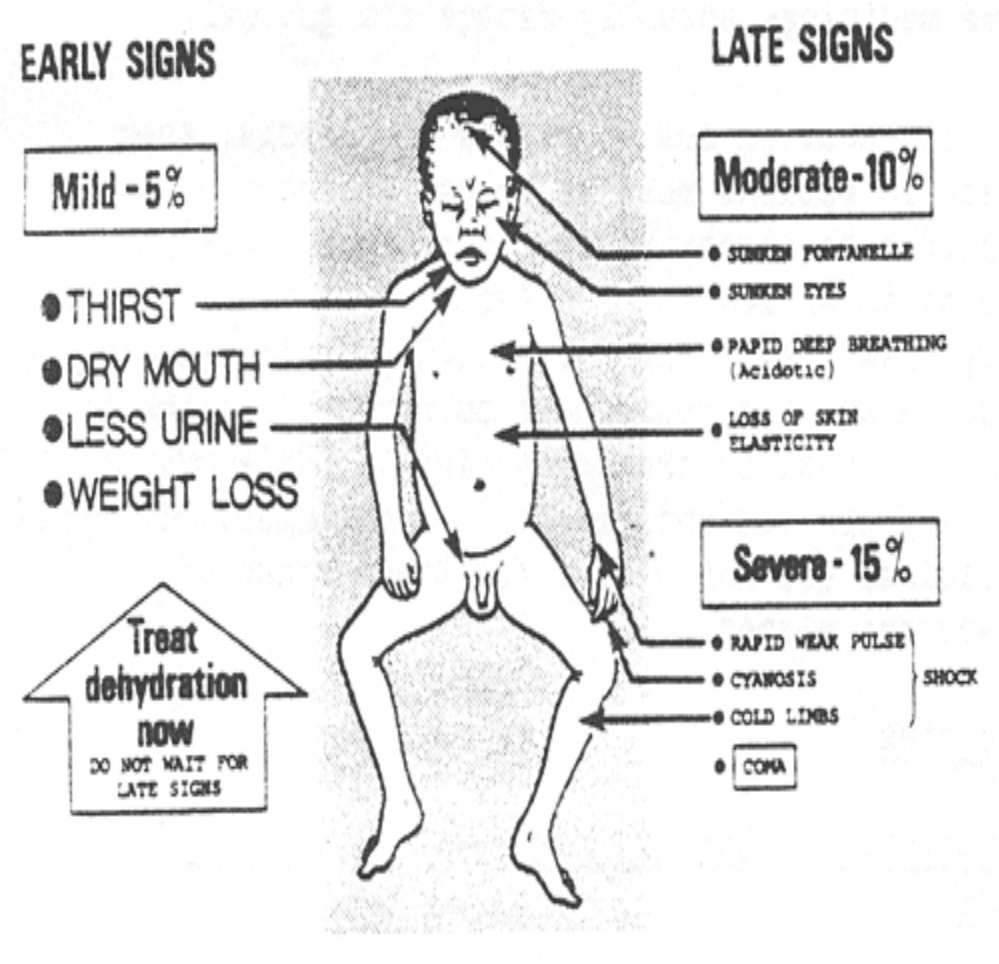
Dehydration occurs when a person loses too much fluid (from high fever, vomiting, or poor oral intake). Give plenty of fluids (not only water) and watch for signs of dehydration.

Bring patient to clinic or emergency room if any of the following SYMPTOMS develop:

- Decrease in urination (check number of wet diapers or trips to the bathroom)
- Few or no tears when child cries
- Dry mouth, tongue or lips
- Sunken eyes
- Listlessness, agitation, or confusion



- Fast heartbeat (>100/min)
- Cold or clammy fingers and toes
- Sunken fontanel in an infant
- Poor oral intake
- Persistent vomiting



3) Prevent spread of Dengue within your house

- Place patient under bed net or have patient use insect repellent while febrile to avoid infecting mosquitoes that can infect others within 2 weeks.

- KILL all mosquitoes in house.

- Empty containers that carry water and cover them.

- Put screens on windows and doors to prevent mosquitoes from coming into house.

4) Watch for warning signs

- As temperature declines 3 to 8 days after symptoms began, Return IMMEDIATELY to clinic or emergency department if any of the following warning signs appear:
  - Severe abdominal pain or persistent vomiting
  - Red spots/patches on skin
  - Bleeding from nose or gums
  - Vomiting blood
  - Black, tarry stools
  - Drowsiness or irritability
  - Pale, cold, or clammy skin
  - Difficulty breathing

5) Schedule for laboratory monitoring and follow up visits

- All the Group A patients should visit local health facility /local doctor (GP/BHU/CH/RHC/DHQ etc) between 3-8 days after onset of first fever and should have evaluation for warning signs and CBC done daily for one to two days soon after the defervescence (Afebrile /critical phase) and any warning signs OR rising HCT or drop in WBC or Platelet count should prompt further referral /admission.
- As temperature declines 3 to 8 days after the first symptoms began, Return IMMEDIATELY to clinic or emergency department if any of the warning signs appear as explained in the previous slide

Evaluation of patients who are on outpatient follow-up visit (Group A follow-up)

- Most dengue patients will improve and they will not develop manifestations of DHF or DSS.
- Patients who do not improve OR are coming on the routine follow up as advised should be looked for warning signs or worsening of their illness during defervescence.
- Around time of defervescence, petechiae can appear, especially on lower extremities.

Clinical parameters that need to be checked and documented every time a patient with dengue presents to a health care worker/facility.

- Level of consciousness
- Capillary refill
- Skin temperature, colour, and moisture level (normal, dry or clammy)
- Peripheral pulse volume
- Heart rate
- Blood pressure
- Respiratory rate
- Urine output

Warning signs & symptoms that should be checked for on follow-up visit and should prompt admission are;

Symptoms

- Sweating
- Abdominal pain
- Persistent vomiting
- Altered sensorium
- Decreased urine output

Drop in Platelets with increase in HCT

Signs

- Cold peripheries
- Tachycardia
- Rising Diastolic BP
- Narrowing pulse Pressure
- Hypotension or more than 20% change from baseline
- Increasing Respiratory Rate
- Ascites, pleural effusion
- Bleeding
- Lethargy, restlessness
- Liver enlargement > 2 cm

Inpatient Management of Group B patients

- Obtain baseline complete blood count
- Intake output record of fluids
- Monitor vital signs @ 4 hourly minimum and more frequent if clinical status unstable
- Encourage oral fluid intake and monitor for warning signs of shock /severe dengue

Clinical monitoring Chart Inpatient

Clinical Monitoring Chart

Name_____ MRNO _____ Date _____ DOA _____
TDI _____Weight (IBW) _____ Sheet No _____

Time	Temp	HR	CRT	BP	PP	RR	UOP	Bleeding if any	Action

MRNO= Medical record Number, DOA= Day of Admission, TDI= Total Duration of Illness,
HR=Heart Rate per minute, CRT= Capillary Refill Time, BP= Blood Pressure, PP= Pulse Pressure,
RR= Respiratory Rate per minute, UOP= Urine Output /kg/hr

Clinical Monitoring

- Monitor all the Clinical parameters 04 hourly in **Group B** patients and Hourly or more frequently in **Group C** patients
- Use new/separate sheet if category changes from group B to group C
- Don’t miss auscultation of chest, examination of abdomen and extremities for any fluid accumulation at regular intervals

Clinical Monitoring

- Call for immediate intervention/advice when
  - Pulse rate is more than 100/minute when afebrile OR more than 120/min when febrile
  - Pulse pressure narrowing down to 25mmHg OR less in supine position
  - Capillary Refill time ≥ 2 sec
  - Significant Bleeding from any site
  - UOP < 0.5 ml/kg/hr

How to identify the leak phase by using the Clinical parameters?

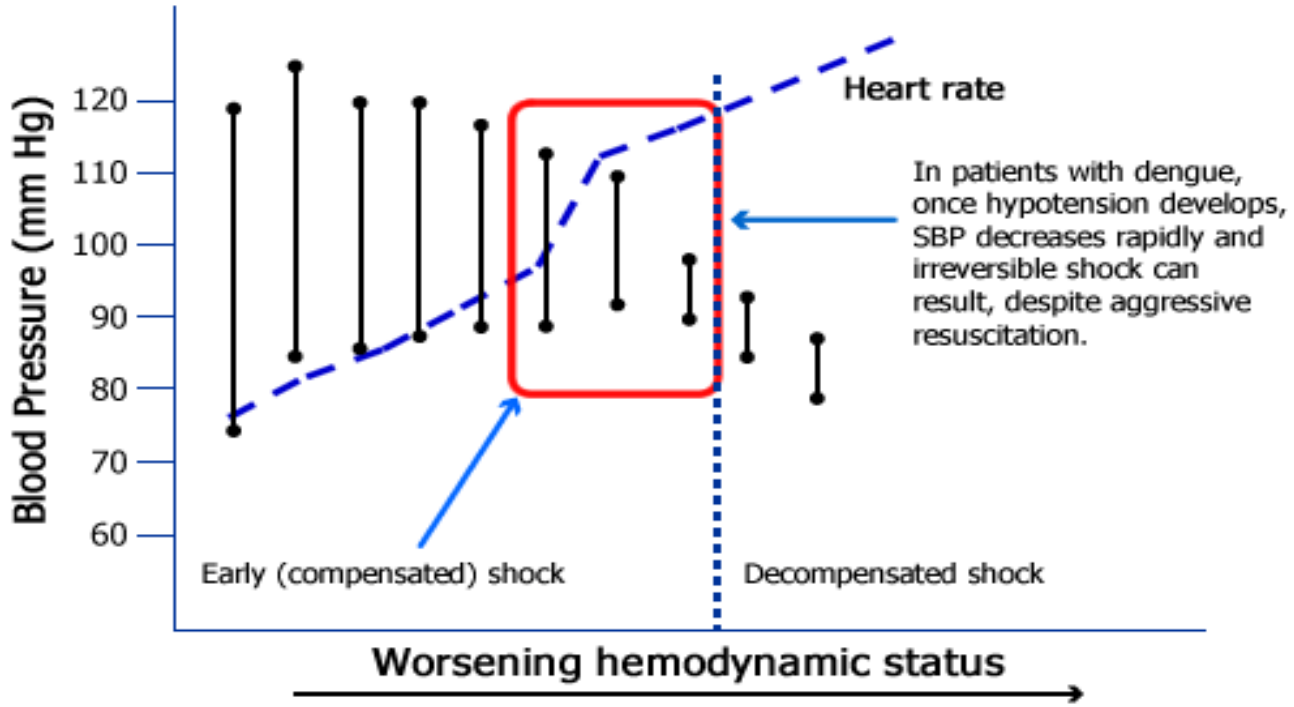
Date	Time	Temp	HR	CRT	BP	PP	RR	UOP (ml/kg)	Bleeding if any	Action
10/4/18/	4.00 am	99.6	80	<2 sec	130/80	50	16			
10/4/18	8.00 am	99.8	86	<2 sec	130/85	45	17			
10/4/18	12.00pm	99	90	<2 sec	130/90	40	17			
10/4/18	16.00pm	98	92	<2 sec	130/100	30	20			
10/4/18	20.00pm	98	96	<2 sec	130/105	25	20			
10/4/18	24.00pm	98.7	98	<2 sec	130/110	20	18			
11/4/18	4.00am	98	100	<2 sec	130/105	25	22			
11/4/18	8.00am	98.5	106	<2 sec	130/100	30	20			
11/4/18	12.00pm	98	106	<2 sec	130/100	30	21			
11/4/18	16.00pm	98.4	108	<2 sec	130/95	35	22			
11/4/18	20.00pm	98.6	110	<2 sec	130/90	40	23			
11/4/18	24.00pm	98.3	112	<2 sec	130/90	40	24			

Narrowing pulse pressure.

Increasing heart rate.

Identify Early Signs of Shock

Identify early signs of shock, including narrowing pulse pressure with rising diastolic, delayed capillary refill, and tachycardia in absence of fever.



Laboratory Monitoring Chart

Name_____ MRNO _____ Date _____ DOA _____ TDI _____Weight (IBW) _____ Sheet No _____

Blood Group _____

Date	Time	HCT	TLC	PLT	ALT	AST	RBS	Cr	Ca^{+}_{+}	USG	Action

HCT= Haematocrit, TLC= Total Leucocyte Count, PLT= Platelet Count, ALT= Alanine Amino transferase, AST (SGOT)=Aspartate Aminotransferase, RBS= Random Blood Sugar,Cr= Serum creatinine, Ca^{++}= Serum Calcium, USG= Ultra Sonography

Lab Monitoring

- Monitor HCT every 6 hourly during the febrile phase of Group B patients and every 1-3 hourly during the critical phase depending on the severity, similarly check before and after any Colloid fluid infusion/ blood transfusion to check the response and not to miss concealed bleeding.
- Lab monitoring for TLC, Platelets, ALT, AST, RBS, Serum Creatinine, Serum Calcium should be done daily during the inpatient management and more frequent if any derangements noted depending on the severity.
- Use new/separate sheet if category changes from group B to group C.
- HDU/ ICU patients may need further monitoring like ABGs and frequent electrolytes etc and that should be done as per recommended standards.

Lab Monitoring Cont’

- Call for immediate intervention/advice when
  - HCT is rising rapidly ≥ 20% of the base line or normal standard for the age and weight
  - PLT ≤ 50000/cumm
  - Rising ALT/AST ≥ 1000
  - USG showing fluid collections (pericholecyctic fluid collection and early sign of DHF)
  - Rising Creatinine or falling Calcium levels in critical phase
  - Hypoglycaemia

How to identify the leak phase by using the laboratory parameters?

Date	Time	HCT	TLC	PLT	ALT	AST	RBS	Cr	Ca^{++}	USG	Action
10/4/18	9:00am	39	3800	114000							
10/4/18	9:00p	39	3200	89000							
11/4/18	9:00am		3400	78000							
Increase the frequency of monitoring from 4-8 hourly interval depending on the rate of changes											
11/4/18	3:00pm	48	3500	65000							
11/4/18	9:00pm	47	3700	60000							
12/4/18	3:00am	39	4000	54000							
12/4/18	9:00am	44	4200	52000							
12/4/18	3:00pm	42									
12/4/18	9:00pm	41									
13/4/18	9:00am	40	4500	50000							
13/4/18	9:00pm	40	4800	46000							
14/4/18	9:00am	38	5000	48000							
14/4/18	9:00pm	37	5400	51000							

The rising haematocrit is the first indicator of the leak phase and it's the time to get alerted

The leukocytes recovers before the platelets

Platelets starts trending below 100,000 /cumm and usually recovers after the critical phase is over

Inpatient Management of Group B patients

- If not tolerating oral fluids or the intake is not adequate or the haematocrit (HCT) is rising(leak phase) give isotonic crystalloids(Normal Saline OR Ringer Lactate) in stepwise manner based on ideal body weight
  - 5-7 ml/kg/hr for 1-2 hours
  - 3-5 ml/kg/hr for 2-4 hours
- If patient remains clinically stable and there is no or minimal change in HCT, Continue the isotonic crystalloids
  - 2-3 ml/kg/hr for 2-4 hours
  - Recheck HCT
  - Recheck the clinical status and document before any change.

Inpatient management cont’

- If patient’s clinical parameters are worsening OR HCT is rising
  - Increase isotonic crystalloid to 5-10 ml/kg/hr for 1-2 hours
  - Recheck HCT
  - Reassess clinical status of patient
- If patients clinical parameters are improving decrease the rate of fluids in a stepwise manner
  - 5-10 ml/kg/hr for 1-2 hours
  - 3-5 ml/kg/hr for 2-4 hours
  - 2-3 ml/kg/hr for 2-4 hours

  Clinical status must be reassessed before each change

- If patient condition is not improving OR patient develops compensated shock OR hypotensive shock, this patient should be immediately shifted to monitored beds in HDU/ICU (Group C management group)

Summary of fluid management of Group B Patients.

Febrile Phase

- Management of this phase is essentially similar to outpatient management except for the addition of intravenous fluids in patients who are unable to take adequate oral fluids, or in patients with diarrhoea or vomiting.
- Type of I.V. fluid should be Normal Saline or Hartmann's solution.
- The total amount of fluid (both I.V. and oral) should be limited to 2500 ml for 24 hours for an average adult (2 ml/Kg/hr upto a maximum of 50 Kg of weight).
- However, if there is vomiting or diarrhoea this amount should be increased and dehydration should be corrected.
- It should be emphasized that over-hydration during this phase will not prevent patients developing shock in the Critical phase. In fact it may cause fluid overload during the Critical phase.

- **<u>Critical Phase (Leak Phase)</u>**

- The fluid requirement, **both oral and intravenous**, **in critical phase (36-48 hours)** is calculated as **M+5% (maintenance + 5% deficit).**
- Maintenance (M) is calculated as follows:
  - 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 50kg

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

Therefore the **maximum fluid** requirement for an **average adult** for the entire phase of critical 48 hours is **4600 ml**.

Fluid requirement based on IBW

IBW (kg)	Maintenance	M+5% (ml)	IBW (kg)	Maintenance	M+5% (ml)
5	500	750	35	1800	3550
10	1000	1500	40	1900	3900
15	1250	2000	45	2000	4250
20	1500	2500	50	2100	4600
25	1600	2850	55	2200	4950
30	1700	3200	Avoid more than this limit to avoid fluid overload		

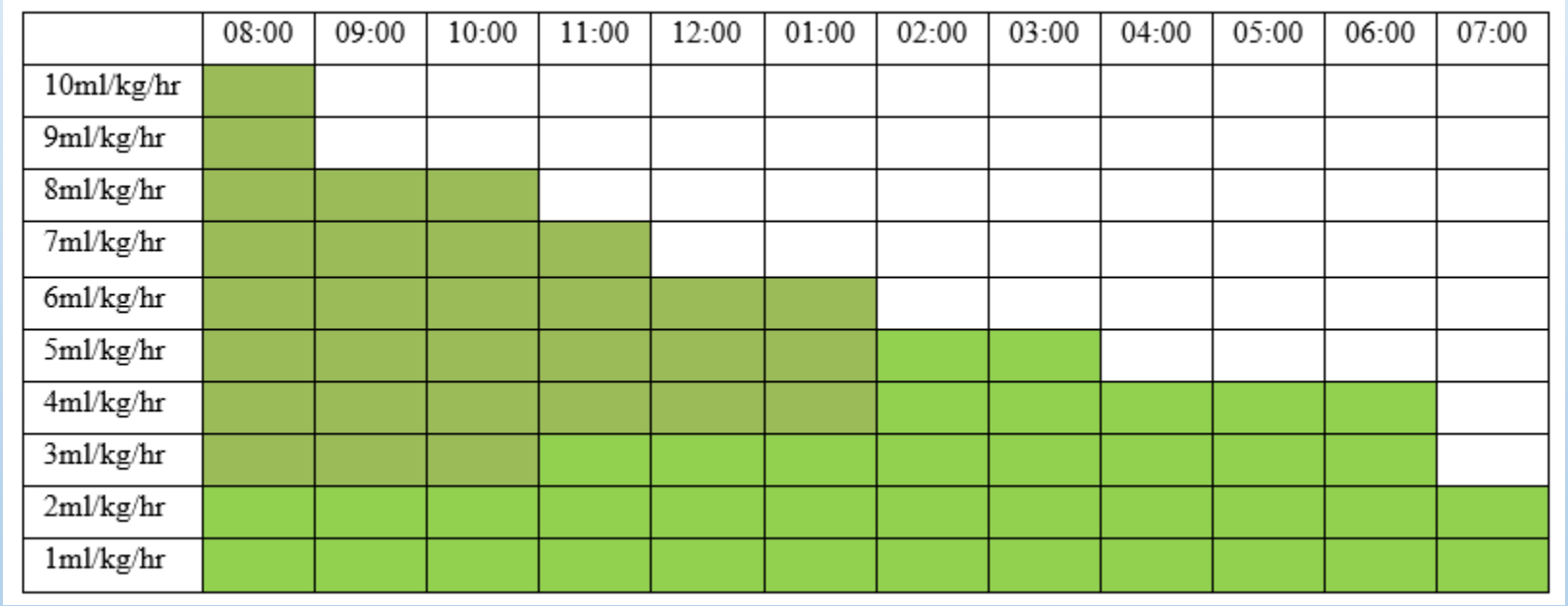
Table : Fluid requirement based on IBW

Usual pattern of fluid replacement in a patient who is admitted for monitoring and found to have leakage of fluids

	08:00	09:00	10:00	11:00	12:00	01:00	02:00	03:00	04:00	05:00	06:00	07:00
10ml/kg/hr												
9ml/kg/hr												
8ml/kg/hr												
7ml/kg/hr												
6ml/kg/hr												
5ml/kg/hr												
4ml/kg/hr												
3ml/kg/hr												
2ml/kg/hr												
1ml/kg/hr												

Example: Usual pattern of fluid replacement during the critical phase. Frequent monitoring and adjustment accordingly.

Usual pattern of fluid replacement in a patient who present in shock



- Extra volume will only be required occasionally if the patient is excessively vomiting or having watery diarrhoea
- If the body weight is less than 50 kg, calculation should be done according to the ideal body weight or actual body weight whichever is less.
- Fluid quota is aimed at giving just adequate amount of fluid to maintain perfusion to vital organs without causing fluid overload.
- Once the fluid quota is exceeded chances of fluid overload is high.
- All patients will not need the full fluid quota of M+ 5% and some may need less than this.

Inpatient Management For group C patients

- Obtain baseline complete blood count and all other relevant laboratory investigations and repeat every 4 hourly or more frequent if required.
- Intake output record of fluids
- Monitor vital signs @ 1-2 hourly minimum and more frequent if clinical status unstable
- Encourage oral fluid intake if tolerating
- Monitor for complications and end organ damage

If patient's HCT is increasing give isotonic crystalloid at 10-20ml/kg bolus over one hour

- Reassess clinical status hourly
- If clinical status has improved reduce crystalloids to 7-10 ml/kg/hr for 1-2 hours, if continued improvement continue reducing fluids 1-2 hourly with regular assessment before every change
- If clinical status has not improved, recheck HCT, if HCT increasing repeat Isotonic crystalloid bolus as above OR colloid (10%Dextran-40) bolus at the rate of 20ml/kg over 15 minutes, repeat HCT if improving taper fluids at the rate of
  - Colloid 10-20 ml/kg over ½-1 hour, reassess
  - Colloid 7-10 ml/kg/hr for 1-2 hours, reassess if improving switch to crystalloids.

The ABCS of severe dengue management

If patient's HCT is decreasing along with hemodynamic worsening

- Check clinically, hematologically and radiologically for any revealed or concealed bleeding (B)
- Transfuse PRBC(Packed Red Blood Cells) at the rate of 5-10 ml/kg OR 10-20 ml/kg whole blood immediately.
- Check for Acidosis(A), along with Renal Function tests and liver function tests
- Check serum Calcium(C) as hypocalcaemia is found in majority of DHF patients and in more severe cases calcium supplementation should be done
- Check blood sugar(S) and correct it accordingly.

Indications for colloids(Dextran-40)

- Signs of fluid overload
  - Dyspnoea, Tachypnoea
  - Puffy Eyelids, tense/distended abdomen
  - Fluid at lung bases (crepts)

- Persistently high HCT of > 30% from the baseline for more than 3-6 hours.

How to give Dextran-40?

- Always give in a bolus dose
  - 10ml/kg/hr in children as a bolus over 15 minutes
  - 500ml/hr in adults as a bolus at the rate of 10ml/kg over 15 minutes and can go up to a max of 20ml/kg.
- HCT before and immediately after the bolus
  - If HCT drops >10 indicates significant improvement or
  - If HCT drops below baseline indicates bleeding
- Maximum dose
  - 30ml/kg/24hrs or 60ml/kg/48 hrs of leakage in children
  - 1500 ml/24 hrs or 3000 ml/48 hrs of leakage

Management of fluid overload

- Fluid overload is a usually caused by over hydration due to multiple reasons, whenever fluid overload is observed quickly review the total fluid intake, check for ABCS and correct them.

- If the patient is still in shock or in the critical phase, or plasma leakage and no signs of reabsorption 10ml/kg/hr or 500ml/hr in adults of colloid bolus(Dextran-40) should be given before giving frusemide, in shock cases the blood pressure usually restores within 10-30 minutes, then administer 1mg/kg or 40 mg in adults of frusemide IV and continue the Dextran-40 to complete its dose.

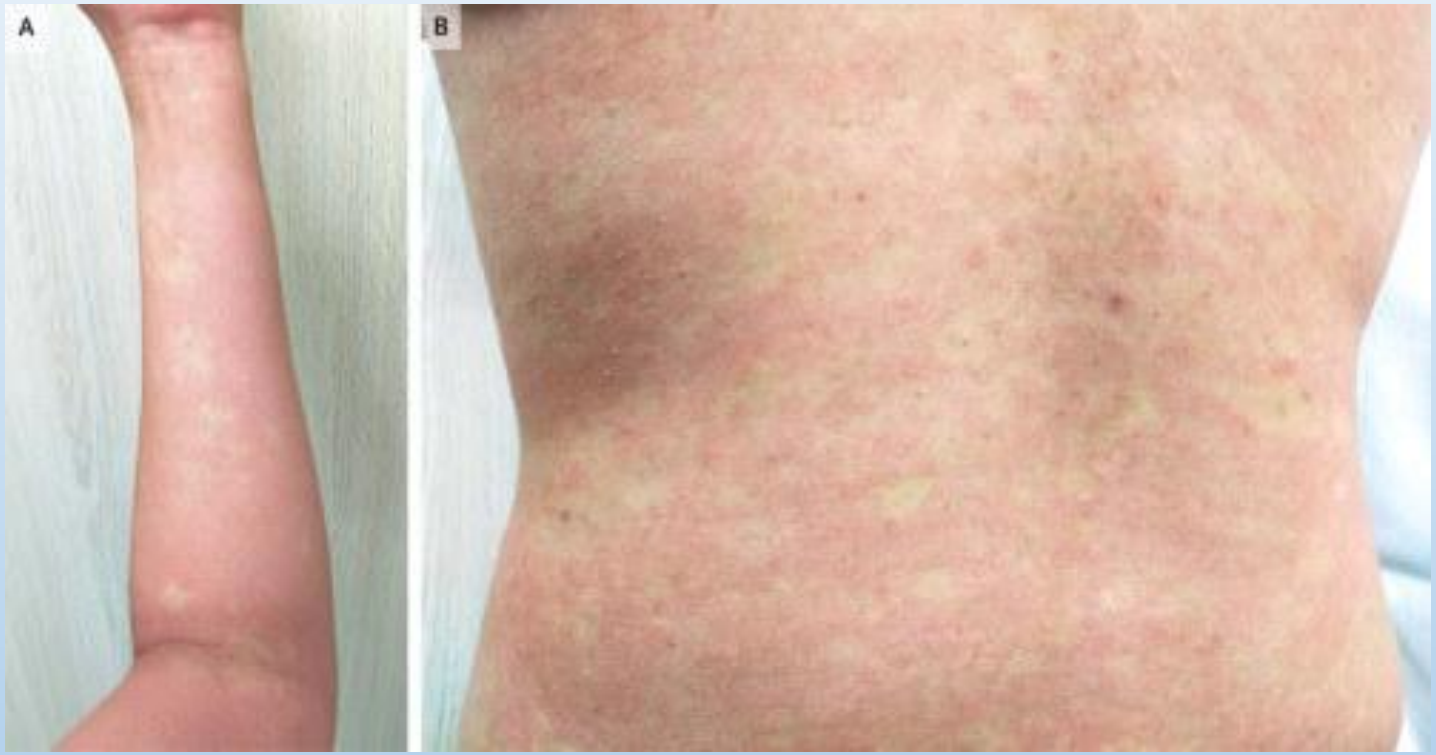
- The IV fluid can be reduced to 1ml/kg/hr or 40ml/hr and can be adjusted in order to obtain a urine output of 0.5ml/kg/hr.
- If HCT is rising again the dose of Dextran can be repeated, frusemide can be repeated if required after every 30-60 minutes.
- If the patient is in the convalescence phase with stable vitals and fluid overloaded frusemide may be used without dextran.

Management of convalescence phase

- This is common for both group B and C patients and can be recognised by the improvement in the clinical parameters and hemodynamic status with good peripheral perfusion, stable vital signs and a normalising HCT or could be below normal.

  - The IV fluid should be discontinued
  - Hypervolemia may occur and may require diuretic therapy if any signs of respiratory distress are present as discussed in the fluid overload management
  - Hypokalemia may be found and should be corrected with supplements if required
  - Convalescent rash which is confluent petechial and at times itchy on the extremities is a sign of relief for the doctor.

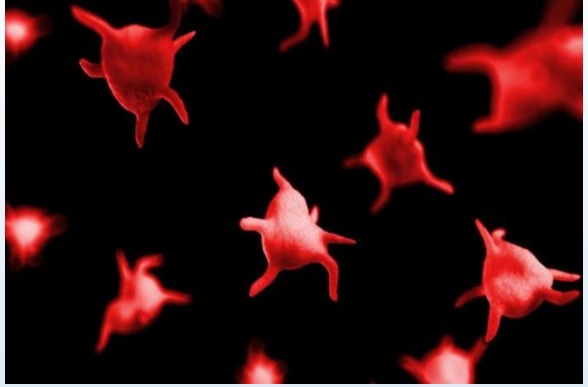
Convalescent rash of dengue



Nonblanching, maculopapular, erythematous rash surrounding scattered patches of unaffected skin on the (A) arm and (B) trunk, classically characterized as white islands in a sea of red.

https://www.dynamedex.com/condition/dengue

Platelet transfusion



- Prophylactic transfusion with platelets does not produce sustained changes in the coagulation status and platelet count in patients with DHF.
- It does not change or reduce the bleeding outcome in DHF either.
- Platelet transfusions can lead to fluid overload resulting in pulmonary oedema causing respiratory embarrassment and allergic reactions including anaphylaxis. Therefore, prophylactic transfusion of platelets is not recommended at any counts
  However, platelet transfusions may be required in a patient with thrombocytopenia who is to undergo an urgent surgery, has active bleeding which continues in spite of repeated blood transfusions, DIC or in patients with intracranial haemorrhage.

Prophylactic platelet transfusion plus supportive care versus supportive care alone in adults with dengue and thrombocytopenia: a multicenter, open-label, randomized, superiority trial

- Conclusion: In adult patients with dengue and thrombocytopenia, prophylactic platelet transfusion was not superior to supportive care in preventing bleeding, and might be associated with adverse events.

- www.thelancet.com Vol 389 April 22, 2017

Lack of Efficacy of Prophylactic Platelet Transfusion for Severe Thrombocytopenia in Adults with Acute Uncomplicated Dengue Infection.

- The incidence of clinical bleeding was 6% among patients with platelet count >150×10^3 platelets/μL, 12% among patients with platelet count of 100–149×10^3 platelets/μL, 11% among patients with platelet count of 80–99×10^3 platelets/μL, 10% among patients with platelet count of 50–79×10^3 platelets/μL, 11% among patients with platelet count of 20–49×10^3 platelets/μL, 13% among patients with platelet count of 10–19×10^3 platelets/μL, and 0% among patients with platelet count <10×10^3 platelets/μL
- Our study further strengthens the evidence that **thrombocytopenia in acute dengue infection does not correlate with bleeding risk**
- In pediatric DSS, prophylactic transfusion of **platelets and fresh frozen plasma did not reduce bleeding or expedite platelet recovery**; instead, **it caused fluid overload and prolonged hospitalization**. In addition, the improvement in platelet count was transient, lasting <5 h .
- We have shown that **prophylactic platelet transfusion did not improve relevant outcome measures, such as clinical bleeding, platelet increment, and platelet recovery.**

Clinical Infectious Diseases, Volume 48, Issue 9, 1 May 2009, Pages 1262–1265

Effectiveness of Platelet Transfusion in Dengue Fever: A Randomized Controlled Trial

- In this trial, almost half the patients showed no response to a high-dose platelet transfusion. **Platelet transfusion did not prevent development of severe bleeding or shorten time to cessation of bleeding and was associated with significant side effects.**

- Therefore, platelet transfusion should not be routinely done in the management of dengue fever.

- Transfus Med Hemother. 2013 Oct; 40(5): 362–368

Preventive transfusion in Dengue shock syndrome-is it necessary?

- We compared 53 patients with Dengue shock syndrome (DSS) who received preventive transfusions with 53 who did not. **Significant differences in the development of pulmonary edema and length of hospitalization (P<.05) and none in hemorrhage (P=.136) were observed.**
- **Preventive transfusions did not produce sustained improvements in the coagulation status in DSS.**

- J Pediatr. 2003 Nov;143(5):682-4. doi: 10.1067/s0022-3476(03)00503-1

Effect of Platelet Transfusion on Clot Strength in Dengue Fever with Thrombocytopenia Related Bleeding: A Thromboelastography-Based Study

- This study observed that platelet transfusion in dengue patients with bleeding complication improved the absolute platelet count with no improvement in clot strength.

- Transfus Med Hemother 2019;46:457–460

Indications for Blood transfusion in dengue patients

- Bleeding of >6-8 ml/kg/hr in children and >300 ml in adults
- HCT is dropping but no clinical improvement
- When a patient with dengue present in shock but no rising of HCT, as in dengue shock without blood loss the HCT should rise at least 20% above the baseline and can go up to ¬40% in profound shock.

Diuretics/frusemide

Intravenous frusemide (10-20mg) could be used in the following circumstances:

1. In fluid overloaded patients who are haemodynamically stable
2. In fluid overloaded patients who are haemodynamically unstable in the midway of a colloid infusion or a blood transfusion during the critical phase

Antibiotics

Use of antibiotics has no role in Dengue infection, the only place where empiric antibiotics can be used is a patient in sepsis secondary to organ failure or superadded infections which are rare.

Special Circumstances during management.

- Patient with rising ALT/AST of 1000units or above, manage as pre-hepatic coma to prevent encephalopathy and add vitamin K and possibly FFP if the coagulation profile is deranged.

- **Patients in encephalopathy**: a majority of these are secondary to hepatic failure from prolonged shock , other causes are electrolyte abnormalities, hypoglycaemia that are correctable , rarely some cases could be due to intracranial bleeding

- **Diabetic patients**: avoid glucose containing crystalloids and switch to regular insulin during the inpatient management and maintain the level around 200mg/dl

- **Anticoagulant therapies**: discontinue aspirin warfarin etc for 3-5 days during the critical phase and consult cardiologist.

- **Cardiac patients**: the fluid management in these patients is more complex if there is a baseline element of cardiac dysfunctions and failures. The monitoring frequency will be more and the fluid replacement should always be done in HDU settings

- **Pregnancy**: not to miss HELLP and chances of vertical transmission should be considered.

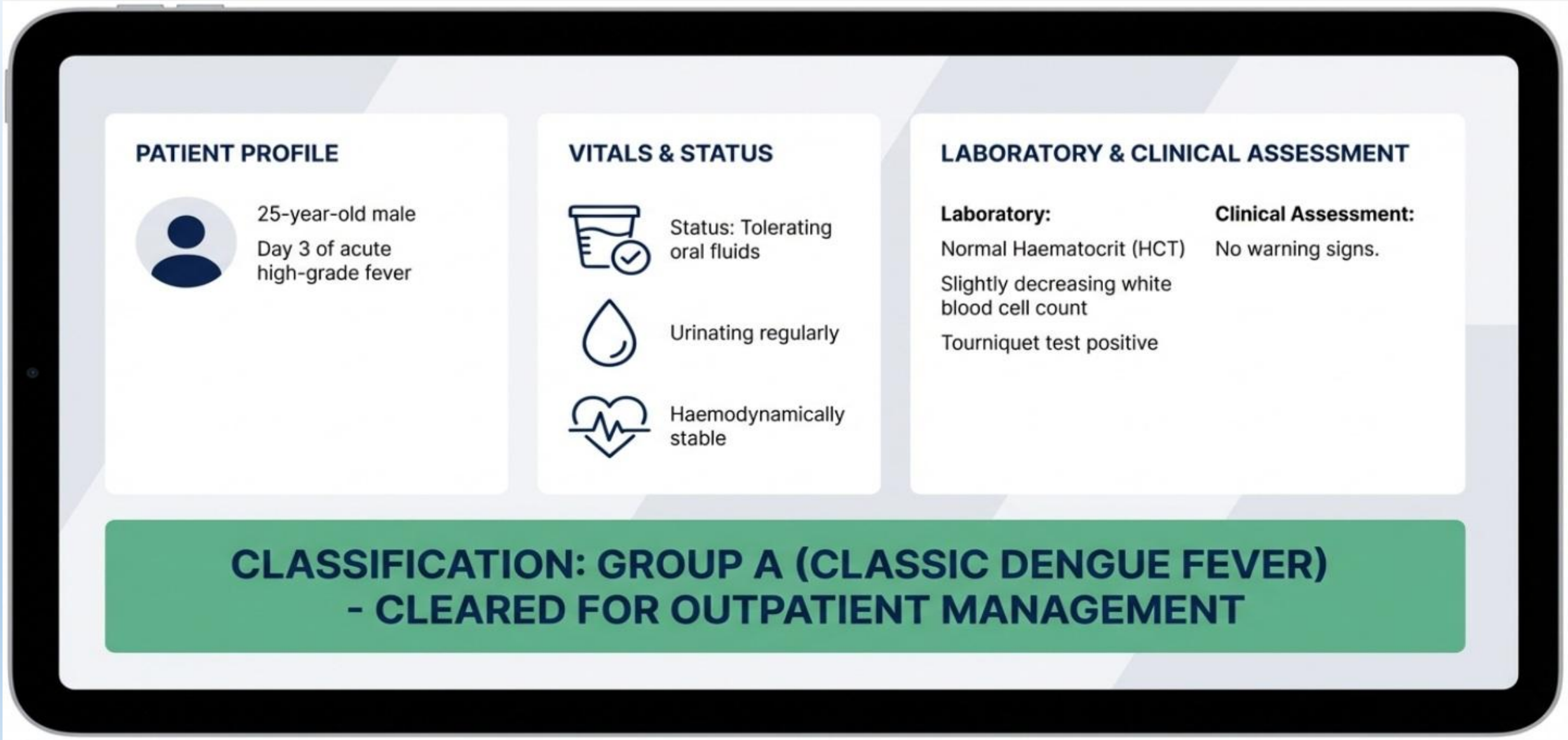
- **Infants**: usually have a shorter leak/ critical phase and the usually seen leukopenia may not be observed, similarly the unusual presentations like diarrhoeas and convulsion may mask the diagnosis, the monitoring should be more frequent compared to the adults

- **Obese patients**: the respiratory reserve is less and any fluid mismanagement will lead to quick deterioration so IBW should be calculated and fluid replacement should be done as per IBW.

The Triage Matrix: Defining Dengue Severity

Group A - Sent Home	Group B - Inpatient	Group C - Emergency/ICU
Undifferentiated/Classic Dengue Fever • No warning signs. • Tolerates adequate volume of oral fluids. • Passes urine at least once every 6 hours.	**Dengue with Warning Signs** Key signs: • Intense abdominal pain/tenderness • Persistent vomiting • Clinical fluid accumulation • Mucosal bleed • Lethargy/restlessness • Liver enlargement >2cm • Concurrent increase in Haematocrit (HCT) with rapid platelet drop (Also includes patients with comorbidities/social risks)	**Severe Dengue / Dengue Shock Syndrome (DSS)** Features: • Severe plasma leakage leading to shock or respiratory distress • Severe bleeding • Severe organ impairment (AST/ALT ≥ 1000)

Scenario


PATIENT PROFILE
25-year-old male
Day 3 of acute high-grade fever
VITALS & STATUS
Status: Tolerating oral fluids
Urinating regularly
Haemodynamically stable
LABORATORY & CLINICAL ASSESSMENT
Laboratory:
Normal Haematocrit (HCT)
Slightly decreasing white blood cell count
Tourniquet test positive
Clinical Assessment:
No warning signs.
CLASSIFICATION: GROUP A (CLASSIC DENGUE FEVER) - CLEARED FOR OUTPATIENT MANAGEMENT

Group A Protocol: Outpatient Management

Supportive Care

Emphasise adequate bed rest and high oral fluid intake.

Medication Rule

Paracetamol only (Maximum 4g/day in adults).

Monitoring

Follow up daily for disease progression (FBCs, watching for decreasing platelets or increasing HCT).

Strict Return Advice: Instruct immediate return if warning signs appear. Watch for the critical phase (defervescence).

Clinical Pearl

DO NOT use NSAIDs or corticosteroids. They increase the increase the risk of GI bleeding and immunosuppression.

Scenario 2: The Patient with Warning Signs

PATIENT PROFILE

40-year-old female

Day 5 of illness
(defervescence phase)

VITALS & STATUS

Status:

- Complaining of severe, continuous abdominal pain
- Persistent vomiting
- Cannot tolerate oral fluids

LABORATORY & CLINICAL ASSESSMENT

Laboratory:
Progressive increase in Haematocrit (HCT) concurrent with a rapid decrease in platelet count.

CLASSIFICATION: GROUP B (DENGUE HAEMORRHAGIC FEVER GRADE I/II)
- Requires immediate Inpatient Admission

Group B Protocol: Step-Down Fluid Titration

Fluid Choice: Isotonic crystalloids (0.9% Normal Saline or Ringer's Lactate).

Step 1
Start at 5–7 ml/kg/hr
Duration: 1–2 hours

Step 2
Reduce to 3–5 ml/kg/hr
Duration: 2–4 hours

Step 3
Reduce to 2–4 ml/kg/hr

Clinical Pearl
Discontinue IV fluids after 48 hours maximum to prevent fluid overload.

Scenario 3: The Critical Patient in Shock

PATIENT PROFILE

12-year-old

Day 6 of illness

VITALS & STATUS

- Profound hypotension
- Narrow pulse pressure (<20 mmHg)
- Cold extremities, prolonged capillary refill time, tachycardia

LABORATORY

Extremely high baseline Haematocrit (HCT) indicating severe plasma leakage.

CLASSIFICATION: GROUP C (SEVERE DENGUE / DENGUE SHOCK SYNDROME))
- Emergency ICU referral required

Group C Protocol: Emergency Resuscitation

Pathway 1: Compensated Shock
(Circulatory failure manifested by narrow pulse pressure)

Start IV Isotonic Crystalloids
5–10 ml/kg/hr over 1 hour
Re-evaluate continuously.

Pathway 2: Hypotensive Shock
(Systolic BP <90mmHg or >20% reduction)

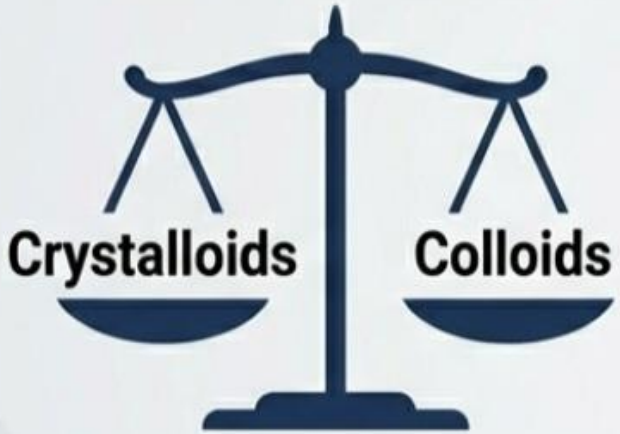
Immediate IV bolus of Crystalloids or Colloids
10–20 ml/kg over 15–30 minutes

Critical Rule

Obtain HCT levels before hydrating, but lack of HCT should never delay the start of life-saving hydration.

The Fluid Debate: Crystalloids vs. Colloids

The Evidence (RCT Data)



- Based on three randomized controlled trials (RCTs) comparing fluid regimes in dengue shock, there is no overall advantage to the use of colloids over crystalloids for general outcomes.

The Exception: When to use Colloids

- Intractable shock (pulse pressure <10 mmHg).
- When blood pressure must be restored urgently.

Why?

Hyper-oncotic colloids (osmolarity >300 mOsm/L) restore the cardiac index and reduce Haematocrit levels faster than crystalloids in these specific, severe cases.

PRINCIPLES OF MANAGEMENT

Shock
(Under-treatment)

Fluid Overload
(Over-treatment)

- ☑ **1. ANTICIPATION:** Monitor warning signs during defervescence.
- ☑ **2. FLUID IS THE DRUG:** Oral for mild, IV for severe.
- ☑ **3. TRIAGE:** Early recognition prevents death.
- ☑ **4. PUBLIC HEALTH:** Early notification is vital for outbreak control.

Dengue Co-Infection with COVID-19

As the management plan and IPC requirements for both are very different these patients need to be managed in isolation units for COVID-19 patients.

Frequent monitoring during the critical phase of Dengue fever and careful volume resuscitation just to maintain perfusion to vital organs and to avoid volume overload

Avoid prophylactic anticoagulation during the critical phase of Dengue fever

The risk vs benefits for various treatment options can be assessed on a case to case basis by the treating physician

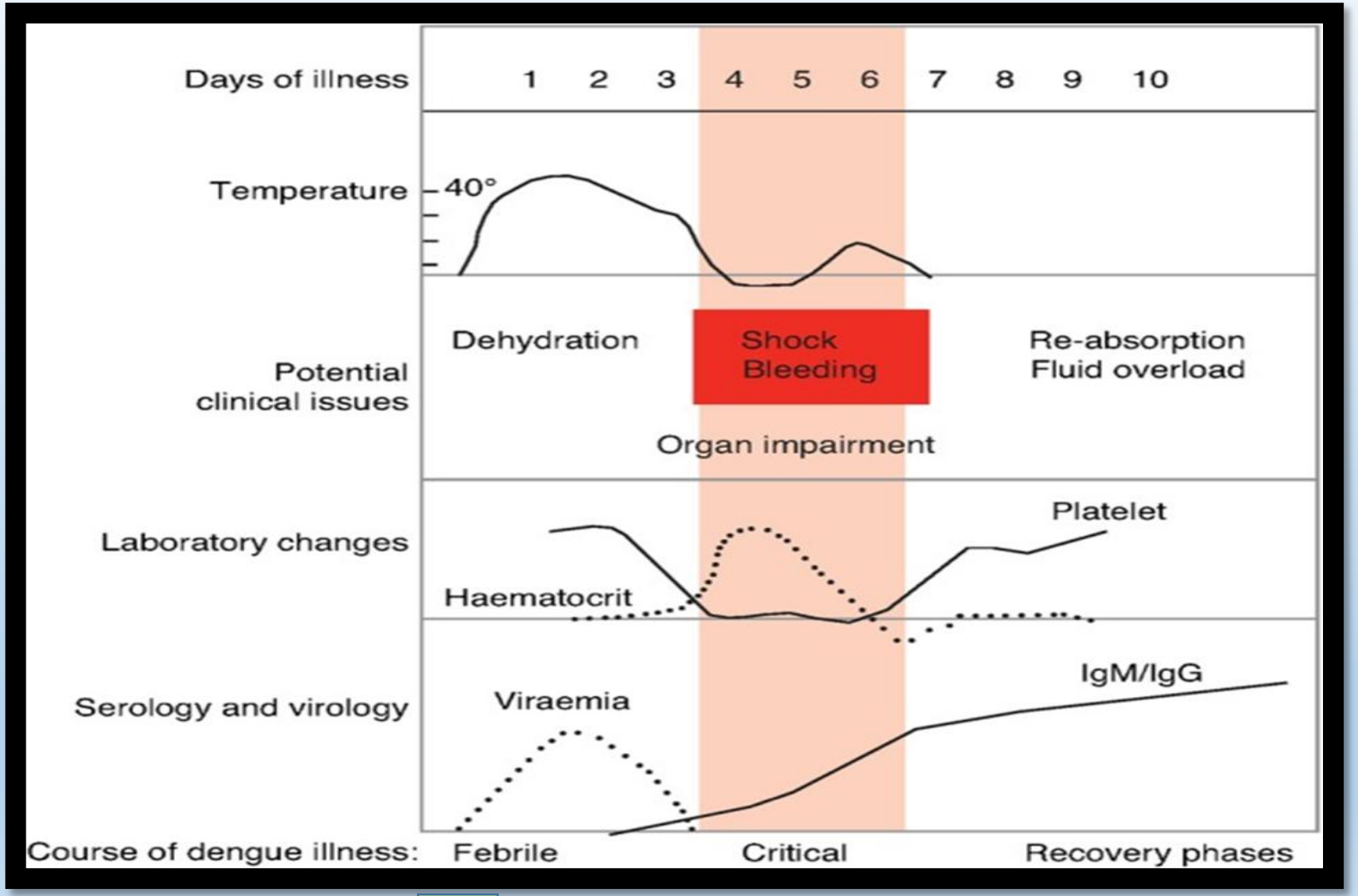
Rare Complications

- Sepsis
- Upper gastrointestinal bleeding
- Bleeding into abdominal cavities
- Myocarditis
- Pancreatitis
- Eye complications
  - uveitis
  - macular edema and blot hemorrhages
  - cotton wool spots
  - retinal vasculitis
  - exudative retinal detachment

- Neurologic complications
  - encephalitis
  - meningitis
  - Guillain-Barre syndrome
  - myelitis
  - acute disseminated encephalomyelitis
  - mono or polyneuropathy
  - Intracranial hemorrhage
  - myositis and hypokalemic paralysis

Natural course of Symptomatic Dengue

The potential clinical issues occurs in 10-15 % of the patients only.



Important to know about Dengue

- There are 4 distinct, but closely related, serotypes of the virus that cause dengue (DEN-1, DEN-2, DEN-3 and DEN-4).
- Recovery from infection by one provides lifelong immunity against that particular serotype.
- Cross-immunity to the other serotypes after recovery is only partial and temporary.
- Subsequent infections by other serotypes increases the risk of developing severe dengue.

Discharge criteria

The following criteria should be fulfilled before discharge from hospital.

- ✓No fever for at least 24 hours without the usage of antipyretic drugs
- ✓At least two days have lapsed after recovery from shock
- ✓Good general condition with improving appetite
- ✓Normal HCT at baseline value or around 38 - 40 % when baseline value is not known
- ✓No distress from pleural effusions
- ✓No/minimal ascites
- ✓Platelet count is gradually improving
- ✓No other complications

DENGUE CASE REPORTING FORM

EPID NO/S No:_____

Health Facility/reporting site details

Date _____Health Facility Name_____

Address _____Contact No _____

Reporting Doctor Name _____

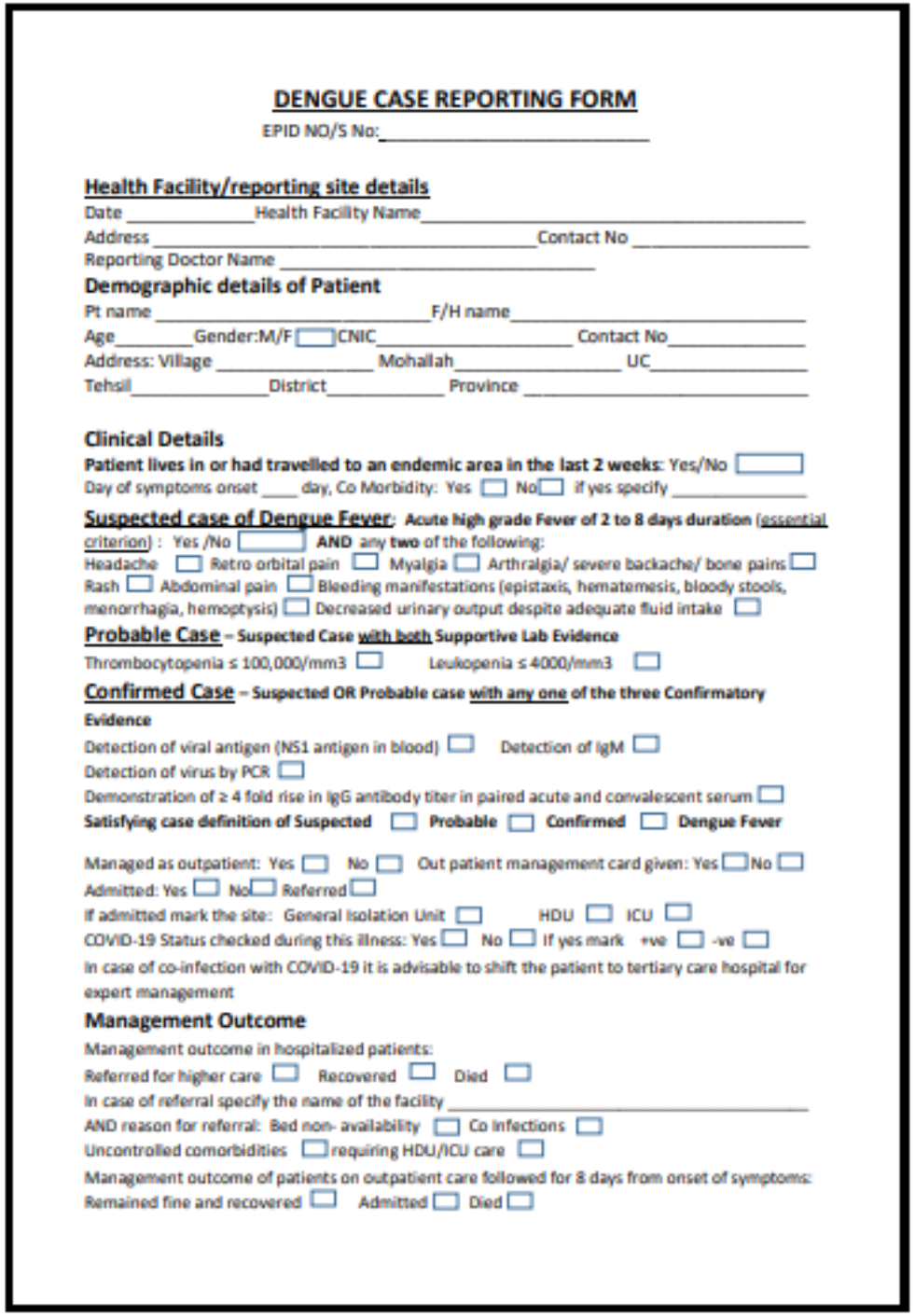
Demographic details of Patient

Pt name _____F/H name_____

Age_____Gender:M/F ☐ CNIC_____ Contact No_____

Address: Village _____ Mohallah_____ UC_____

Tehsil_____District_____ Province _____



DENGUE CASE REPORTING FORM

EPID NO/S No:_____

Health Facility/reporting site details

Date _____Health Facility Name_____

Address _____Contact No _____

Reporting Doctor Name _____

Demographic details of Patient

Pt name _____F/H name_____

Age_____Gender:M/F ☐ CNIC_____ Contact No_____

Address: Village _____ Mohallah_____ UC_____

Tehsil_____District_____ Province _____

Clinical Details

Patient lives in or had travelled to an endemic area in the last 2 weeks: Yes/No ☐

Day of symptoms onset ____ day, Co Morbidity: Yes ☐ No☐ if yes specify _____

Suspected case of Dengue Fever: **Acute high grade Fever of 2 to 8 days duration** (essential criterion) : Yes /No ☐ **AND** any **two** of the following:

Headache ☐ Retro orbital pain ☐ Myalgia ☐ Arthralgia/ severe backache/ bone pains ☐

Rash ☐ Abdominal pain ☐ Bleeding manifestations (epistaxis, hematemesis, bloody stools, menorrhagia, hemoptysis) ☐ Decreased urinary output despite adequate fluid intake ☐

Probable Case – **Suspected Case with both Supportive Lab Evidence**

Thrombocytopenia ≤ 100,000/mm3 ☐ Leukopenia ≤ 4000/mm3 ☐

Confirmed Case – **Suspected OR Probable case with any one of the three Confirmatory Evidence**

Detection of viral antigen (NS1 antigen in blood) ☐ Detection of IgM ☐

Detection of virus by PCR ☐

Demonstration of ≥ 4 fold rise in IgG antibody titer in paired acute and convalescent serum ☐

Satisfying case definition of Suspected ☐ **Probable** ☐ **Confirmed** ☐ **Dengue Fever**

Managed as outpatient: Yes ☐ No ☐ Out patient management card given: Yes ☐ No ☐

Admitted: Yes ☐ No☐ Referred ☐

If admitted mark the site: General Isolation Unit ☐ HDU ☐ ICU ☐

COVID-19 Status checked during this illness: Yes ☐ No ☐ If yes mark +ve ☐ -ve ☐

In case of co-infection with COVID-19 it is advisable to shift the patient to tertiary care hospital for expert management

Management Outcome

Management outcome in hospitalized patients:

Referred for higher care ☐ Recovered ☐ Died ☐

In case of referral specify the name of the facility _____

AND reason for referral: Bed non- availability ☐ Co infections ☐

Uncontrolled comorbidities ☐ requiring HDU/ICU care ☐

Management outcome of patients on outpatient care followed for 8 days from onset of symptoms:

Remained fine and recovered ☐ Admitted ☐ Died ☐

Clinical Details

Patient lives in or had travelled to an endemic area in the last 2 weeks: Yes/No ☐

Day of symptoms onset ____ day, Co Morbidity: Yes ☐ No☐ if yes specify _____

Suspected case of Dengue Fever: **Acute high grade Fever of 2 to 8 days duration** (essential criterion) : Yes /No ☐ **AND** any **two** of the following:

Headache ☐ Retro orbital pain ☐ Myalgia ☐ Arthralgia/ severe backache/ bone pains ☐

Rash ☐ Abdominal pain ☐ Bleeding manifestations (epistaxis, hematemesis, bloody stools, menorrhagia, hemoptysis) ☐ Decreased urinary output despite adequate fluid intake ☐

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Uncontrolled comorbidities ☐ requiring HDU/ICU care ☐

Management outcome of patients on outpatient care followed for 8 days from onset of symptoms:

Remained fine and recovered ☐ Admitted ☐ Died ☐

DON'Ts OF Dengue Management

- DON'T use corticosteroids. They are not indicated and can increase the risk of GI bleeding, hyperglycaemia, and immunosuppression.
- DON'T give platelet transfusions for a low platelet count. Platelet transfusions do not decrease the risk of severe bleeding and may instead lead to fluid overload and prolonged hospitalization.
- DON'T give half normal (0.45%) saline. Half normal saline should not be given, even as a maintenance fluid, because it leaks into third spaces and may lead to worsening of ascites and pleural effusions.
- DON'T assume that IV fluids are necessary. First check if the patient can take fluids orally. Use only the minimum amount of IV fluid to keep the patient well-perfused. Decrease IV fluid rate as hemodynamic status improves or urine output increases.

- DON’T miss checking ideal body weight.
- DON’T miss to check that the blood collection for laboratory workup is standardised and the haematology analyser is calibrated regularly.
- DON’T give NSAIDS for fever control.

DO's of Dengue Management

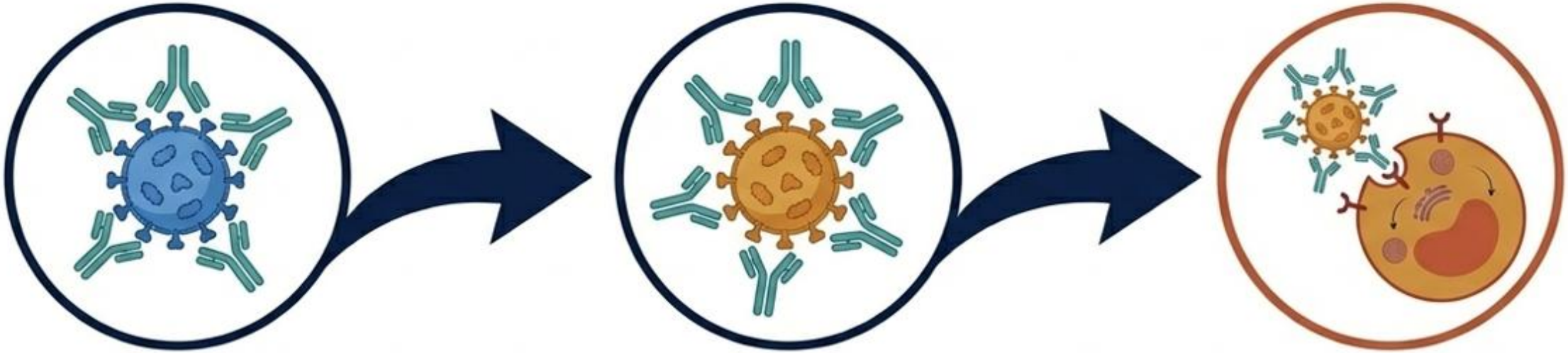
- DO tell outpatients when to return. Teach them about warning signs and their timing, and the critical period that follows defervescence.
- DO recognize the critical period. The critical period begins with defervescence and lasts for 24–48 hours. During this period, some patients may rapidly deteriorate.
- DO closely monitor fluid intake and output, vital signs, and hematocrit levels. Intake and output should be measured at least every shift and vitals at least every 4 hours. Hematocrits should be measured every 6–12 hours at minimum during the critical period.
- DO check for earlier leak phase by doing ultrasound.

DO's of Dengue Management

- DO recognize and treat early shock. Early shock (also known as compensated or normotensive shock) is characterized by narrowing pulse pressure (systolic minus diastolic BP approaching 20 mmHg), increasing heart rate, and delayed capillary refill or cool extremities.
- DO administer colloids (such as albumin/10% dextran-40) for refractory shock. Patients who do not respond to 2–3 boluses of isotonic saline should be given colloids instead of more saline.
- DO give PRBCs or whole blood for clinically significant bleeding. If hematocrit is dropping with unstable vital signs or significant bleeding is apparent, immediately transfuse blood.

Dengue Vaccination

The Biological Roadblock: Antibody-Dependent Enhancement (ADE)



1. First Infection

Mild symptoms. Body produces antibodies against one of the 4 DENV serotypes.

2. Cross-Reaction

Non-neutralising antibodies persist but cannot defeat a different serotype.

3. The Trojan Horse

Upon secondary infection, antibodies facilitate viral uptake into immune cells, triggering severe Dengue Haemorrhagic Fever.

This leads to viral replication within immune cells and a severe, life-threatening inflammatory response.

Vaccine Strategy: The Tetravalent Approach

- Because protection against only one serotype can increase the risk of severe disease during a future infection with a different one, current approved vaccines (like Dengvaxia and QDENGA) are tetravalent
- They are specifically designed to stimulate the immune system to produce functional neutralizing antibodies against all four serotypes simultaneously
- Dengvaxia targets the pre-membrane (prM) and envelope (E) proteins of all four serotypes
- QDENGA uses a DENV-2 genetic backbone but includes components designed to protect against all four strains

Dengue Vaccine

- Dengvaxia is a tetravalent, live-attenuated dengue vaccine FDA approved for use in children aged 6-16 years
- give vaccine ONLY if patient
  - has lab-confirmed previous dengue virus infection, AND
  - is living in endemic region for dengue
- DO NOT vaccinate a person without lab-confirmed evidence of previous dengue infection
  - dengue vaccine can increase risk of hospitalization or severe dengue in patients without prior dengue infection
  - lab testing requirements for vaccination with dengue vaccine
    - positive viral culture for dengue
    - IgM seroconversion in paired sera (1 during acute infection and 1 after recovery)
    - IgG seroconversion or 4-fold IgG titer increase in paired sera
    - positive dengue antigen testing (NS1)
    - positive polymerase chain reaction (PCR) for dengue virus RNA

The Dengue Vaccine Matrix

	Dengvaxia (CYD-TDV)	Qdenga (TAK-003)	Butantan-DV	mRNA Candidates
Valency	Tetravalent	Tetravalent	Tetravalent	Tetravalent
Dose Schedule	3 Doses	2 Doses	1 Dose	TBD
Seronegative Efficacy	Low / Harmful ⚠	Moderate	High ↗	Experimental ⚙
Key Limitation	Pre-screening required	DENV-3 gap	Pending long-term data	Ultra-cold chain needs ❄

We are here in terms of approved till date

Research into "Universal" Antibodies

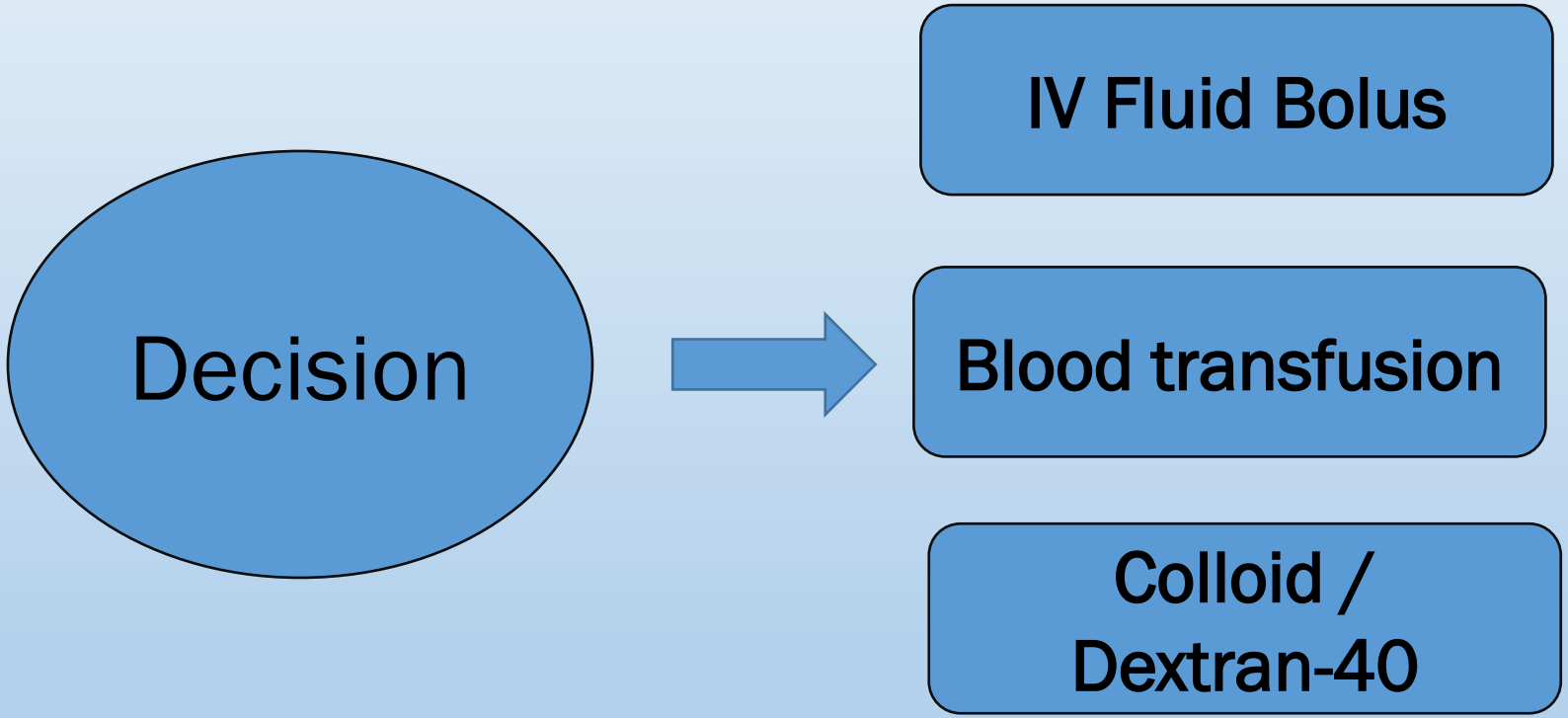
- While current vaccines use a four-pronged (tetravalent) approach, researchers are exploring ways to elicit broadly neutralizing antibodies

For example:

- Preclinical research has used algorithms to create antigens that elicit antibodies capable of neutralizing all four serotypes regardless of prior exposure
- Other studies involve virus-like particles (VLPs) designed to induce high levels of neutralizing antibodies against all four strains without causing ADE
- These "broadly reactive" candidates are still under evaluation and are not yet available in approved vaccines

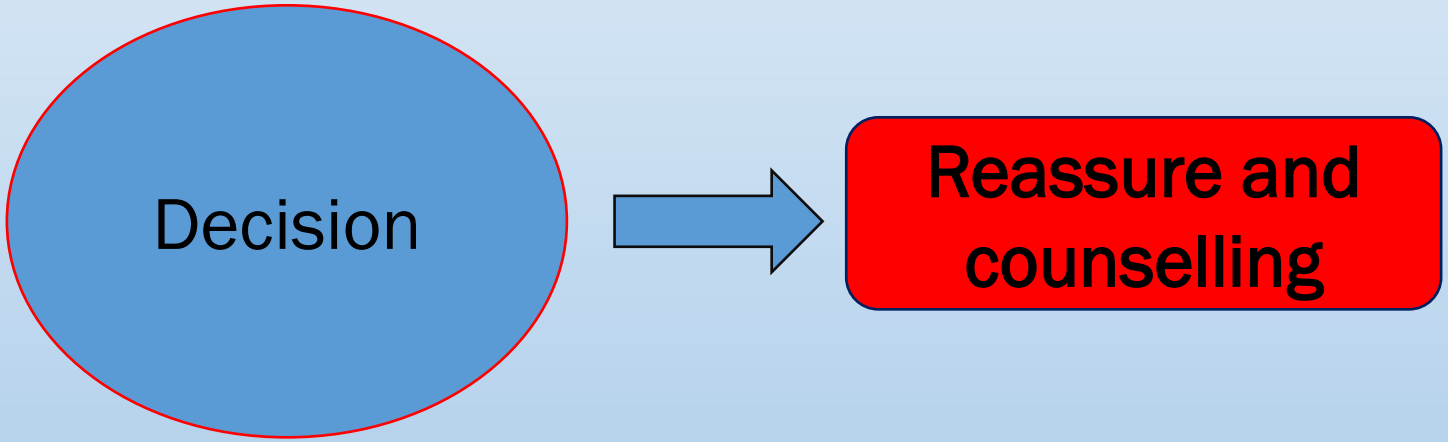
Case scenario 1

- Afebrile Pt.
- Restless
- Irritable
- Pulse rate ↑
- Pulse volume poor
- CRFT>2 sec
- Skin cold
- Pulse pressure<20
- HCT ↑
- Urine output<0.5 ml/kg



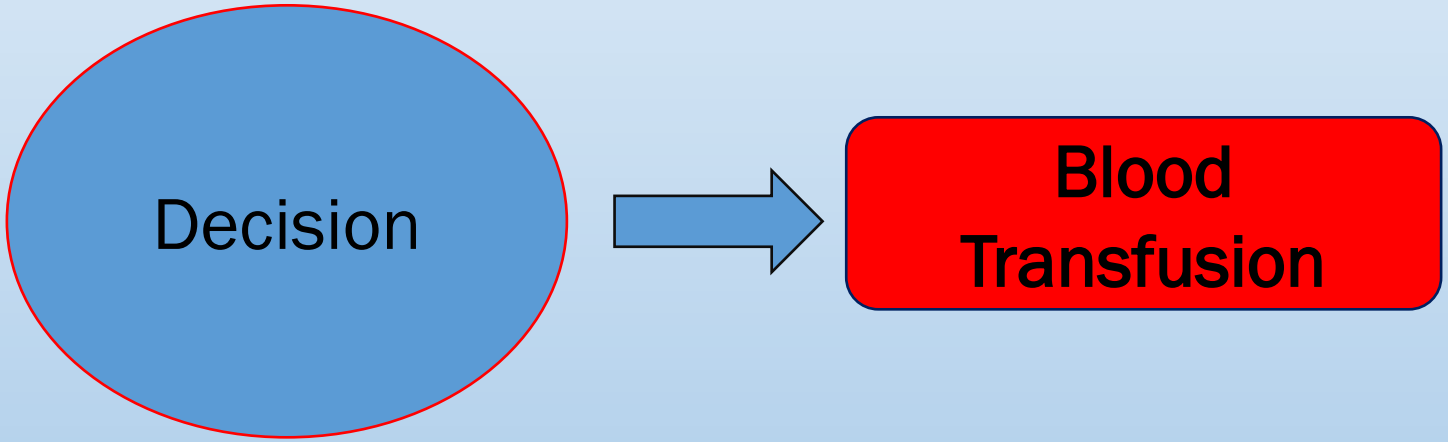
Case Scenario 2

- Total duration of illness 8days
- Afebrile
- Alert
- BP 140/90 mmhg
- Pulse volume good
- Skin rash
- CRFT<2 sec
- Urine output > 0.5ml/kg/hr
- PR 72/min
- PP 50
- HCT 42



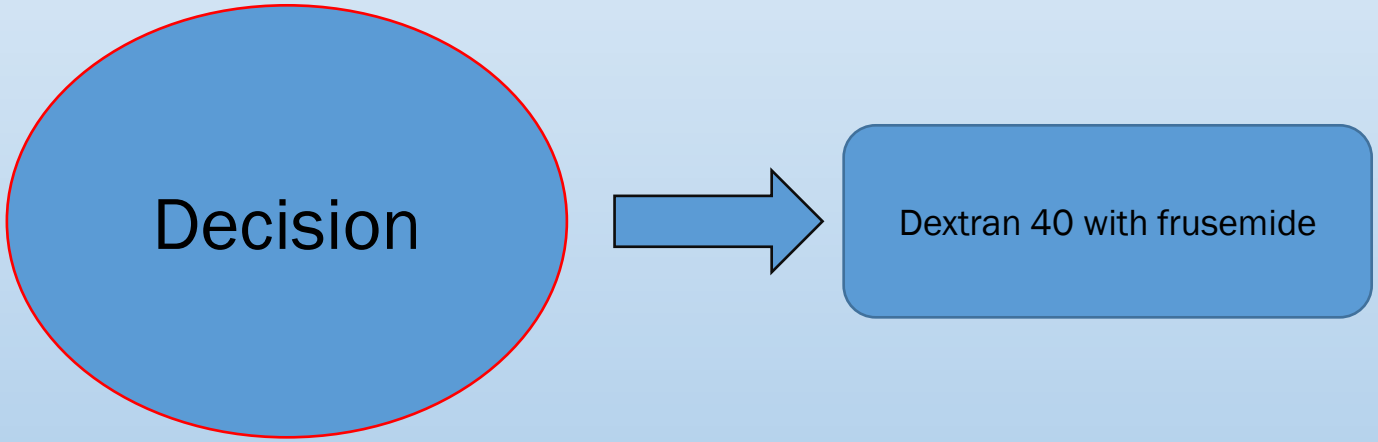
Case Scenario 3

- Afebrile
- Restless
- Confused
- Pulse volume poor
- Skin pale
- CRFT>2 sec
- Urine output < 0.5ml/kg/hr
- PR ↑
- BP ↓
- PP ↓
- HCT ↓



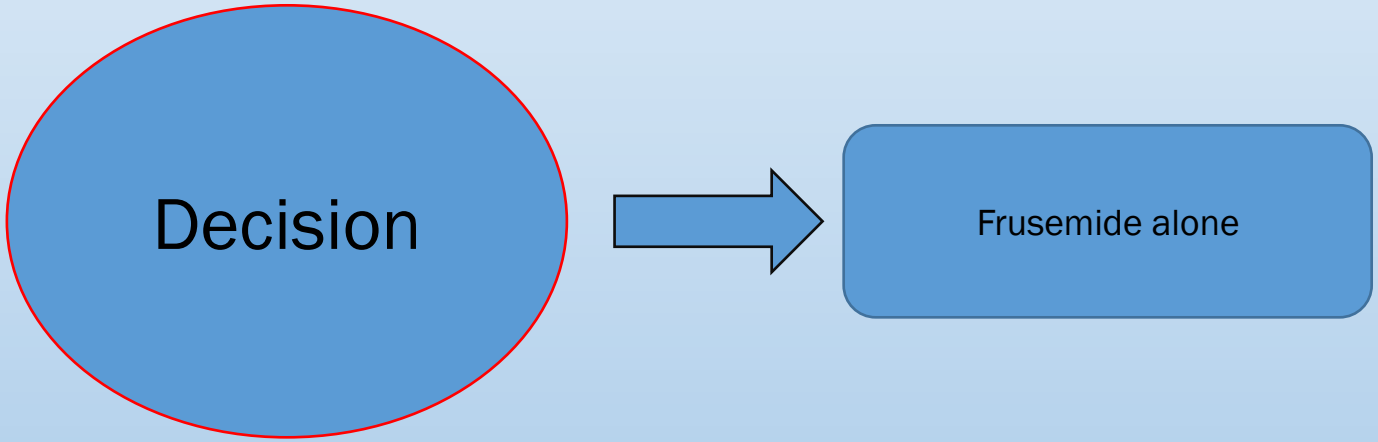
Case Scenario 4

- Total duration of illness 6 days
- Afebrile patient
- Puffy eyelids
- Distended abdomen
- Tachypnea/Dyspnoea/ Orthopnea
- Respiratory distress
- Pulse volume good
- Skin colour/temp normal
- Pulse pressure wide
- Urine output > 1ml/kg/hr
- CRFT< 2 sec
- PR ↑
- BP ↑
- HCT ↑



Case Scenario 5

- Total Duration of illness 10 days
- Afebrile patient
- Puffy eyelids
- Distended abdomen
- Tachypnea/Dyspnoea/ Orthopnea
- Respiratory distress
- Pulse volume good
- Skin colour/temp normal
- Pulse pressure wide
- Urine output > 1ml/kg/hr
- CRFT< 2 sec
- PR ↑
- BP ↑
- HCT ↓



Outbreak Preparedness Plan for Hospitals

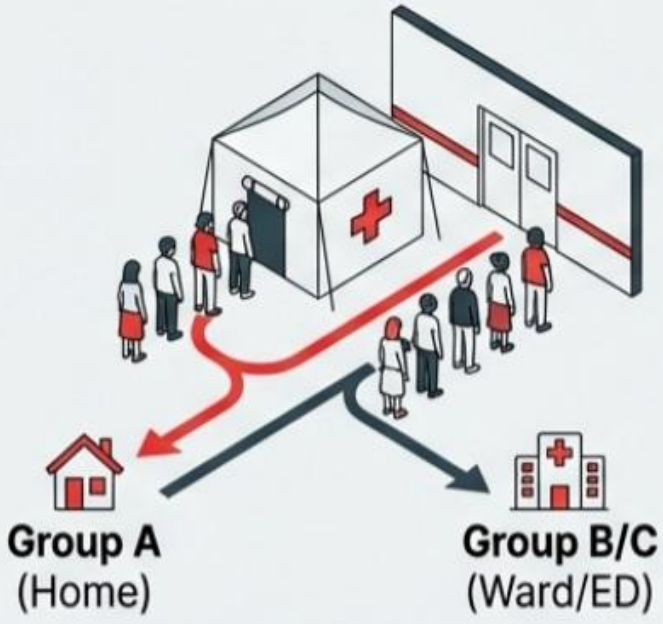
- There have been an increasing number of dengue outbreaks in many parts of the country.
- Therefore, having a hospital emergency preparedness plan for dengue outbreaks is vital in early diagnosis and appropriate clinical management of cases to minimize complications and deaths.

Plan should include the following key elements

1. Dengue management committee
2. Outpatient care (with triage and resuscitation areas)
3. Assess bed occupancy in each unit (with a view to identifying additional beds during outbreaks)
4. High-dependency care beds
5. Staffing and surge capacity needs
6. Stock management of essential medicines and supplies
7. Laboratory facilities

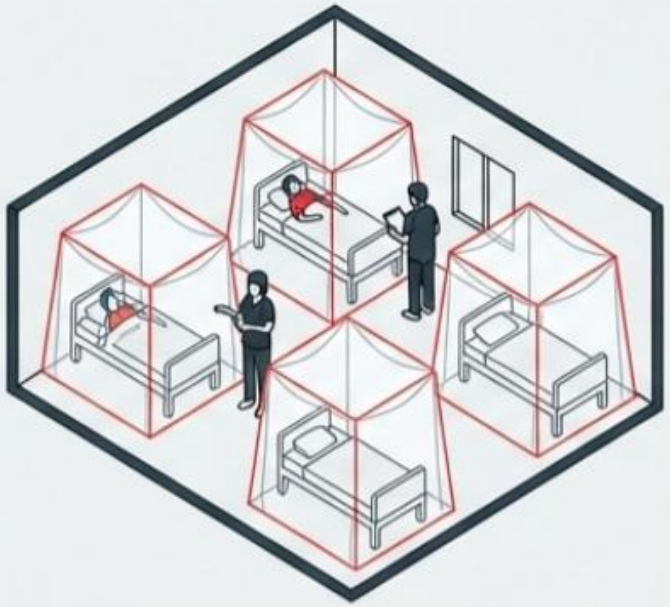
HOSPITAL PREPAREDNESS & SURGE CAPACITY

TRIAGE FEVER CLINICS



Separate Group A (Home) from Group B/C **immediately**. Prevent ED overcrowding.

DENGUE UNITS



Cohort patients in designated wards with mosquito netting. Staffing ratios must support **High-Dependency care**.

CRITICAL STOCKPILES

Point-of-Care HCT Centrifuges

NS1 Rapid Diagnostic Kits

Colloids (Dextran-40)

- **Point-of-Care** HCT Centrifuges
- NS1 Rapid Diagnostic Kits
- Colloids (Dextran-40) – **Ensure supply chain resilience**.

- Hospitals should develop and strengthen their capacity to screen and triage suspected dengue patients at the outpatient departments.
- Hospital staff including doctors, nurses and other categories should be trained and assigned appropriate duties 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.

Medicines | Supplies & equipments | Laboratory services

Medicines:

- ✓ Paracetamol tablets
- ✓ Oral Rehydration Solution
- ✓ I.V. Fluids –
  - Crystalloids: 0.9% saline
  - Colloids: hyper-oncotic (plasma expanders) - 10% Dextran 40 & 6% starch
  - 25% or 50% Dextrose
- ✓ Parenteral Vitamin K
- ✓ IV Calcium Gluconate (10% solution)
- ✓ IV KCl (20 mmol concentrated solution)
- ✓ IV Sodium bicarbonate (8.4% solution)

Supplies & equipments

Laboratory services

Supplies and equipment

- ✓Thermometers
- ✓Sphygmomanometers
- ✓Weight machines.
- ✓Measuring tap for height
- ✓I.V. access sets
- ✓Oxygen delivery systems
- ✓Micro centrifuge (for bedside haematocrit assessment)
- ✓Microscopes (for platelet count estimation)
- ✓Glucometers (for blood sugar estimation)
- ✓Observation charts

Medicines

Laboratory services

Laboratory support

- Laboratories should be equipped round the clock for basic tests such as FBC, count, haematocrit, platelet count, white blood count (WBC), and differential
- More complicated patients will need;
  - Blood sugar,
  - Liver function tests,
  - Renal function tests,
  - Serum electrolytes (including serum calcium),
  - Blood gases,
  - Coagulation assays,
- chest x-rays & Ultrasonography

Blood Bank:

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

Medicines

Supplies & equipments

Staff Requirement in a Dengue unit

HCW Category		Dengue General unit	HDU/ICU
Doctor /Medical Officer		1 per 8-10 beds	1 per 3-4 beds
Nurses		1 per 3-4 beds	1 per 1-2 beds
Phlebotomist		1 per 10 beds	1 per 5 beds
Lab technician		1 per unit	1 per unit
Consultants	Physician (adult/peads)	1 on call from each category	Intensivist full time
	Hematologist	1 on call	1 on call
	Sonologist	1 on call	1 on call
	Psychologist	1 on call	1 on call

A clinical pharmacist where available for daily prescription review and optimization of doses where required

Monitoring parameters for managers/monitors

Parameter	Fulfilled/satisfactory	Not satisfactory	Comments
Display and labelling of different areas			
Adequate staffing with training			
Dengue outbreak documentation			
Mosquito free clinical areas			
Documentation, History, Epidemiology			
BP sets functional paediatric and adult			
Weight Machine/ height and IBW calculation technique			
Frequency and accuracy of clinical and laboratory monitoring and availability of forms			
Laboratory: Haematology analyser validation/calibration			
Diagnostic kits for NS1 and Dengue serology available			
General cleanliness of the clinical area			
Education of patient and Family			

INTEGRATED VECTOR MANAGEMENT (IVM) & LEGAL FRAMEWORKS

1. OPERATIONAL IVM

- **Source Reduction**: Elimination of artificial containers (tyres, pots).
- Metric: **Pupal Productivity Surveys** (Targeting the 'super-producer' containers).

2. LEGAL ENFORCEMENT (Ref: Senate Bills/Public Health Acts)

- **Power of Inspection**: Authority to enter premises to check for breeding.
- **Power of Disinfection**: Mandatory vector control in outbreaks.
- **Penalties**: Fines for non-compliance in maintaining mosquito-free zones.

INNOVATIONS: BIOLOGICAL CONTROL & ANTIVIRALS

THE WOLBACHIA METHOD

- Mechanism: Infecting Aedes mosquitoes with Wolbachia bacteria blocks viral replication.
- Strategy: Self-sustaining biological control reducing transmission capacity in the wild population.

THERAPEUTIC HORIZON

- Emerging Antivirals (e.g., Mosnodenvir).
- Goal: Block replication in the febrile phase to prevent progression to severe dengue.

Novel Therapeutic Options not yet standard of care

- DEN-HOST Trial (Ongoing, 2025+): This largest-ever dengue therapeutics trial tests host-directed agents—baricitinib (JAK inhibitor), dexamethasone (corticosteroid), and N-acetylcysteine (for liver injury)—to curb progression in hospitalized moderate-severe cases.

- AV-1 Monoclonal Antibody (Phase 2, 2025): An NIH-funded trial evaluates this human antibody for safety, viral clearance, and symptom reduction post-exposure to weakened dengue virus.

- CDX-Ac2-26 (Preclinical, 2025-2026): Cyclodextrin-delivered Annexin A1 mimetic reduces inflammation, mast cell degranulation, and CCL2 in mouse models without affecting viral load; combines effectively with antivirals like sofosbuvir.

- Cepharanthine (Preclinical): Inhibits DENV entry across serotypes and cuts IL-6 production, targeting early replication and cytokine secretion.
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Supportive care remains standard, with these agents showing promise for adjunctive use in high-risk patients.

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Thanks

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