KINGDOM OF CAMBODIA

Ministry of Health

2018

National guideline for Clinical Management of Dengue

NATIONAL CENTRE FOR PARASITOLOGY,
ENTOMOLOGY AND MALARIA CONTROL

2018

National guideline
for Clinical Management of Dengue

Foreword

Dengue illness continues to be a major health problem in the South-east Asian region and Cambodia is no exception. Recent trends on morbidity and mortality of dengue has caught the attention of the Royal Government of Cambodia. The out-patient and in-ward departments of the hospitals of Cambodia are seeing increasing number of patients with dengue.

This newly revised national guideline on management of clinical dengue in both children and adults, developed by the National Dengue Control Program of the National Centre for Parasitology, Entomology and Malaria Control (CNM), Ministry of Health Cambodia in collaboration with the Clinical Sub-committee on Dengue case management is expected to further improve existing knowledge and bridge any gaps on this subject. I take this opportunity to thank all the experts who were involved in developing this guideline.

This authoritative document should be used in all levels of health care provision in Cambodia for the management of dengue and dengue hemorrhagic fever patients. I am sure this document will help in further strengthening the case management and ultimately reduce the number of cases and significantly bring down the deaths due to dengue.

Phnom Penh, December 14th 2018

Professor ENG HUOT

Secretary of State

Preface

Dengue fever (DF), Dengue hemorrhagic fever (DHF), Dengue shock syndrome (DSS) and its complications are serious global health problems.Approximately two fifths of the world's population are at risk, and more than 100 countries have experienced for DF/DHF outbreaks. The annual incidence of dengue is up to 50 million cases per year, in which with 500,000 cases were hospitalized and 20,000 dies.

Cambodia is one of the highest dengue burdened countries inSouth-East Asia. The regular dengue epidemic occur every 3 to 5 years in pattern such as 1985, 1990, 1995,1998, 2003, 2007, and 2012. Dengue outbreaks have occurred not only at urban or dense populated areas, it also has started to spread into very remote localities in almost 22 among 25 provinces, due to improvement of accessibility and greater population movement. Since year 2001- 2007, due to better improvement of dengue surveillance system, the average dengue cases admitted at Public Health Facilities and reported every year were 12,000 cases, which with around one hundred cases or more died. From 2008 - 2010, the annual dengue case fatality rate has dropped to less than 1% (0.68% in year 2008, 0.32% in year 2009 and 0.30% in year 2010).

The global strategy for control of dengue and dengue hemorrhagicfever, has emphasized on surveillance system, 2 rounds of pre-emptive strike larvicide application a year, Improvement of clinical management and nursing care, community and school-based health education, emergency and rapid of integrated of vector management response. The ultimate goal of the National Dengue Control Program is to reduce dengue case fatality rate due to DHF and DSS to less than 0.1% by the year 2020.

This clinical management guideline of DF/DHF has been revised based on the WHO SEAR guideline of 2011, old national dengue guideline 2004 and fit with the actual and practical practice of our clinicians at central and provincial referral hospitals.

The clinical sub-clinical committee wishes to congratulate its expert members, the National Dengue Control Program, National Center of Parasitology, Entomology and Malaria Control, Ministry of Health for the great achievement and success to come-out with this guideline to be used by all medical doctors at the referral and operational district hospitals.

With the availability of this guideline, we anticipate a further improvement of the diagnosis and treatment of DF/DHF and DSS will be achieved.

Clinical sub-committee on Dengue case management

December 2017

Acknowledgements

The guideline development group wishes to express a deep thankfulness to Dr. Luciano Tuseo at the World Health Organization for his strong commitment and support. Appreciation is also extended to Prof. Ung Sophal, the Chair of Clinical Subcommittee, H.E. Dr. Phiwad Poshyananda, the Co-Chair of the Ministry of Health Cambodia and Cambodian-Thailand Malaria/Dengue Project remarkably provided their supports and guidance during the process of guideline edition. A special thank is extended to Prof. Siripen Kalayanarooj from the WHO Collaborating Centre for the case management of Dengue/DHF/DSS, Queen Sirikit National Institute of Child Health, Bangkok, Thailand, and Dr. Hasitha Tissera, the Director of the National Dengue Control Program, the Ministry of Health, Sri Lanka for reviewing and editing the guideline.

Acronyms and abbreviations

↑	Increase
↓	Decrease
Ab	Anti-body
ADP	Adenosine Diphosphate
Ag	Antigen
aPTT	activate Partial Thromboplastin Time
AR	Acetate Ringer
BP	Blood Pressure
BS	Blood Sugar
BT	Bleeding Time
BUN	Blood Urea Nitrogen
BW	Body Weight
C	Celsius
CamEWARN	Cambodia Early Warning Response Network
CBC	Complete Blood Count
CDC	Communicable Diseases Control Department
CFR	Case Fatality Rate
CNS	Central Nervous System
CRP	C reactive protein
CRT	Capillary Refill time
CT	Clotting Time
Cr	Creatinine
CAVH	Continuous Arterio-Venous Hemoperfusion
CVVH	Continuous Veno-Venous Hemoperfusion
D5%	5% Dextrose

ACRONYMS AND ABBREVIATIONS

5%D/N/2	5% Dextrose in half-strength normal saline
DEN-1	Dengue Virus Serotype 1
DEN-2	Dengue Virus Serotype 2
DEN-3	Dengue Virus Serotype 3
DEN-4	Dengue Virus Serotype 4
DF	Dengue Fever
DHF	Dengue Hemorrhagic Fever
DSS	Dengue Shock Syndrome
EDS	Expanded Dengue Syndrome
ESR	Erythrocyte Sedimentation Rate
ETU	Emergency Treatment Unit
FDP	Fibrin Degradation Product
FWB	Fresh whole blood
ICD	International Classification of Diseases
ICU	Intensive Care Unit
IgG	Immunoglobulin G
IgM	Immunoglobulin M
INR	International Normalization Ratio
IPD	In-Patient Department
IV	Intravenous
IVP	Intravenous Perfusion
gm	Gram
G-6-PD	Glucose 6 Phosphatase Deficiency
Hct	Hematocrit
H	Hour
HDU	High Dependency Unit

HMIS	Health Management information System
kg	kilogram
KVO	Keep Vein Open
LFT	Liver Function Test
LV	Left Ventricle
NSS	Normal Saline Solution
OPD	Out Patient Department
Plt	Platelet
PR	Pulse Rate
PRC	Packed red cell
mg	milligram
ml	milliliter
NCPAP	Nasal Continuous Positive Airway Pressure
NDCP	National Dengue Control Program
NS1Ag	Non-structural protein 1 Antigen
NSS	Normal Saline Solution
RBC	Red Blood Cell
RL	Ringer Lactate
RI	Regular Insulin
RR	Respiratory Rate
RV	Right Ventricle
PT	Prothrombin Time
TT	Thrombin Time
SaO2	Oxygen Saturation
UOP	Urine Output
WBC	White Blood Count
WS	Warning Signs

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Part 1

Introduction

Dengue fever (DF), and dengue hemorrhagic fever (DHF), are caused by dengue virurs, Flavivirus type, from Flaviviridae family. Four different serotypes of dengue virus (DEN-1, DEN-2, DEN-3 and DEN-4) can cause the disease. It is transmitted to human by Aedes aegypti, and sometimes Aedes albopictus mosquito bite.

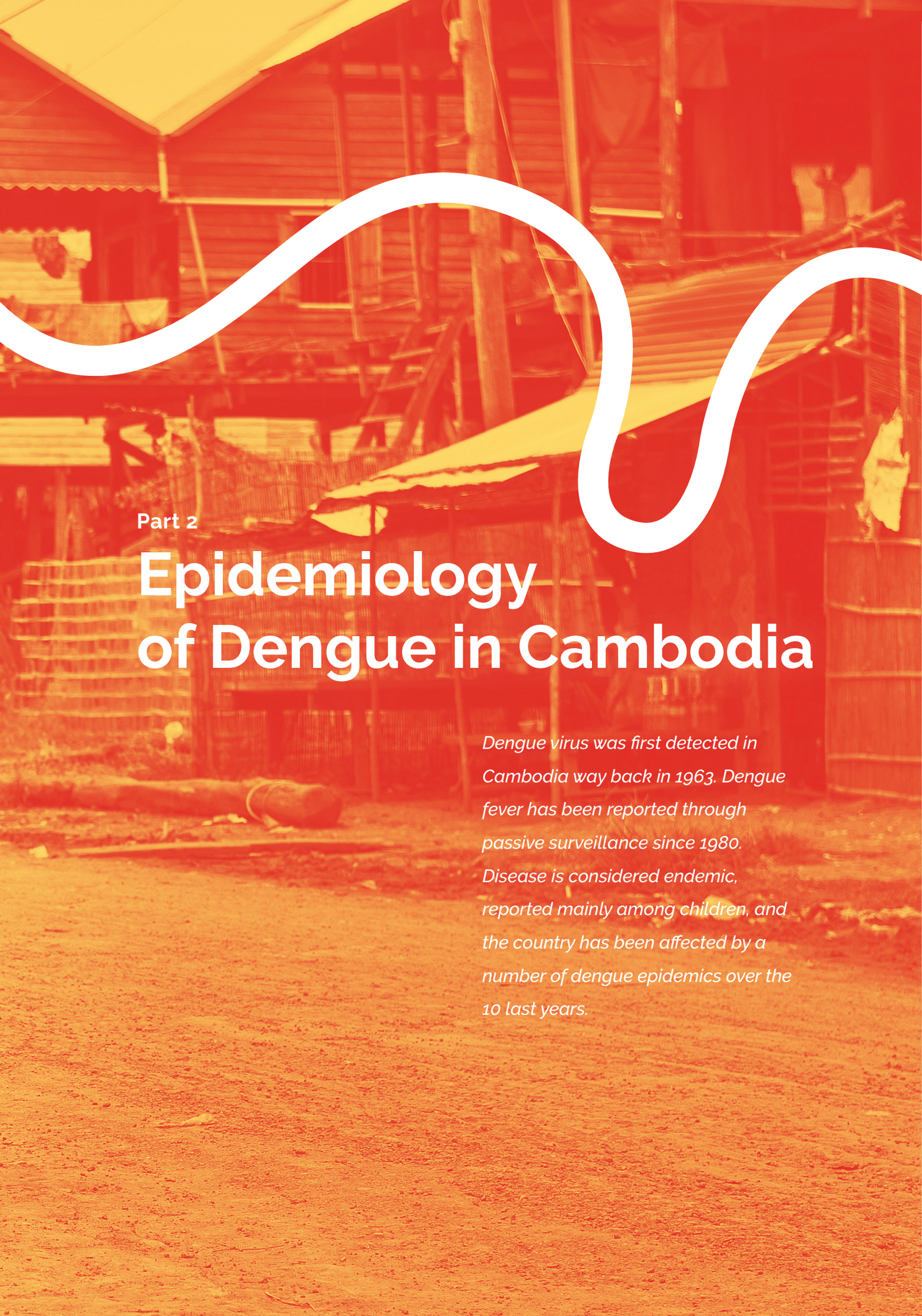
Infection in humans by one serotype produce long term immunity against re-infection by the same serotype, but only temporary and partial protection against the other serotypes.

Infections with any of the dengue viruses may cause symptomatic illness or asymptomatic seroconversion. Symptomatic dengue infection is a systemic and dynamic disease. It has a wide clinical spectrum that includes undifferentiated fever, classical dengue fever and dengue hemorrhagic fever (DHF) with dengue shock syndrome. The clinical manifestation depends on the virus strain and host factors such as age, immune status, etc. After the incubation period, the illness begins abruptly and patients with moderate to severe disease experience three phases − febrile, critical and recovery (Figure 4). Due to its dynamic nature, the severity of the disease will usually only be apparent around defervescence i.e. during the transition of the febrile to the afebrile phase, around day 3 to day 7 of illness.

Clinical features of Dengue Haemorrhagic Fever (DHF) include plasma leak combined with hemorrhagic diathesis with the risk of developing a shock syndrome that can be fatal. In case of dengue haemorrhagic fever, blood test always reveals a thrombocytopenia, and hemoconcentration due to plasma leakage, or hypoproteinemia.

Infections with any of the dengue viruses may cause symptomatic illness or asymptomatic seroconversion.

Delayed and/or inappropriate treatment leads to high mortality rate of DHF.
Health promotion on clinical signs, especially on danger signs during the early critical phase, and appropriate management at health facilities can reduce the mortality rate of this potentially life-threatening disease.



Part 2

Epidemiology of Dengue in Cambodia

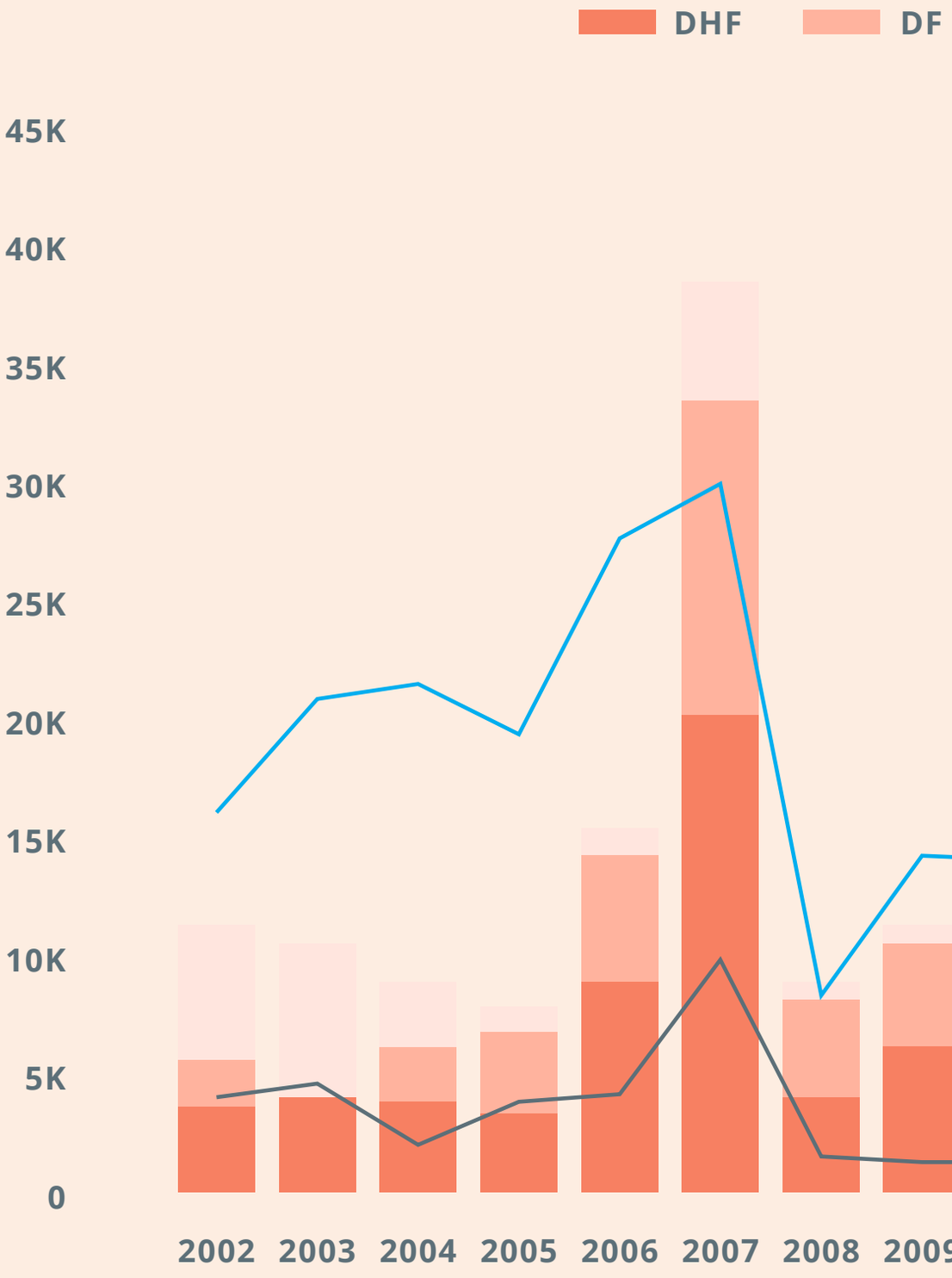
Dengue virus was first detected in Cambodia way back in 1963. Dengue fever has been reported through passive surveillance since 1980. Disease is considered endemic, reported mainly among children, and the country has been affected by a number of dengue epidemics over the 10 last years.

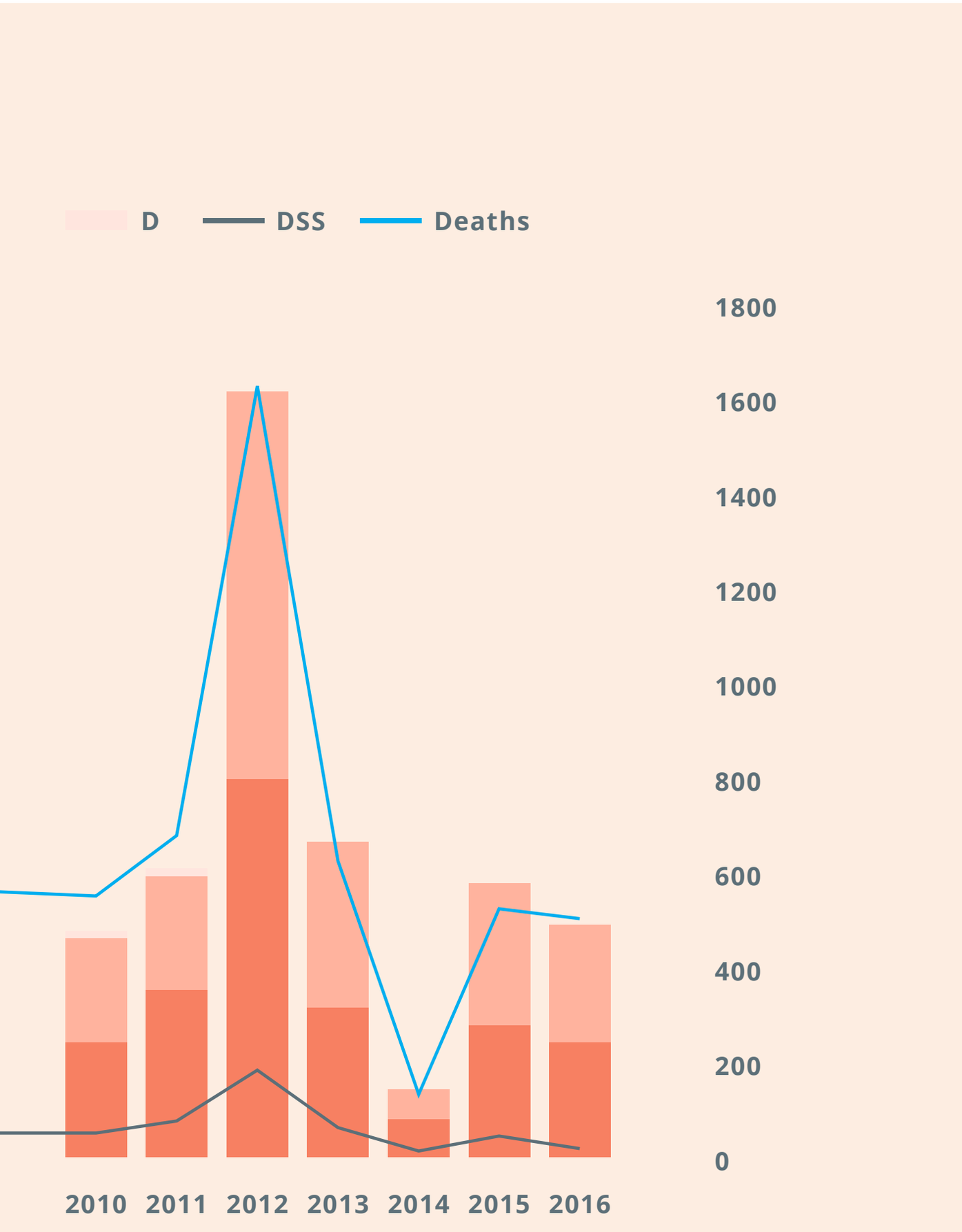
In Cambodia, dengue is a major health problem. The National surveillance reported on average 103 cases per 100,000 population with C.F.R less than 1% annually during the past 5 years. Of all the reported cases in children under 16, most (79%) cases were aged 9 years and younger. The highest age specific incidence rate was in the 5 to 9 years age group followed by the 0 to 4 years age group.

These patterns have been consistent since 2002. No differences in gender were observed overall and annually for the past five years. Incidence and case fatality rates vary widely by province. Among the hospitalized reported cases, the percentage of DHF and DSS increased steadily from 30% to 60% during 2002 - 2007 (Figure 1). All 4 dengue virus serotypes have circulated in Cambodia with however a predominance of DENV2 and DENV3 since 2002. Since 2002, the cycles of epidemic seems to be less marked with a same pattern appearing each year during 2002 - 2006. The seasonal epidemics have occurred (April – May), peaked (July – August) and waned off (October – November) consistently during the same months over the past 5 years. Noticeably, the magnitude of the 2007 and 2012 epidemic was dramatically high with 39,851 dengue cases and 407 deaths (CFR=1.2%) and in year 2012, up to 42,362 cases, in which with 189 deaths (CFR= 0.46%), reported to the National surveillance. This epidemic also began earlier in February - March and peaked during June and July.

FIGURE 1:

Proportion of Dengue cases by severity, Cambodia, 2002-2016




D
DSS
Deaths
1800
1600
1400
1200
1000
800
600
400
200
0
2010
2011
2012
2013
2014
2015
2016

Part 3

Pathogenesis

The pathogenesis of DHF is poorly understood.

DHF occurs in a small proportion of dengue patients. Although DHF may occur in patients experiencing dengue virus infection for the first time, most DHF cases occur in patients with a secondary infection.

DHF caused especially by secondary dengue infection is due to the occurrence of abnormal immune response involving production of cytokines, activation of T lymphocytes and disturbance of the hemostatic system. The elevated mediators include C3a, C5a, TNF-α, interleukin (IL)-2, IL-6, IL-10, Interferon (IFN)-α and histamine (Malasit P 1987 and Kurane I et al., 1990).

The antibody-dependent enhancement whereby, upon the second infection with a heterotypic dengue virus (Halstead SB 1988), the subneutralizing concentration of the cross-reacting antibody from the previous infection may opsonize the virus and enhance its uptake and replication in the macrophage or mononuclear cells. Secondary infection with a heterotypic dengue virus is associated with increased risk of developing DHF/DSS in individuals who have recovered from a primary dengue virus with a first serotype. This leads to changes in vascular permeability. In addition, viral products such as NS1 may pid.

Part 4

Pathophysiology of DHF

a. Plasma leakage:

The plasma leakage is due to the increased vascular permeability. The evidence of plasma leakage includes hemoconcentration, pleural effusion, ascites and hypoproteinemia lead to shock and profound shock if not properly managed with fluids. The rising hematocrit may not be evidenced because of either severe bleeding or early IV fluid replacement.

b. Abnormal hemostasis

The bleeding diathesis is caused by vasculopathy, platelet alteration (thrombocytopenia and platelet dysfunction) and coagulopathy.

(1) Vasculopathy

A positive tourniquet test indicating the increased capillary fragility is found in the early febrile stage. It may be a direct effect of dengue virus as it appear in the first few days of illness during the viremic phase (Halstead SB 1988).

(2) Platelet alteration

Platelet defects may be both quantitative (thrombocytopenia) and qualitative (platelet dysfunction).

a. Thrombocytopenia

Patients with DHF usually have platelet count < 100 000 cells/mm^3 during the critical stage. The pathogenesis of thrombocytopenia involves two major mechanisms, a decreased platelet production by bone marrow suppression and an increased peripheral destruction and increased utilization of platelets (Srichaikul T and Nimmannitya S 2000).

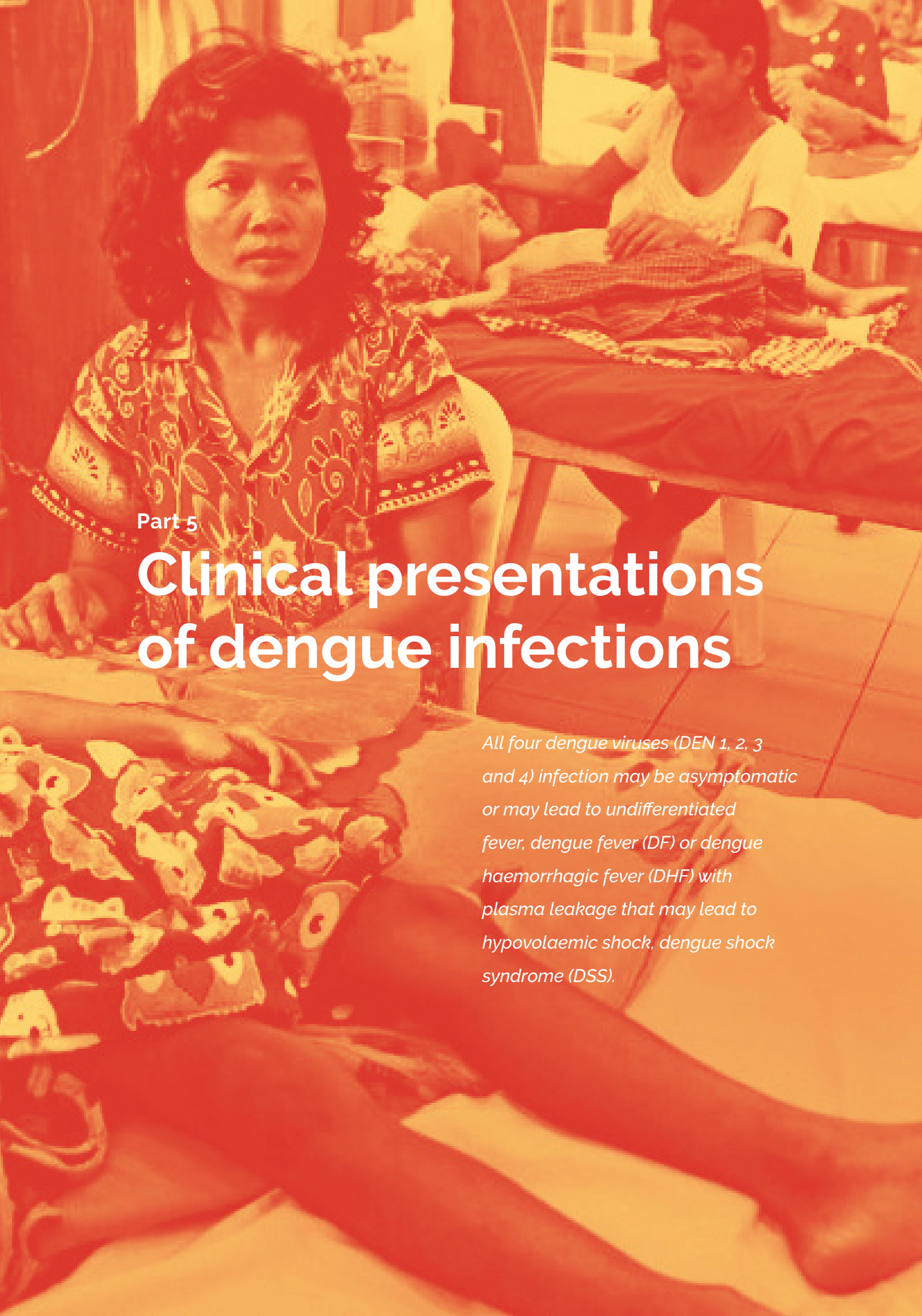
Subsequently, the number of platelets is increased in the convalescent stage and reaches the normal level within 7 – 10 days after defervescence (Funahara Y et al., 1987).

b. Platelet dysfunction

The platelet dysfunction as evidenced by the absence of adenosine disphosphate (ADP) was found in both shock and non-shock dengue patients. The majority of the patients had normal platelet aggregation response to ADP 2 – 3 weeks later (Srichaikul T et al., 2000).

(3) Coagulopathy

During the acute febrile stage, plasma clotting time revealed a prolonged prothrombin time (PT) and a partial thromboplastin time (PTT), as well as reduced fibrinogen levels. Variable reductions in the activities of several coagulation factors, including prothrombin, factors V, VII, VIII, IX and X, antithrombin and Fibrin degradation product (FDP) slightly elevated (Suvatte V et al., 1973).

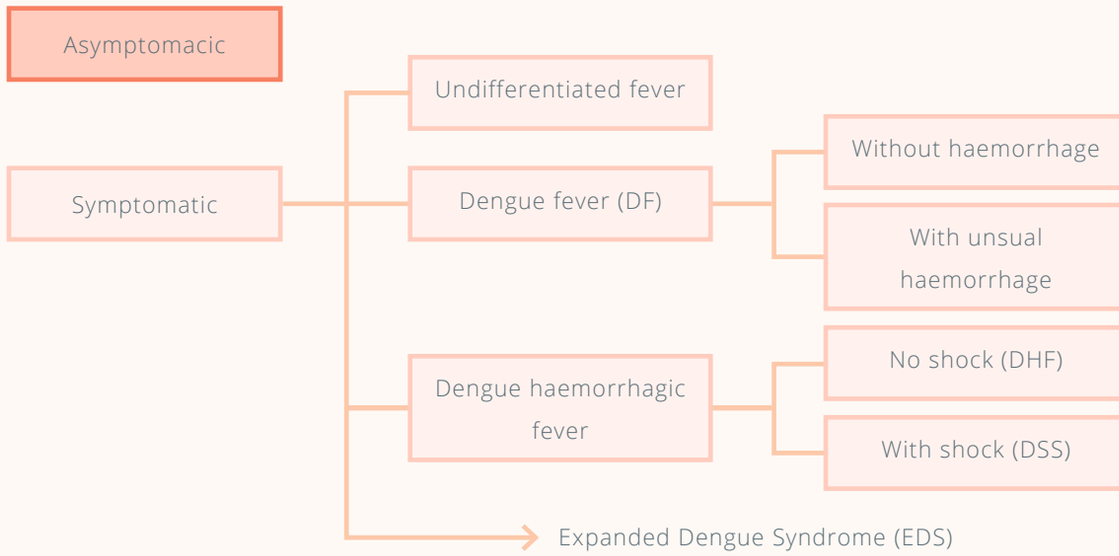


Part 5

Clinical presentations of dengue infections

All four dengue viruses (DEN 1, 2, 3 and 4) infection may be asymptomatic or may lead to undifferentiated fever, dengue fever (DF) or dengue haemorrhagic fever (DHF) with plasma leakage that may lead to hypovolaemic shock, dengue shock syndrome (DSS).

FIGURE 2: Manifestation of dengue virus infections:



1. Early Diagnosis of Dengue illnesses

Dengue is suspected in patients with acute high fever 2 – 7 days in dengue endemo-epidemic areas with 2 or more of the followings:

- Headache
- Retro-orbital pain
- Myalgia
- Arthralgia
- Severe body pain
- Anorexia, nausea, vomiting, diarrhea
- Rash
- Bleeding manifestations: positive tourniquet test*, petechiae, epistaxis, gum bleeding, hematemesis or melena.
- Leucopenia* (WBC < 5000 cells/cumm)
- Rising hematocrit 10 – 20%
- Platelet count < 150, 000cells/cumm

* Recommended practical diagnosis of dengue infection is: Positive tourniquet test (or petechiae) plus leucopenia.

Tourniquet test:

The tourniquet test is performed by inflating a blood pressure cuff to a point midway between the systolic and diastolic pressures for five minutes.

The test is considered positive when 10 or more petechiae per sq. inches areobserved.

In DHF, the test usually gives a definite positive result with 20 petechiae or more. The test may be negative or only mildly positive in obese patients and

during the phase of profound shock. It usually becomes positive, sometimes strongly positive after recovery from shock.

1.1 Dengue fever (DF)

Clinical features: Vary according to age.

- Infants and small children infected with the dengue virus for the first time usually develop a simple fever syndrome.
- Children and adults may have a mild febrile syndrome, or the classic dengue syndrome with high fever of abrupt onset, sometimes with two peaks, severe headache, nausea and vomiting, pain behind the eyes, joints and bones pain. Rash varies from redness to cutaneous erythema and maculopapular rash.
- Positive tourniquet test and /or petechiae can be present.
- Leucopenia and mild thrombocytopenia are usual.
- After an average intrinsic incubation period of 4–6 days (range 3–14 days), various non-specific constitutional symptoms and headache, backache and general malaise may develop. Typically, the onset of DF is sudden with a sharp rise in temperature and is frequently associated with a flushed face36 and headache. Occasionally, chills accompany the sudden rise in temperature. Thereafter, there may be retro-orbital pain on eye movement or eye pressure, photophobia, backache, and pain in the muscles and joints/ bones. The other common symptoms include anorexia and altered taste sensation.

The following are common clinical presentations of dengue illnesses:

Fever: The bodytemperature is usually between 39 °C and 40 °C, and the fever may be biphasic, lasting 5–7 days in the majority of cases. Most patients will have high continuous fever for 2-7 days.

Haemorrhagic manifestations: Skin haemorrhage may be present as a positive tourniquet test and/or petechiae. Other bleeding such as epistaxis gum bleeding, hypermenorrhea, hemoglobinuria, hematuria and gastrointestinal bleeding rarely occur in DF, complicated with thrombocytopenia.

Ache and Pain: Severe headache, retro-orbital pain, myalgia and arthralgia.

Rash: Diffuse flushing or fleeting eruptions may be observed on the face, neck and chest during the first two to three days, and a conspicuous rash that may be maculopapular or rubelliform appears on approximately the third or fourth day. Towards the end of the febrile period or immediately after defervescence, the generalized rash fades and localized clusters of petechiae may appear over the dorsum of the feet, on the legs, and on the hands and arms. This convalescent rash is characterized by confluent petechiae surrounding scattered pale, round areas of normal skin. Skin itching may be observed.

In some epidemics, DF may be accompanied by haemorrhagic complications such as epistaxis, gingival bleeding, gastro-intestinal bleeding, haematuria and menorrhagia. In those cases, it is important to differentiate DF with unusual bleeding from DSS and DHF:

- In case of DF, there is no aggravation of symptoms during the afebrile phase, but rather an improvement.
- Hematocrit remains normal while platelet count is normal or decreased.
- DF is generally a mild disease. Recovery (convalescence rash) with or without itching may be observed. Convalescence may be short and uneventful. Bradycardia is common during convalescence.

It should be noted that the use of medications such as analgesics, antipyretics, anti-emetics and antibiotics can interfere with liver function and blood clotting.

Laboratory findings:

- Leucopenia (WBC ≤ 5,000 cells per mm^3)
- Hematocrit always normal or slightly elevated
- Platelets count may be normal or mildly to moderately decreased (rarely could be very low < 50,000per mm^3)

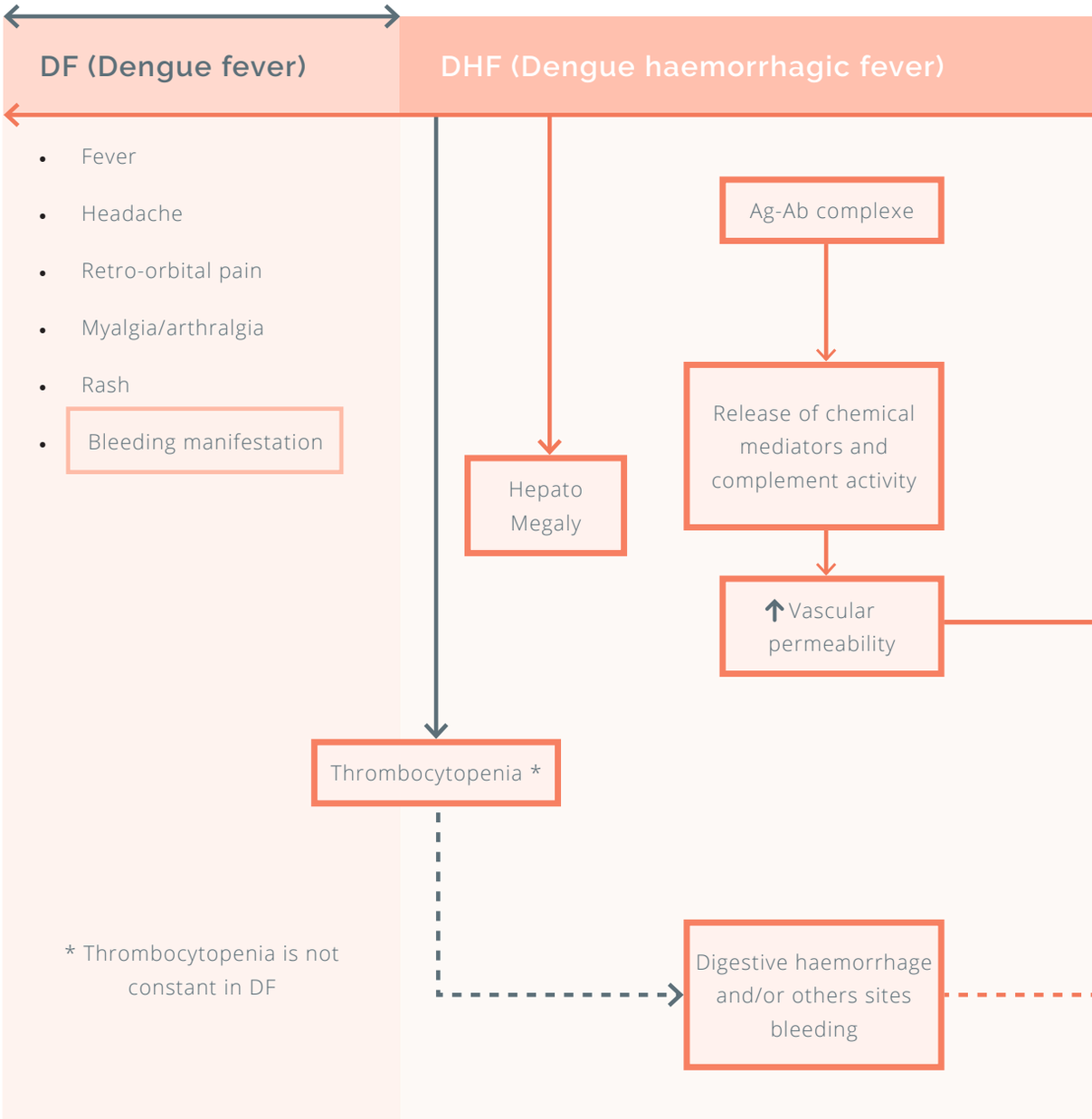
2. Clinical presentations

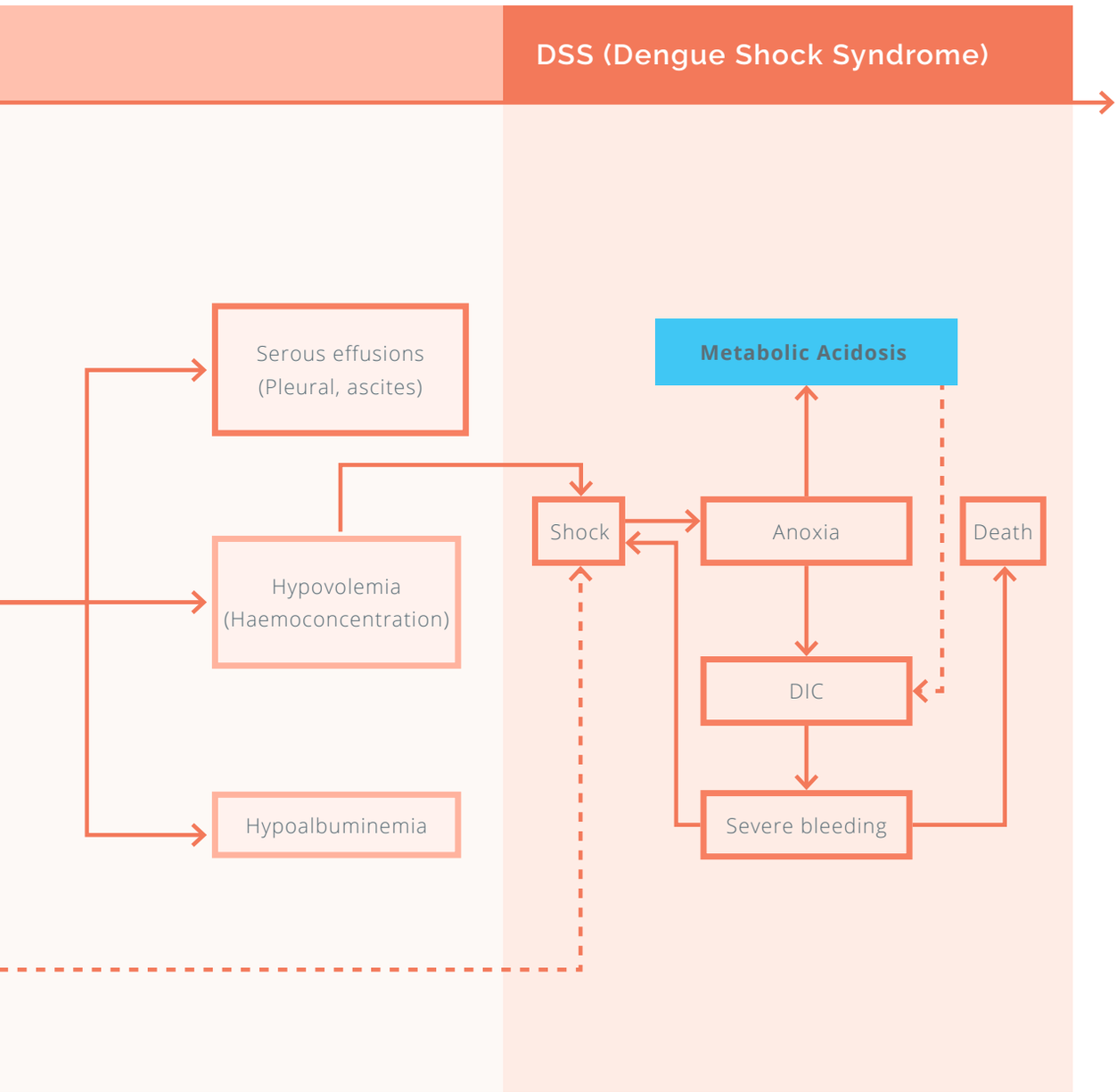
In dengue endemic areas, positive tourniquet test and leukopenia (WBC ≤5000 cells/mm^3) help in making early diagnosis of dengue infection with a positive predictive value of 70%–80%. The laboratory findings during an acute DF episode of illness are as follows:

- Total WBC is usually normal at the onset of fever; then leucopenia develops with decreasing neutrophils and lasts throughout the febrile period.
- Mild haematocrit rise (≈10%) may be found as a consequence of dehydration associated with high fever, vomiting, anorexia and poor oral intake.
- Platelet counts are usually normal, as are other components of the blood clotting mechanism. Mild thrombocytopenia (≤150 000 cells/mm^3) is common and dengue fever DF patients may have platelet count below 100 000 cells/mm^3; but severe thrombocytopenia (<50 000 cells/mm^3) is rare.

FIGURE 3:

Pathogenesis and pathophysiology of dengues infection




DSS (Dengue Shock Syndrome)
Serous effusions
(Pleural, ascites)
Hypovolemia
(Haemoconcentration)
Hypoalbuminemia
Metabolic Acidosis
Shock
Anoxia
Death
DIC
Severe bleeding

Towards the end of febrile phase there is a drop in the total number of WBC as well as in the number of polymorphonuclear cells, a relative lymphocytosis with more than 15% atypical lymphocytes.

- Serum biochemistry is usually normal but liver enzymes and aspartate amino transferase (AST) levels is usually elevated (Not more than 200 UI) in majority of dengue cases.

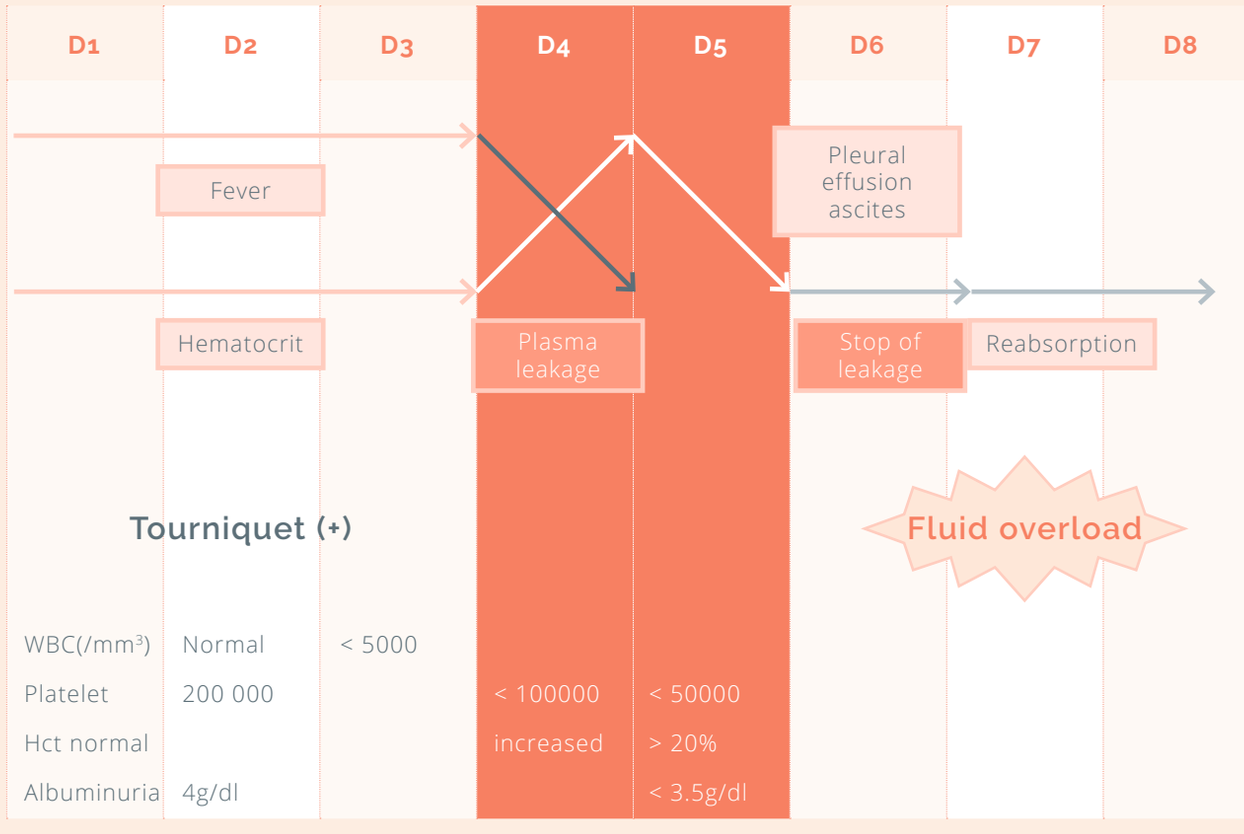
a. Dengue Fever (DF)

DF is different from DHF/DSS in that there is no plasma leakage. More than half of DF patients may have thrombocytopenia.

b. Dengue Hemorrhagic Fever (DHF)

In the first few days of DHF patients will have signs and symptoms similar to that of DF, however in DHF usually beyond day 3 will develop feature of plasma leakage. Early detection of plasma leakage with proper fluid intervention will prevent shock.

FIGURE 4: Clinical courses of DHF



Natural course of dengue hemorrhagic fever

(1) Febrile phase

During 2 to 7 days in 1 or 2 peaks (usually 3-4 days). Patients with high continuous fever, aches and pain (headache, retro-orbital pain, myalgia, arthralgia), bleeding manifestation and rash are highly suspicious to have dengue infections. Some patients may have a sore throat, an injected pharynx, and conjunctival injection. Anorexia, nausea and vomiting are common. The earliest abnormality in the full blood count is a progressive decrease in total white cell count, which should alert the physician to a high probability of dengue. Platelet count also decreases progressively but remains above 100,000/mm^3 during this phase. In addition to these somatic symptoms, with the onset of fever patients may suffer an acute and progressive loss in their ability to perform daily functions.

(2) Critical or leakage phase

During the transition from the febrile to afebrile phase, patients without an increase in capillary permeability (Dengue fever) will improve without going through the critical phase.Patients who have plasma leakage may experience warning sign and become worse when the temperature decrease (without antipyretic). The duration of critical phase of DHF without shock is 24 to 48 hours, but for DHF with shock is 24hours. Progressive leukopenia followed by a rapid decrease in platelet count usually precedes plasma leakage. An increasing haematocrit above the baseline may be one of the earliest additional signs. The period of clinically significant plasma leakage usually lasts 24-48 hours. The degree of plasma leakage varies. A rising haematocrit precedes changes in blood pressure (BP) and pulse volume.

The degree of haemoconcentration above the baseline haematocrit reflects the severity of plasma leakage; however, this may be reduced by early intravenous fluid therapy. Pleural effusion and ascites are usually only clinically detectable after intravenous fluid therapy,unless plasma leakage is significant. A right lateral decubitus chest radiograph, ultrasound detection of free fluid in the chest or abdomen, or gall bladder wall oedema may precede clinical detection. In addition to the plasma leakage, hemorrhagic manifestations such as easy bruising and bleeding at venipuncture sites occur frequently.

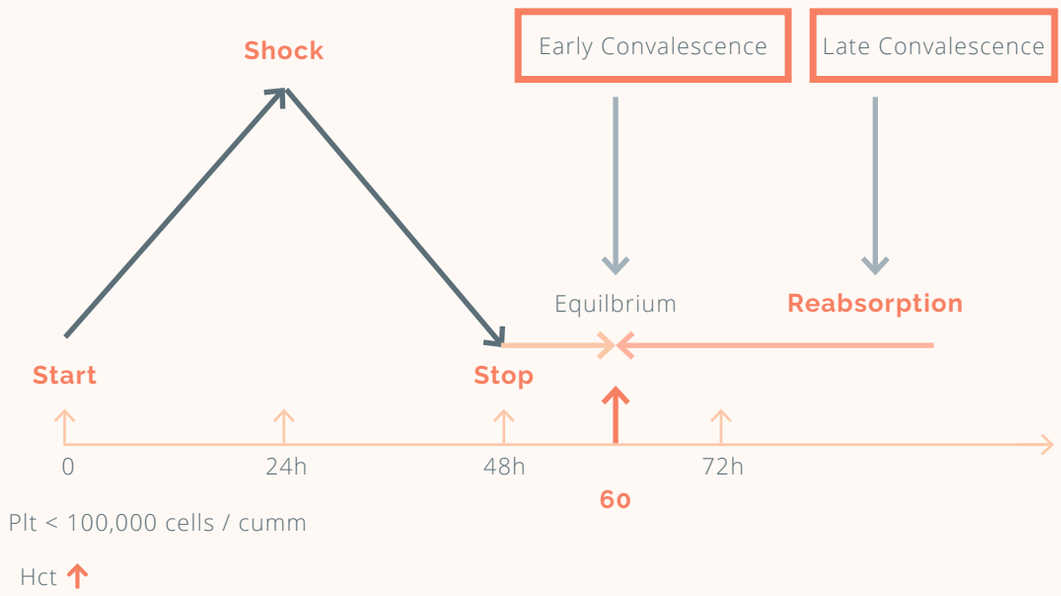
Warning signs usually precede the manifestations of shock and appear towards the end of the febrile phase, usually between days 3-7 of illness. Persistent vomiting and severe abdominal pain are early indications of plasma leakage and become increasingly worse as the patient progresses to the shock state. The patient becomes increasingly lethargic but usually remains mentally alert. These symptoms may persist into the shock stage. Weakness, dizziness or postural hypotension occur during the shock state. Spontaneous mucosal bleeding or bleeding at previous venipuncture sites are important hemorrhagic manifestations. Increasing liver size and a tender liver is frequently observed. However, clinical fluid accumulation may only be detected if plasma loss is significant or after treatment with intravenous fluids. A rapid and progressive decrease in platelet count ≤100 000 cells/mm^3 and a rising hematocrit above the baseline may be the earliest sign of plasma leakage. This is usually preceded by leukopenia (≤ 5000 cells/mm^3).

Substantial number of DSS patient will not have warning signs at all.

(3) Convalescent phases (early convalescence and late/reabsorption phase)

The duration of convalescent phase lasts 3 to 7 days, generally 3-4 days after critical phase. Reabsorption phase (ascites and pleural effusion is returned to the intravascular space) is to be recognized by clinicians, especially in cases with signs and symptoms of fluid overload.

FIGURE 5: Convalescence Phase



Grading the severity of DHF

DHF is classified into four grades of severity, where grades III and IV are considered to be DSS. The presence of thrombocytopenia with concurrent hemoconcentration differentiates grades I and II DHF from DF. Evidence of plasma leakage is the most important finding in the diagnosis of DHF, even without other evidence like thrombocytopenia or bleeding which may not be available at that time.

Grade I

Fever accompanied by non-specific constitutional symptoms; the only hemorrhagic manifestation is a positive tourniquet test and/or easy bruising.

Grade II

Spontaneous bleeding in addition to the manifestations of grade I patient, usually in the forms of skin or other haemorrhages.

Grade III

Circulation failure manifested by a rapid, weak pulse and narrowing of pulse pressure (compensated shock), with the presence of cold, clammy skin and lethargy.

Grade IV

Hypotension or profound shock with undetectable pulse and /or restlessness.

Dengue hemorrhagic without shock (DHF)

The following must all be present:

- Fever, or history of fever, lasting 2-7 days, occasionally biphasic.
- Hemorrhagic tendencies, evidenced by at least one of the following:
    - A positive tourniquet test,
    - Petechiae, ecchymosis or purpura
    - Bleeding from the mucosa, gastro-intestinal tract, injection sites or other locations
    - Hematemesis or melena
    - Menorrhagia or bleeding from vagina
- Thrombocytopenia (100, 000 cells per mm^3 or less).
- Evidence of plasma leakage due to increased vascular permeability, manifested by at least one of the following:
    - A rise in the hematocrit equal to or greater than 20% of baseline (see appendix);
    - Signs of plasma leakage such as pleural effusion, ascites and hypo-albuminemia ≤3.5gm% (Normal ≤4gm% in obese patient)

c. Dengue Shock Syndrome (DSS)

All the above four criteria for DHF must be present, plus evidence of circulatory failure manifested by:

- Rapid and weak pulse
- Narrow pulse pressure (≤20mmHg)or manifested by:
    - Hypotension for age, and
    - Cold, clammy skin and restlessness.

Note: Presentation of shock by narrowing of pulse pressure is usually due to plasma leakage while presentation with hypotension/ fainting is usually due to bleeding. Other causes of shock in dengue infected patients are possible due to hypoglycemia, severe vomiting and co-infections (septic shock)

The initial stage of shock, compensated shock (DSS grade III)

- Systolic BP is normal or increased
- Diastolic pressure increases
- Pulse pressure narrows (≤20 mm Hg)
- Tachycardia
- Tachypnoea
- Reduced skin perfusion: cold extremities and delayed capillary refill time of > 2 seconds and weak volume peripheral pulses
- Conscious level: normal

Severe shock (DSS grade IV)

- Hypotension (decreased systolic and diastolic pressure)
- Severe tachycardia
- Cold, mottled and cyanosed extremities and limbs
- Deep rapid breathing
- Weak peripheral pulses
- Mental state – patient becomes confused and extremely lethargic. Seizures may occur and agitation may alternate with lethargy.

Hypotension is a late finding and signals an imminent total cardiorespiratory collapse.

d. Expanded Dengue Syndrome (EDS)

- Prolonged shock with liver and other organs failure, encephalopathy (confusion, convulsion, coma) is the common presentation.
- Co-morbidities
- Co-infectionsTachycardia

3. High-risk dengue patients

- Infants < 1 year of age, obesity, elderly, pregnancy
- Bleeding
- Prolonged shock (DHF grade IV)
- Encephalopathy
- Behavior changes
- Underlying disease

4. Differential Diagnosis of Dengue illnesses

a. Febrile phase

Dengue is commonly misdiagnosed as with other febrile illnesses such as viral infections, acute pharyngitis, acute tonsillitis and acute gastroenteritis. Zika and Chikgungunya viruses are also in the differential diagnosis of dengue.

- **Measles**
  Very high fever at 39-40°C with conjunctivitis,Koplik spots, nasal and bronchial catarrh. Maculo-papular rash appears on the 4th– 5th day of disease and persistent **fever during the rash**.

- **Rubella (German measles)**
  It is moderate fever during 3-4 days followed by a rash, which characterizes the **disease**. **Retro-cervical and sub occipital lymphadenopathies are often found**.

- **Leptospirosis (Weil's disease)**
  In the early non-specific bacteremic phase of leptospirosis, the clinical signs & symptoms can simulate dengue infection. These symptoms include acute high grade fever (39–40°C), chills, headache, myalgia, back pain, severe vomiting, abdominal pain and conjunctival injection. Jaundice occurs during the 2nd phase of the disease. The platelet count may fall and thrombocytopenic purpura and frank bleeding ensue. There is a history of exposure to contaminated water.

- **Typhoid fever**
  Fever progressively increasing up to 39-40°C and persistent after the 7th day, coated tongue, and rumbling of the right iliac fossa.

- **Malaria:**
  Fever with thrombocytopenia often associated with history of travel or living in a malaria endemic zone. The fever persists over 7 days.

b. Shock phase

- **Meningococcemia**
  The shock with thrombocytopenia, caused by the meningococcemia before the appearance of a necrotic purpura, can simulate DSS.

- **Other septic shock**
  The presence of a thrombocytopenia concomitant with a hemoconcentration is in favour of DSS.

DSS is often misdiagnosed as septic shock and cause more prolonged shock with serious complications of organs failure. Disseminated Intravascular Coagulation (DIC) is present in both DSS and septic shock.

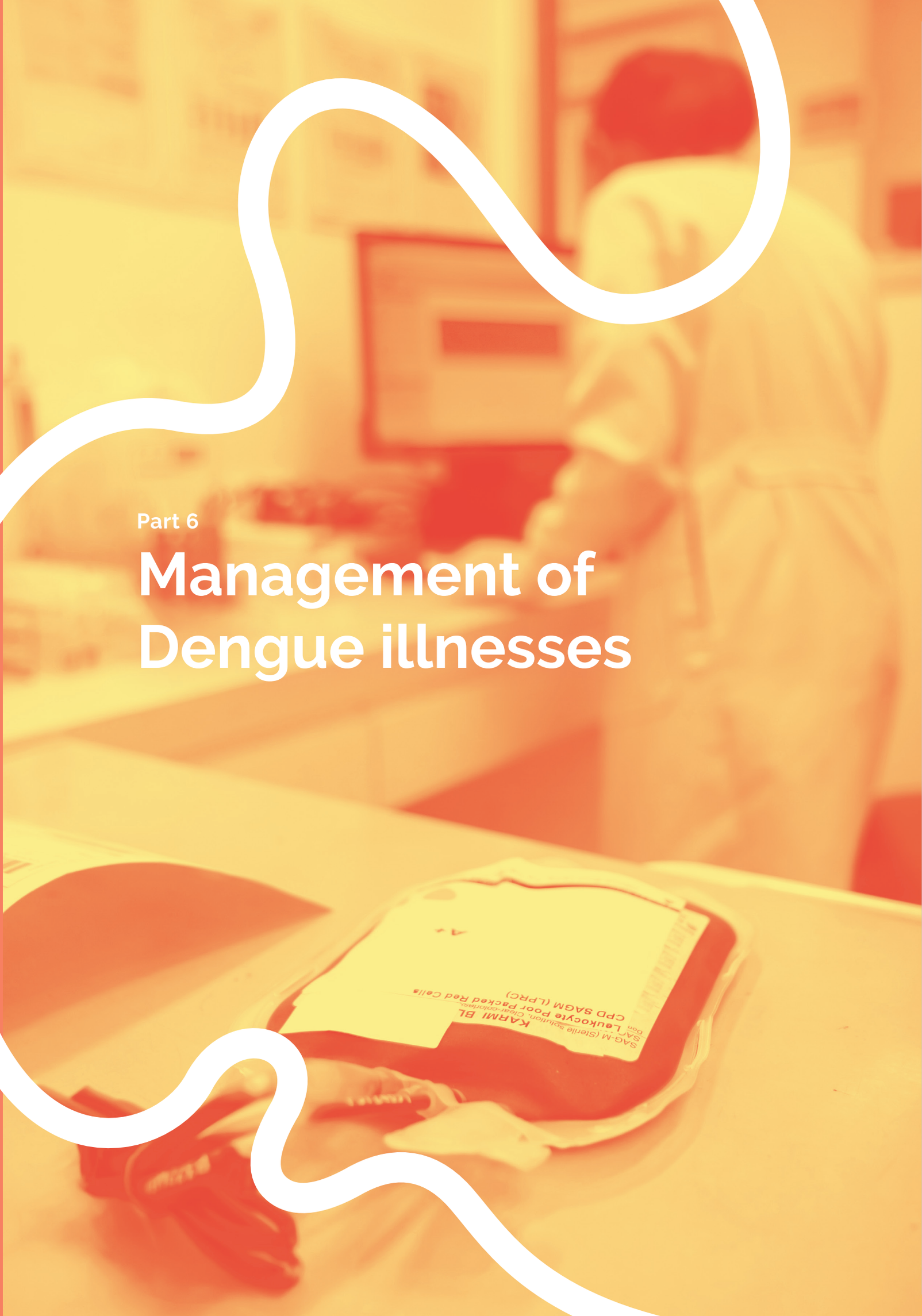
The differential diagnosis between DSS and Septic shock are in *Table 1* below:

TABLE 1: SHOCK WITH FEVER - DIFFERENTIAL DIAGNOSIS BETWEEN DSS AND SEPTIC SHOCK

DSS	SEPTIC SHOCK
Platelet usually ≤ 50,000 cells/cumm.	Platelet is usually normal at presentation of shock and may drop later
ESR/CRP is normal	ESR/CRP is raised
Pulse is small volume, narrow pulse pressure is common	Hypotension is common
Usually leukopenia, but leukocytosis are observed in complicated cases	Usually leukocytosis
Evidence of plasma leakage: pleural effusion and/or ascites	No
LFT: Hypoalbuminemia (Albumin < 3.5 gm% or < 4 gm% in obese person) with rapid rise in AST, up to > 10,000 U within 12-24 hs	LFT: No hypoalbuminemia and may see mild elevation of AST, usually not > 500 U

Differenting dengue from surgical acute abdomen

Do CBC and ultrasound to differentiate this to conditions. DHF will have rising Hct and thrombocytopenia and pleural effusion/ascites.



Part 6

Management of Dengue illnesses

If any patient suspected to have dengue infection that presents with any of the following symptoms is admitted:

- Drop of temperature with deterioration of general appearance.
- Prostration.
- Unable to drink or loss of appetite.
- Severe vomiting.
- Severe abdominal pain.
- Any sign of bleeding (such as epistaxis, gum bleeding. hematemesis, melena or vaginal bleeding etc.).
- Platelet < 100 000cells/mm^3.
- Rising Hct 10 – 20%.
- Signs of shock (such as weak and rapid pulse, Prolonged CRT > 2 seconds, irritability, cold and clammy skin, narrow pulse pressure or hypotension).
- No urine output 4 – 6h.
- Change of behavior including somnolent, convulsion or coma.
- Parental concern.

1. Febrile phase

1.1 Fever

Management of fever we use two of the following methods:

- **Tepid sponge:**
  Tepid sponge is indicated.
- **Antipyretic:**
  Paracetamol 10mg/kg/dose 6 hourly (not more than 4 times per day) is used to reduce the fever if temperature is greater than 38.5 °C.

1. Over-dosage of Paracetamol may cause liver impairment and then renal dysfunction.
2. Aspirin and Ibuprofen are contraindicated because they may provoke massive gastro-intestinal bleeding. Furthermore aspirin may cause acidosis and Reye's syndrome (severe encephalopathy).

1.2 Vomiting

In case of repeated vomiting, Domperidone 0.3mg/kg/dose (2 – 3 times per day) is considered.

1.3 Intense abdominal pain

Management of severe abdomen of dengue is as the following:

- Put the patient in comfortable position
- Relief of pain: Ice-box on abdomen and use pain killers
- Should consider to peptic ulcer on older children and treat with H2 blocker or PPI
- Should consider warning signs of plasma leakage and signs of shock
- Should check for signs of shock and use of NSAIDs and antibiotics
- Should rule out any acute abdominal conditions

1.4 Convulsions

Diazepam 0.5 mg/kg/dose per rectal route (Max: 10mg/dose)
Check glucose, electrolytes and calcium levels and correct accordingly

1.5 Food and ORS

- Fruit juice rice water, coconut water, oral rehydration solution
- Soft and balanced nutrition is preferred.

Remark

- *Intravenous fluid therapy is not necessary, except in dengue patient with severe dehydration and inability to drink (repeated vomiting or lethargy)*
- *Inappropriate IV fluid therapy in the febrile phase may cause fluid overload which may lead to death because of respiratory failure and congestive heart failure*

1.6 Home management and message to the parents/family

The parents should take their children to the hospital immediately in case as following:

- No clinical improvement when temperature dropped
- Abdominal pain
- Repeated vomiting
- Refuse to eat and drink
- Epistaxia or gum bleeding
- Digestive bleeding manifestation (hematemesis or/ and melena)
- Lethargy or continuous restlessness

- Cold, clammy skin and extremities
- Decreased urine output or no urine for 4 – 6 hours

1.7 Follow up with clinical and CBC indicators

Clinical sign and symptom and laboratory finding often precede entering critical phase:

a. Clinical indicator

Patient in the febrile phase should be followed up for the following signs and symptoms every 4 - 6 hours, but every to 2 – 4 hours if near to critical period.

1. Temperature drops with deterioration of general condition
2. Severe vomiting
3. Severe abdominal pain
4. Dehydration
5. Decreased urine output by age (< 0.5ml/kg/h)
6. Any signs of bleeding
7. Consciousness

b. Lab indicator

- Hemoconcentration with increase in hematocrit towards 20% of baseline
- Thrombocytopenia (< 100 000/mm^3)

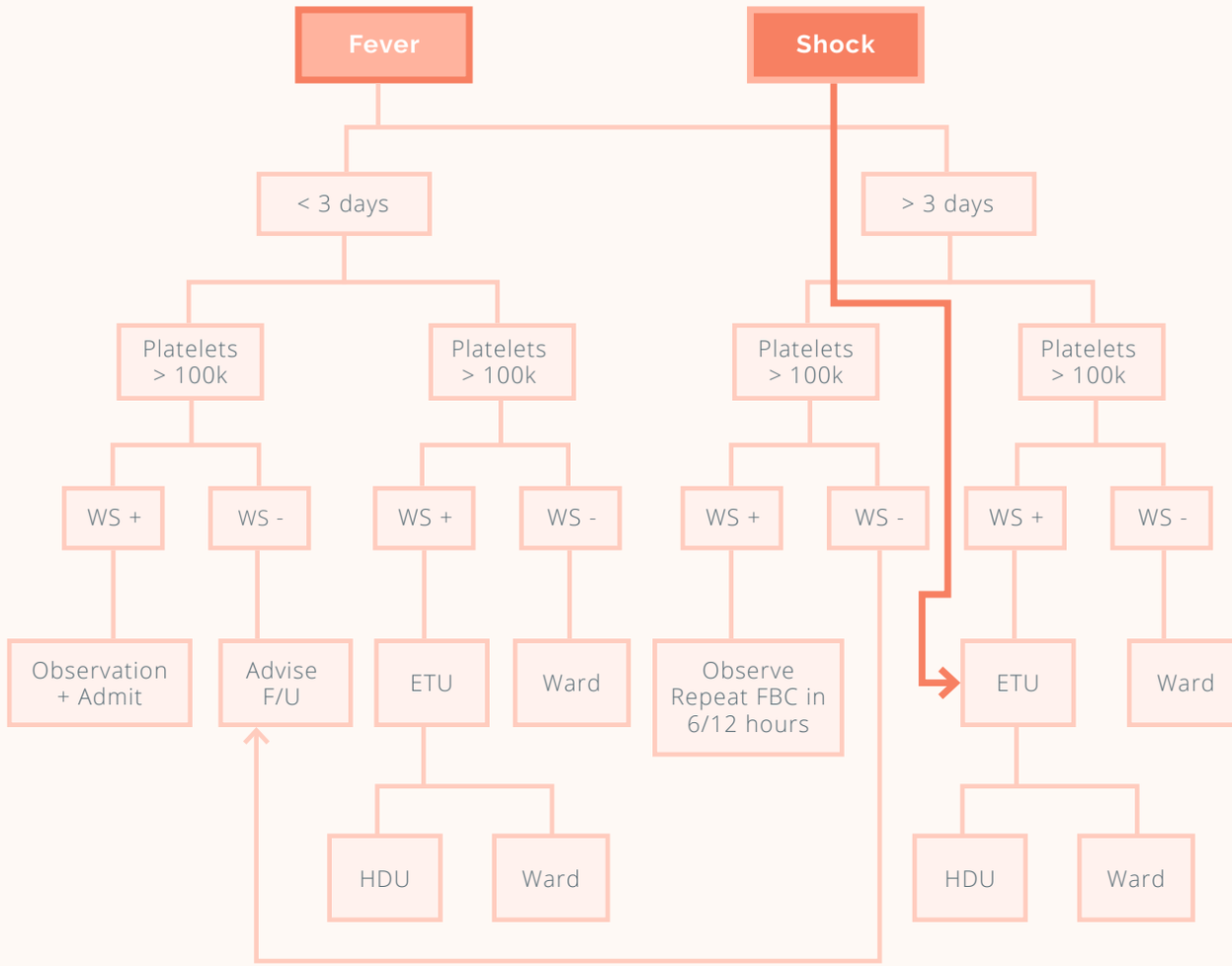
1.8 Warning signs

No clinical improvement or worsening of the situation just before or during the transition to afebrile phase or as the disease progresses.

- Persistent vomiting, lack of water intake
- Severe abdominal pain
- Lethargy and/or restlessness, sudden behavioural changes
- Bleeding: Epistaxis, black coloured stools, haematemesis, excessive menstrual bleeding, dark-coloured urine (haemoglobinuria) or haematuria
- Giddiness
- Pale, cold and clammy hands and feet
- Less/no urine output for 4–6 hours

1.9 OPD Triage

FIGURE 6: OPD Triaging of patients



ETU- Emergency Treatment Unit

HDU- High Dependency Unit (Dengue Unit)

Warning Signs (WS) of DHF/DSS:

- No clinical improvement when temperature drops
- Abdominal pain
- Vomiting
- Lethargy/ Restlessness
- Thirsty/ No appetite
- No urine > 4-6 hrs

1.10 Indicators for admission

All patients suspected of dengue infection with any of the following signs should be admitted:

- Very weak, cannot eat or drink
- Any signs of bleeding
- Platelet counts < 100 000 cells/cumm and/or rising Hct 10 – < 20%
- No clinical improvement when defervescence
- Severe abdominal pain
- Severe vomiting
- Rapid pulse with no fever
- Capillary refill time (CRT) > 2 seconds
- Cold, clammy skin, mottling
- Narrow pulse pressure < 20mmHg (eg. 100/80mmHg or 90/80mmHg)
- Hypotension by age
- No urine output 4 – 6 hours
- Change of consciousness: drowsiness, restlessness, irritability
- Take-careless child/faraway with suspected to dengue infection

1.11 High-risk patients who need special attention

Infants < 1 year:

- Often a special clinical signs and symptoms: convulsion, encephalopathy, dual-infection (diarrhea is quite common)
- Treatment often postponed by (sometimes difficult) diagnose (doctors' delay)
- Leakage period is shorter than older children and adults, usually only 12-24 hours
- Fluid overload is common due to less chest compliance and may be prolonged duration of IV fluid or receive hypotonic salt solution

Complications: liver dysfunction, overfilling (found more often than by older children or adults)

Overweight/Obesity:

- Delayed diagnosis because false negative Tourniquet test is common
- There is a risk of over- or under-filling (The amount IV fluid should be calculated based on the ideal weight of the child).Fluid overload is common due to less lung compliance
- Compared with malnourished or normal-weight children, obese children are more prone to severe forms of DHF
- Difficulties making IV fluid, especially in the critical period. Dextran is indicated earlier than in normal children

Prolonged shock:

- Metabolic acidosis, prolonged hypoxia à DIC with severe gastro-intestinal bleeding

Massive hemorrhage, especially unknown internal bleeding à severe shock, irreversible renal and hepatic failure

Patients with underlying diseases:

- Thalassemia, Hemophilia
- G-6-PD deficiency
- Congenital heart disease etc.
- Referred patients

DHF grad IV or prolonged shock,

Patients with change of consciousness (encephalopathy).

2. Leakage/Critical phase of DHF/DSS

2.1 Monitoring (refer annexure 1: Monitoring Chart for Dengue patients)

> Monitor the vital signs (temperature, pulse rate and volume, capillary refill time, blood pressure, respiratory rate every 1 - 2 hours and urine outputevery 4 - 6 hours.

> Do Hct every 6 hours for 24-48 hours

2.2 Management of DHF without shock (DHF grade I and II

To compensate the plasma leakage, the administered volume should not be more than required to maintain an efficient circulation during the critical phase. Inappropriate IV fluid therapy will cause respiratory distress by massive pleural effusion or pulmonary edema.

Start IV infusion with:

- For infants ≤ 6months: 5%D½S 1.5-3 ml/kg/h over 1 to 3 hours
- For children >6months: 5%D/NSS or 5%DAR or 5%DLR at 1.5-3 ml/kg/h over 1 to 3 hours

> **When improvement**, continue the infusion at the same dose of IVF for another 3 hours. Recheck the vital signs; if the vital signs keep improving, reduce the infusion to 1.5 ml/kg/h for another 3 to 6 hours. If the vital signs keep improving, continue the infusion at 1.5 ml/kg/h for another 24 to 48 hours while controlling the vital signs every 3 hours and then stop the infusion. The duration of IV fluid should not be > 48-60hours

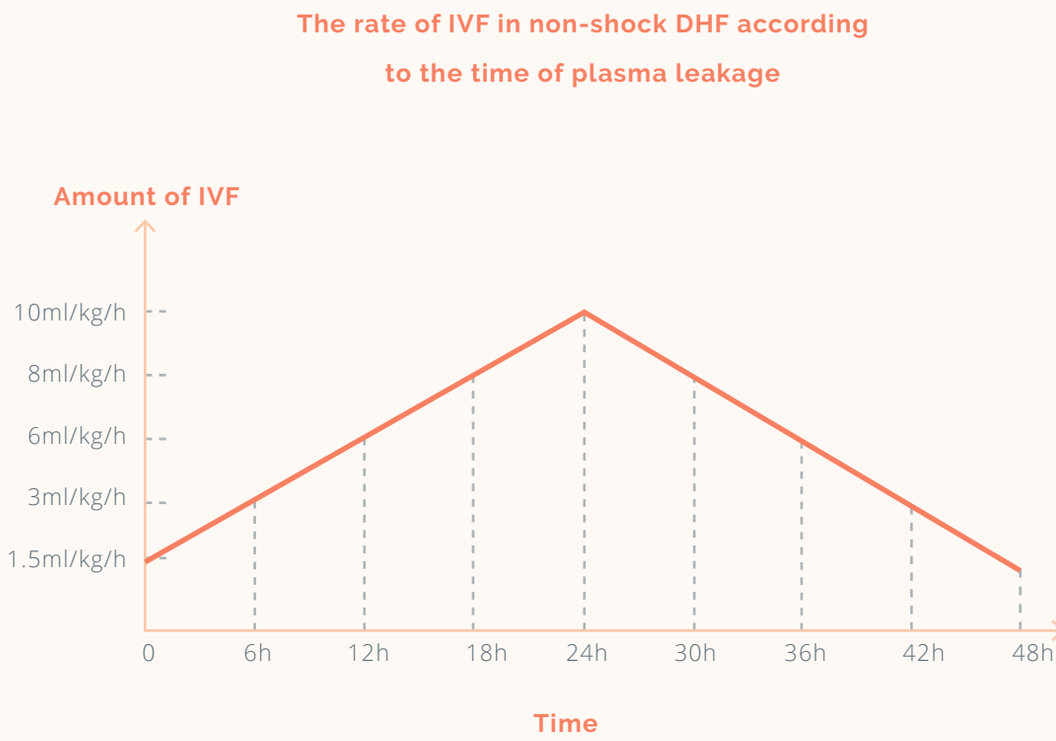
Check ABCS: Hct, blood gases(A), blood sugar (S), bleeding test (B), calcemia (C) and see the management of complicated cases. Calcium gluconate 10% and vitamin K1 can be given without waiting for the laboratory results. Glucose can be given immediately when rapid blood sugar test (DTX) is less than 70mg/dL.

> **When no improvement:**

1. When the situation worsens (pulse rapid and weak, decrease urine output): increase the IV infusion to 3-6 ml/kg/h for 1 to 3 hours. according to the degree of rising Hct.

2. If still worsening, determine hematocrit and increase the rate of the IV infusion to 10 ml/kg/h. See scheme for the treatment of DHF degree III and IVF therapy.

FIGURE 7: Treatment scheme for DHF GRADE I and II



The amount of fluid (both oral + IV) expected that the DHF Grade I & II patients should receive depends on 2 parameters

1. Degree of thrombocytopenia: first day of plasma leakage the platelet count is usually between 50,000 – 100,000 cells/cumm; second day of plasma leakage, platelet count is usually < 50,000 cells/cumm.
2. Degree of plasma leakage: first day we expect rising Hct to be 10-20%; if Hct> 20%, probably it is the second day of plasma leakage and we have to aware of possible shock

If we can make clinical diagnosis of DHF in patients with poor appetite and cannot drink ORS, i.e. rising Hct> 20%, the recommended IV fluid is about maintenance (3 ml/kg/hr).
If the rising Hct is < 20%, the fluid recommended fluid is < maintenance (1.5 ml/kg/hr).
If patients can drink some ORS, the IV fluid should be less.

TABLE 2: RATE OF IV FLUID IN ADULT COMPARE TO CHILDREN		
NOTE	CHILDREN	ADULT
Half the maintenance M/2	1.5	40-50
Maintenance (M)	3	80 100
M + 6% Deficit	3	100-120
M + 8% Deficit	8	120-150
M + 10% Deficit	10	300-500

2.3 Management on DHF grade III and IV

Appropriate place for management of DHF and DSS patients:

> **Treatment Possibilities:**

- aside from crystalloid solutions, there is the need for oxygen, 10% Dextran 40 in NSS, fresh frozen plasma or fresh whole blood, bicarbonate solution 10% Dextrose, Vitamin K1

> **Laboratory Possibilities:**

- testing of liver function (ASAT, ALAT), kidney function (creatinine, uremia), electrolytes, calcaemia, glycemia, blood gasses, coagulation tests (PT, PTT)
- Chest X-Ray and abdominal and pleural ultrasound
- Blood group and rhesus
- Hematocrit check whenever necessary

> **Medical staffs:**

- Nurses, medical doctors, lab technicians must be enough.

> **DHF grade III:**

- Do immediately Hct and blood sugar (DTX). If blood glucose more than 6 mmol/L (110mg/dL) start infusion of NSS, AR or LR at 10ml/kg/h during 1-2h + Oxygen.
- If blood glucose less than 6 mmol/L (110 mg/dL) start infusion of crystalloid solutions (5% D / NSS; 5%DAR or 5% DLR) at 10ml/kg/h during 1-2h + Oxygen.
- Monitor vital signs, especially the BP and the radial pulse every 15 - 30 minutes until they are stable (usually not exceed 1 hour), then every 1 hour. Maintain glucose level between 70mg/dL to 120mg/dL

- If the patient's condition improves within 1-2hours, reduce the rate from10 -> 6 ml/kg/h during 3 hours and monitor vital signs every 1-3 hours.
- If further improvement, reduce the rate from 6->3 ml/kg/h during 6-12 hours. Monitor vital signs every1- 3 hours.
- If still improvement reduce the rate to 1.5 ml / kg / h and maintained during 24-30hours. The duration of fluid should not exceed 36 hours
- If the vital signs are not stable (BP is lowered, narrow pulse pressure, pulse rapid and weak, urine decrease) check the Hct.

1. **If the Hct is increased change crystalloid to colloid solution preferably Dextran 40% 10ml/kg/h, After Dextran, swithch IV fluid to crystalloid and repeat Dextran if necessary (not exceeding 30ml/kg/24h) if Hct progressively rises to again. Monitor vital signs every 30 minutes.**
    - If no improvement: check Hct, blood gases(A), blood sugar (S), bleeding test (B), calcemia (C) and see the management of complicated cases. Calcium gluconate 10% and vitamin K1 can be given without waiting for the laboratory results. Glucose can be given immediately when rapid blood sugar test (DTX) is less than 70mg/dL.
    - If improvement, continue with a crystalloid solution at a rate appropriate for the timing after shock (see figure below). The duration of IV fluid is 24 hours.
2. **If Hct decreased, transfuse fresh whole blood 10ml/kg/h or fresh packed cells 5ml/kg/h for 1 hour:**
    - If no improvement: check Hct and ABCS and see the management of complicated cases.
    - If improvement, continue with crystalloid solution at rate 6ml/kg/h, then reduced to 3 ml and 1.5 ml/kg/h and maintained during 24hours.

If the rate of IV fluid cannot be reduce according to the above diagram, check ABCS and correct the abnormalities.

> **DHF grade IV (DSS):**

- Oxygen;
- Start 10ml/kg bolus in 15 to 30 minutes:
    - If the patient was not received IV fluid before admission, begin the infusion with crystalloid solution without dextrose (check blood sugar, if low, immediate infuse 10% glucose). Maintain glucose level 70 to 120mg/dL.
    - If the patient was already received IV fluid, choose the colloid solution (Dextran40)
    - Give calcium gluconate 10% and vitamin K1 IV
    - If after 15-30 minutes ,BP cannot be restored, consider NaHCO3 1-2ml/kg/dose.
- Urinary catheter is recommended to evaluate urine volume every hour.

FIGURE 8: IV FLUID THERAPY for DHF GRADE III

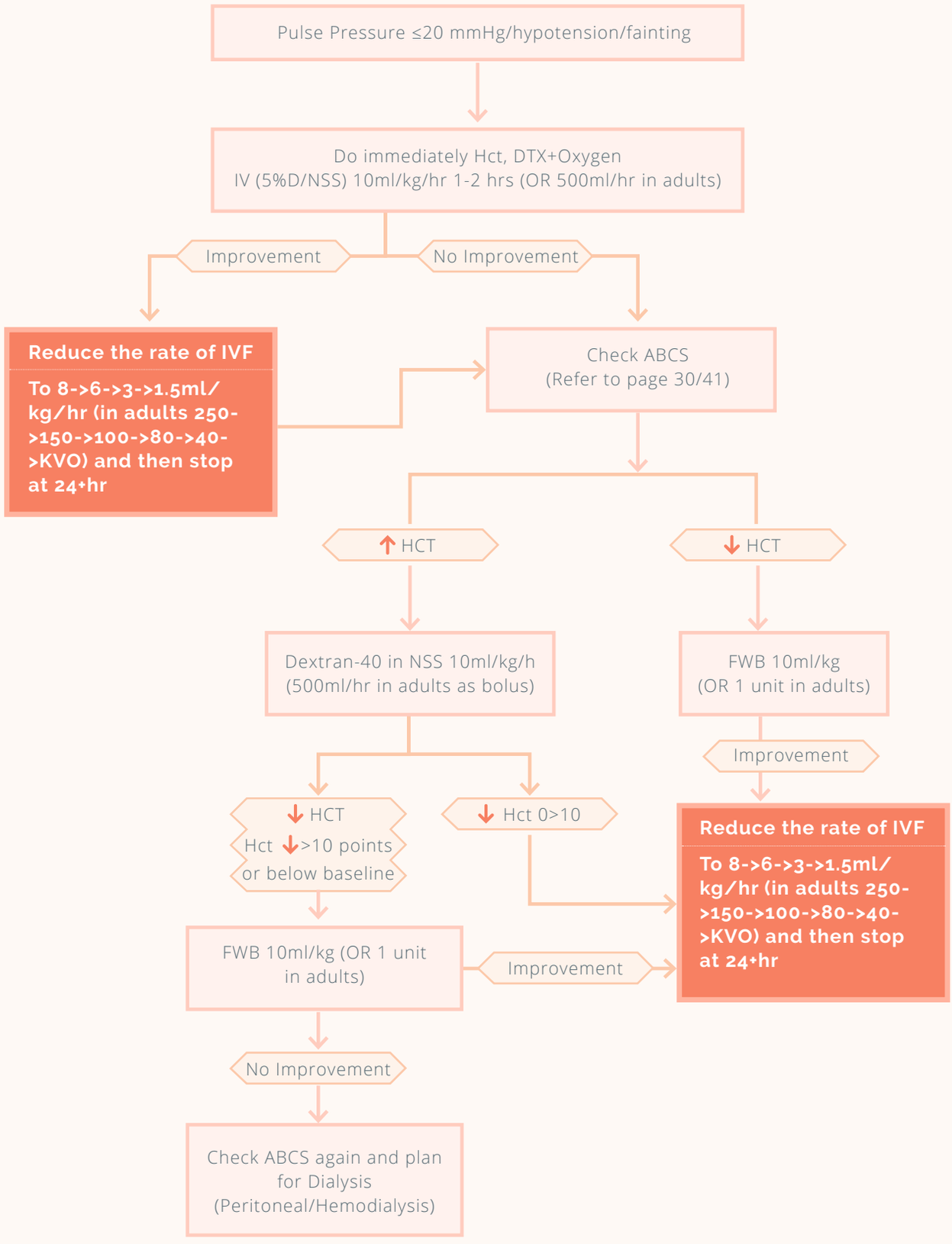
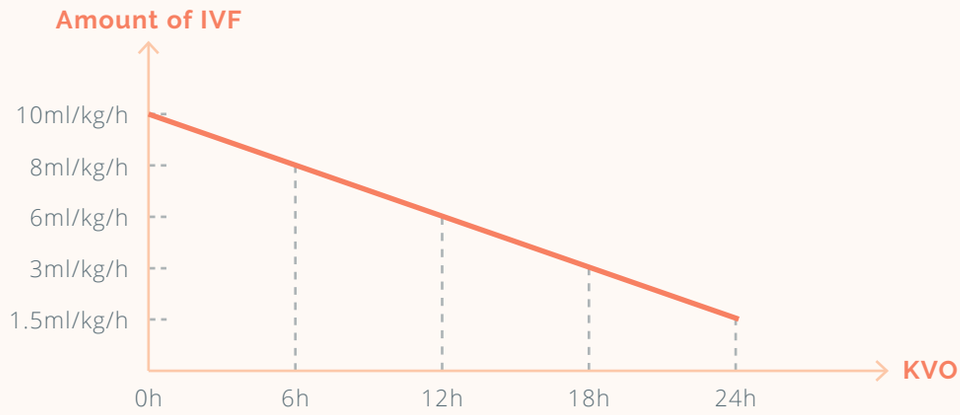


FIGURE 9: The rate of IVF in non-shock DHF according to the time of plasma leakage



Evolution: 3 situations may be happen:

1	**If no improvement and low hematocrit:** *Transfusion 10ml/kg bolus of fresh whole blood (vital signs every 30min)*
2	**If no improvement and high hematocrit:** *Colloid 10ml/kg bolus in one hour. (no exceeding 30ml/kg/24h)*
3	**If improvement:** *See schema Dengue grade III*

If unresponsive and persistent SHOCK, if it is likely that the patient already has multiple organ failure and the prognosis is grave:

- Management of pre-hepatic coma may be necessary.
- Plan for more sophisticated technique: plasmapheresis , hemodialysis, peritoneal dialysis, CVVH, CAVH or other renal replacement therapy, if no urine obtained
- Maintain airway and good oxygenation, may need intubation.
- Hct check is necessary
- Complications usually found and have to correct, are:

• Hyponatremia,

• Hypocalcemia,

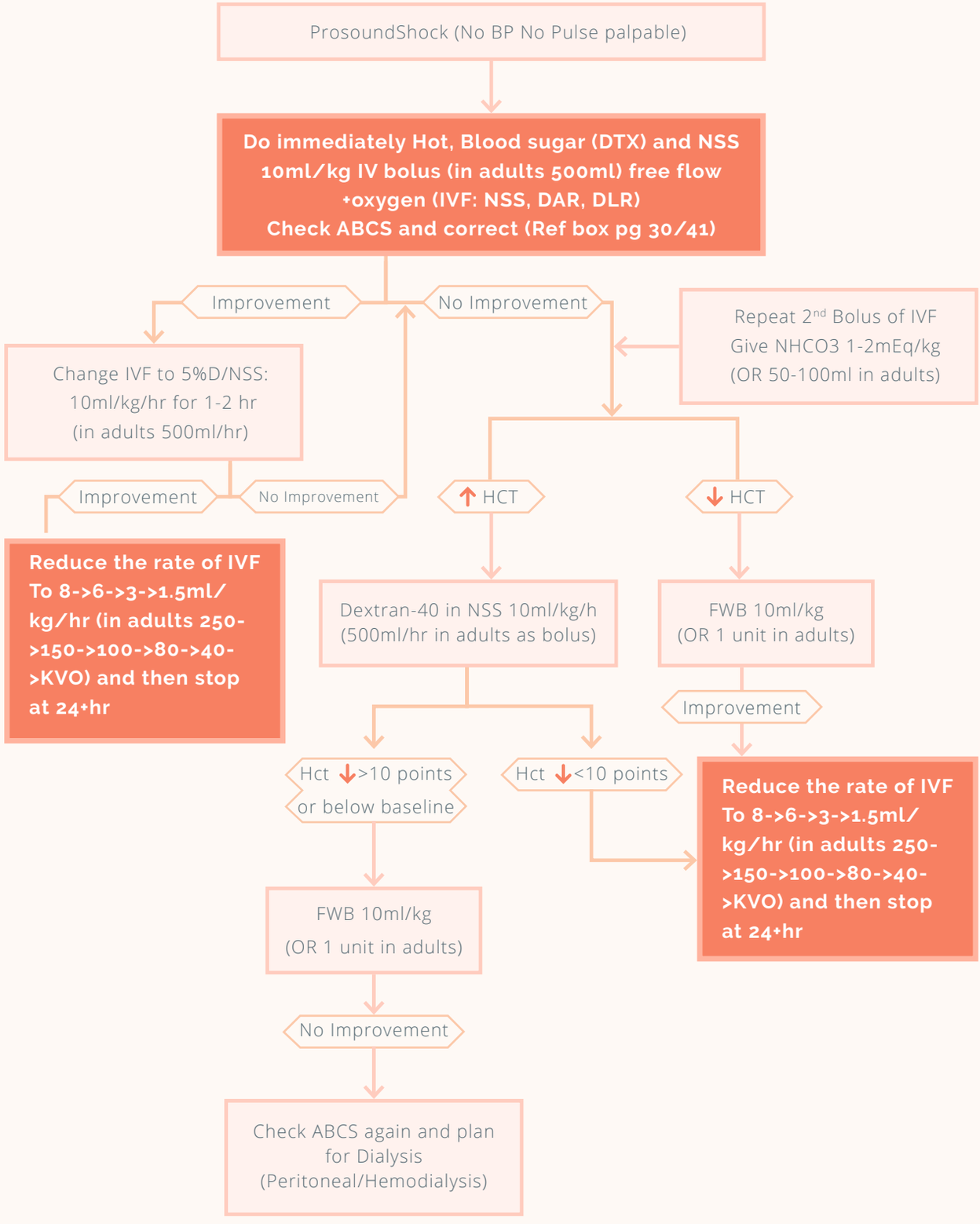
• Hypoglycemia and

• Metabolic acidosis.

> Gastrointestinal bleeding is frequently internal, and may not be recognize early. Fresh whole blood transfusion should be urgent.

> If the above situation is not recognized and managed urgently, then fluid overload will occur.

FIGURE 10: IV FLUID THERAPY for DHF GRADE IV



3. Convalescent phase

The beginning of convalescence is often characterized by the appearance of a pruritic rash on the extremities with confluent erythema and sometimes petechial lesions.Be aware of reabsorption phase when extravasated plasma is reabsorbed into the circulation, especially in cases with signs and symptoms of fluid overload because the patients may suddenly develop acute pulmonary edema or heart failure.

The following signs are signs of recovery:

- Normal temperature
- Stable pulse, BP and respiratory rate.
- No evidence of any bleeding
- Return of appetite
- No vomiting
- Good urinary output
- Stable hematocrit

Note:
During the convalescent phase, sinus bradycardia can occur.
Hepatalgia and thrombocytopenia can last a few more days.

Early recognition of dengue:

< 3 days: NS1 antigen test
> 3days: Detection (Combo test): NS1 test and/or IgM/IgG

3.1 Indication for discharge

The following criteria should be met before patients recovering from DHF/DSS are discharged:

- Absence of fever for at least 24 hours without the use of anti-pyretic therapy
- Return of appetite
- Visible clinical improvement
- Good urine output
- Stable haematocrit
- At least 2 – 3 days after recovery from shock
- No respiratory distress from pleural effusion or ascites
- Platelet count of more than 50 000/mm^3

3.2 Indication for transfer

1. All patients suspected to dengue infection must be transferred from Health Center to referral hospital ;

2. Transfer patient from lower level referral hospital to higher level:

- Age < 1 year
- Patients with underlying diseases e.g. G-6-P-D deficiency, Thalassemia, congenital
- Heart disease
- DHF grade IV or patients with prolong shock
- Significant bleeding (in case no blood bank)
- Unusual manifestations e.g. consciousness change, convulsion, restlessness, stupor, coma.
- DHF grade III with:
    - No respond to IV fluid 10ml/kg/h for 2 – 3 hours of shock (in case that there is no colloidal solution).
    - After one dose of colloid and the patient is still has high Ht.
    - Repeated shock more than 2 times
- Patient with DHF with signs of fluid overload: massive pleural effusion, very tense and distended abdomen with respiratory difficulty.
- Parental concern, not adequate personnel

NB:

Before referring the patient should be:

- Contact the referring hospital every time
- Good record

Part 7

Complications and management

1. Common complications in leakage phase (ABCS)

- Electrolyte imbalance
- Fluid overload
- Prolonged shock
- Massive bleeding
- Other problems:
- Encephalopathy/encephalitis
- Hepatic failure
- Renal failure
- Dual infection

2. Serve complications that may lead to death

2.1 Fluid overload

> **Signs of fluid overload:**

- Puffy eye lids/ very distended abdomen
- Dyspnea/ Tachypnoea
- Positive lung signs

> **Can be found in both critical & convalescence period.**

> **Can cause pulmonary edema**
(leading to respiratory failure + congestive heart failure cause death by hypoxia).

Common causes of fluid overload:

- Early inappropriate IV fluid in the early febrile phase.
- Use of hypotonic solutions (Dextrose ½ saline, Dextrose 1/3 saline)
- Not giving blood transfusion when there is concealed bleeding and continue giving crystalloid and colloid solutions.
- Not calculating amount of IV fluid according to ideal Body Weight in obese/overweight patient.
- Not stopping IV fluid when entering convalescence period.
- Not using colloidal solution when indicated
- Myocardial depression (rare in children)

Management of patient with fluid overload:

The patient should be treated in ICU

- Most patients (reabsorption phase) : High BP + wide pulse pressure
  - Reduce the IV fluid to the rate KVO
  - Oxygen (Mask or NCPAP if needed)
  - Furosemide 1mg/kg/dose IV (40mg in adults). Vital signs (Pulse, Blood pressure, RR, T, Urine output) should be taken before starting and follow-up q 15mn, at least 1h after Furosemide. It must check potassium and correct to at least 4mmol/L.

- But some patients (Critical phase and early convalescence, not yet in reabsorption phase : stable BP or shock; narrow pulse pressure, poor tissue perfusion (CRT > 2 sec)
  - Change IV fluid to colloid solution such as 10% Dextran 40 in NSS at the rate 10ml/kg/h (500ml/hr in adults), give **furosemide 1mg/kg/dose (40mg in adults) after 30 minute (midway) of 10% Dextran 40 in NSS.**
  - Oxygen Mask or NCPAP(see appendix)
  - Insert urinary catheter and record the amount of urine output in ml/kg/h
  - Check Urine (ml), Blood Pressure, Pulse rate, Capillary Refill Time, Respiratory Rate and SaO2 q15mn

- Check ABCS (if available):

  A : Acidosis (Bicarbonate Na 8.4% 1ml/kg/dose)

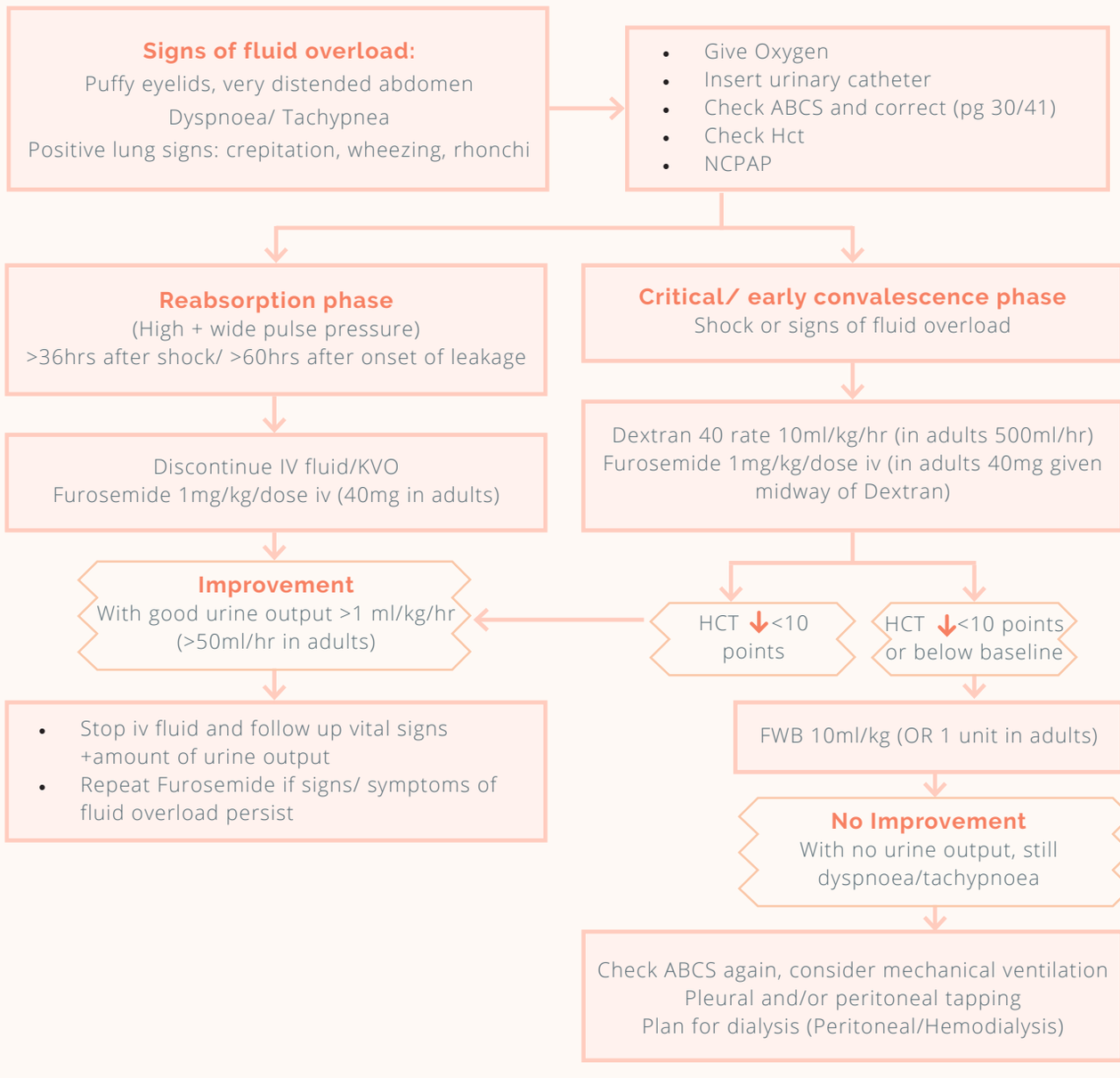
  B : Bleeding › BT, CT, PT and APTT(see massive bleeding complication)

  C : Calcemia (if hypocalcemiaàCagluconate 10% 1ml/kg/dose (Max: 1 ampoule) very slowly IV(>15mn)

  S : Blood sugar (<60mg%) › D10% 5ml/kg/dose.

- After finish Dextran infusion, switch IV fluid to crystalloid at the rate minimal to keep urine output to 0.5 ml/kg/hr (25-30ml/hr in adults) or according to the time after shock or leakage of individual patients. If severe respiratory distress, IV fluid may be reduced to 1 ml/kg/hr and monitor urine output every hour.

FIGURE 11: Management of patients with Fluid overload



2.2 Massive bleeding

- Early massive bleeding is usually due to underlying peptic ulcer or drug induced gastritis (Aspirin, NSAIDs, steroids)
- Usually occur after prolonged shock in patients with advanced disseminated intravascular coagulopathy (DIC) and liver failure.

Signs:

Bleeding in DHF is mostly concealed but can have gastro-intestinal bleeding (Hematemesis or melena). Hypermenorrhea and haemoglobinuria are also common.

Treatment:

- Transfuse blood when estimated blood loss is >10% of the total blood volume (6-8ml/kg in children OR 300ml in adults)
- If the patient has no signs of fluid overload, give Fresh whole blood 10ml/kg/dose (1 unit in adults),
- If the patient has signs of fluid overload, give Pack Red cells 5ml/kg/dose (1 unit in adults), and
- In case of severe thrombocytopenia with severe bleeding, platelet transfusion is considered provided no signs of fluid overload
- Start transfusion when Hct is between 40-45%, don't wait it to drop <30 OR when patient develop shock; However, when Hct is>45% always bring it down by Dextran bolus before blood transfusion
- Keep Hct 10-20% above baseline level during leakage/critical phase
- Always do Hct before and after blood transfusion and

  Repeat blood transfusion if bleeding continuous

2.3 Encephalopathy

The patient usually presents with changes of consciousness as restlessness, irritable or coma. Neurological examination may reveal hyper-reflexia, extensor plantar response (Babinski sign).

Causes:

- Hepatic encephalopathy (severe shock, use of hepatotoxic drug, Thalassemia, Hepatitis B carrier, Rey syndrome)
- Electrolyte imbalance e.g. hyponatremia, hypocalcemia
- Metabolic disturbance e.g. hypoglycemia
- Intracranial bleeding, cerebral thrombosis/ischemia (Rare)

Management with hepatic encephalopathy:

- Maintain adequate airway and oxygenation
- Consider Furosemide and /or Dexamethasone in patients with signs increase intracranial pressure.
- Reduce the ammonia production by giving lactulose (for loosen stool) and local antibiotic – neomycin (no need if systemic antibiotics are already given)
- Vitamin K1 IV for 3 consecutive days
- Prevention hypoglycemia by maintain glucose level > 60mg%.
- Correct metabolic acidosis if present
- Correct electrolyte disturbance
- Transfusion PRCs if indicated
- Empiric antibiotics if superimposed bacterial infection cannot rule out
- Consider H2-blockers with massive GI bleeding
- Avoid unnecessary drugs
- Consider plasmapheresis, hemodialysis, peritoneal dialysis or other renal replacement therapy if clinical deterioration

2.4 Multiple organs dysfunction

Multi-organ dysfunction is a result of prolong and profound DSS. It would comprise of Liver failure, Renal failure and Respiratory failure. Therefore, the management of such patient is in line with the management of hepatic encephalopathy, renal replacement therapy and ventilation (preferably CPAP ventilation).

Part 8

Management of high-risk patients

1. Infancy

Infants with DHF manifest differently from older children and adult with DHF. They usually present with unusual presentations. The 2 most common presentations are convulsion and diarrhea which often make clinicians misdiagnose them as meningitis or acute diarrhea.

For convulsion, they usually have subtle form of seizure and the onset of seizure is a few days after high fever especially when the temperature is coming down. Electrolyte disturbance (hypocalcemia and hyponatremia) and minute bleeding in the CNS is suggested to be the causes of this subtle form of seizure. If the febrile infants do not have flank watery diarrhea, especially after a few day of high fever, it is possible that they may have dengue infections.
Infants with DSS are very difficult to diagnose because non-stop crying may be the only sign of shock. Blood pressure is very difficult to measure especially in irritable, crying infants. Delayed capillary refill time may help in diagnosis of shock in infants.

Frequent follow up of CBC daily or twice a day will help in infant management properly, especially those who come with convulsion and diarrhea. Expect every clinician to look at CBC first before doing the spinal tapping in those with convulsion and also in those patients who present with diarrhea before consider hypotonic salt solution to them. Detection of plasma leakage is sometimes missed because inexperience/young doctors do not recognize hemoconcentration in infants. Hct of 36-38% is quite high for infants, i.e. probably 20% hemoconcentration because their baseline is only 28-32%.

The course of leakage in infants is much shorter than in older children and adults. The duration of leakage is only 12 – 24 hours compare to 24 – 48 hours in older patients. IV fluid in the leakage phase for infants > 6 months old is recommended to be NSS as in older children and even in < 6 months old if they are in shock. If they are under 6 months old with no shock, 5% D/N/2 is recommended. Shorter duration of IV fluid for infants, probably 12-24 hrs is recommended in shock cases. Urine output needs to monitored closely for the decision to reduce and discontinue early before they got signs of fluid overload. Infants have limited lung expansion and develop acute pulmonary edema early and rapidly.

2. Obesity

Obese DHF/DSS patients (infants and pregnancy patients as well) have limited capacity of lung expansion according to their basic physiology, so IV fluid management is strict than in other patients. IV fluid administer has to be as minimal as possible to maintain intravascular volume. Urine output (UOP) is the good indicator for adequate intravascular volume. UOP has to be monitored to be 0.5 ml/kg/hr. When these obese patients complain of abdominal or respiratory discomfort, we have to pay more attention and furosemide with or without dextran-40 are to be considered.

3. Pregnancy

The guidelines for management of dengue infections in pregnancy are not available right now. We need multi-disciplinary team to discuss about the management. The team includes obstetrician, Pediatrician, internal medicine doctor, surgeon and families from each side to discuss and have consensus on individual case management.

In general the management depends on:

- The phase of the dengue illness: febrile, leakage or convalescence
- The gestation of the patients

It is preferably make an early clinical/confirmed diagnosis of dengue with NS1Ag and early admission and observe pregnant dengue patients in a referral hospital with all those subspecialties doctor mentioned above.

- **If the gestation is > 28-32 weeks** and that pregnant woman are in febrile phase, we recommend to do early Caesarian section and takes the rather mature baby out to be taken care so that we can manage only mother which may be easier.
- **If the gestation is 24-28 weeks,** Dexamethazone is preferably given to the mother at least 2 days before the operation (if possible).
- **If the gestation is < 24 weeks,** recommend to on pregnancy and observe mother closely with early detection of plasma leakage with proper IV fluid therapy. Keep IV as minimal to maintain intravascular volume because they have limited respiratory reserve.

If the pregnant mothers are in the critical period, i.e. platelet count ≤ 100,000 cells/cumm., we need to have a serious discussion between multi-disciplinary doctors and families from both sides.

4. Other co-morbidities

Thalassemia/G-6-PD Deficiency and hemoglobinopathy

These patients usually have problems with hemolysis of RBC when encounter with viruses, especially dengue viruses infections. History of dark-colored urine is important. If they have dark-colored urine, it is very important to transfuse PRC as soon as possible to prevent organ hypoxia which may lead to organ injury/failure. These DHF cases with hemoglobinuria are often confused to most doctors because from CBC, they will have definitely hemoconcentration (rising Hct) without thrombocytopenia. The automate CBC machines that we use have the disadvantage for they do not recognize fragmented RBC, instead they count them as platelets so we do not see low platelets.

There is also no need to give a large amount of IV fluid or to alkalinized urine as in other infections with hemoglobinuria because we will give proper amount of IV according to the degree of leakage and these patients naturally have mild respiratory alkalosis due to slight tachypnea with pleural effusion and ascites.

Diabetes Mellitus

These patients IV fluid management is the same except that if there BS is > 300 IU, they need RI to control their sugar level and the IV fluid should not contain 5%Dextrose. Only when their blood sugar is < 200 mg% that 5%Dextrose in IV is to be considered. Urine sugar may not be reliable if the urine sugar is > 3+-4+, for it will cause osmotic diuresis. Differential diagnosis with diabetic keto-acidosis is important because the management is different.

Hypertension

History and baseline BP is important among these patients for proper detection of shock and IV management. Clinical signs of shock, capillary refilled time is used in patients with hypertension to detect shock because we do not usually know their baseline BP.

Part 9

Outbreak preparedness in hospitals

In any part of Cambodia there could be a sudden reporting of dengue patients. Therefore, having a hospital emergency response plan for dengue outbreaks will help in early diagnosis and appropriate clinical management of patients to minimize complications and deaths.

Hospital response plan should include the following key elements:

- Outpatient care (with triage and resuscitation areas)
- Hospital bed occupancy (with a view to identifying additional beds during outbreaks)
- High-dependency care beds
- Staffing and surge capacity needs
- Stock management of essential medicines and supplies
- Laboratory facilities

During an impending outbreak situation, as the first step, hospitals should develop and strengthen the capacity to screen and triage suspected dengue patients at the out-patient department.

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 updated 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 inward care for dengue haemorrhagic fever patients:

Medicines:

- Paracetamol
- Oral Rehydration Solution (ORS)
- IV Fluids
  - Crystalloids – 0.9% and 5%D/NSS, 5% DLR, 5% DAR
  - Colloids – hyper-oncotic (plasma expanders) – 10% Dextran 40 in Normal saline
- 25% or 50% Dextrose
- Vit K1
- Calcium Gluconate
- KCl solution
- Na bicarbonate

Supplies and equipment:

- Thermometers
- Sphygmomanometers
- Iv access sets
- Oxygen delivery systems
- Micro centrifuge (for bedside haematocrit assessment)
- Microscopes (for platelet count estimation)
- Glucometers (for blood sugar estimation)

Laboratory support:

- Laboratories should be equipped round the clock for basic tests such as – Complete blood count (CBC), haematocrit, platelet count, white blood count (WBC), and differential count.
- More complicated patients will need blood sugar, liver function test (AST/ ALT), renal function test, electrolyte (including serum calcium), blood gases, coagulogram, chest x-rays, untrasonography.

Blood Bank:

- Fresh whole blood, packed red cells and other blood products should be available on demand.

Part 10

Reporting dengue

Reporting of clinical dengue is a key strategy in the control and prevention this high epidemic-prone disease by generating essential epidemiological information, determining the incidence and distribution of the disease and monitoring effectiveness of public health interventions.

Cambodia has the potential to report cases of dengue through several systems:

- **National Dengue Control Program (NDCP)** implemented enhanced sentinel surveillance system
- **Communicable Disease Control Department (CDC)** has established syndromic case surveillance system (CamEWARN)
- **Health Management Information System (HMIS)** reporting confirmed cases and deaths. may lead to death because of respiratory failure and congestive heart failure

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Annexures

Monitoring Chart for Dengue Patients

Instuetions - Do CBC daily/bd and PCV 6 hrly. Monitor other parameters 3-4 hrly and when leaking detected monitoring every hour.

Case	= Refer	= Walk in
OPD	= Shock	= Non shock
IPD	= Shock	= Non shock

Indications to call for immediate advice

1. Pulse rate > 120 / min with fever or > 100 / min without fever.
2. Pulse Pressure 25-20 mmHg of Jess (in supine possition)
3. Postural drop of SBP > 20 mmHg
4. Significant bleeding (Maemetemesis, Malena, Bleeding PV etc)
5. UOP < 0.5 ml / Kg / hr
6. CRFT > 2 sec

Date	Time	BP	Temp	PR	RR	PP	RR	HCT (%)	Clinical/ Lab/ Treatment	Nursing Care/ Signs	INTAKE				OUTPUT		
											Blood/ rate & Amount	IV Amount	Oral	Total	Urine/ Stool	Vomit /Bleed	Total

CBC Day of Admission	BW= kgs. Hight = cms	Date of Fever Day of Illness
Hct = WBC =	IBW = kgs.	TT
Plt = Lym =		Liver
PMN =	Maintenance fluid =	Bleeding
		Epistaxis
	M+ 5% Deficit =	Abdomen

Name			Age	HN	AN	Pulse : F = Full M= Moderate W= Weak N= Not Palpable
	Ward	Attending Physician				

2. Classification of Dengue for reporting

Suspected Dengue:

(ICD10-A91.2) very high fever at 39-40°C of 2 to 7 days duration (usually 3-4 days), with 2 or more following signs:

- Flushed face
- Headache
- Retro-orbital pain
- Myalgia / arthralgia
- Rash cutaneous
- Haemorrhagic signs (petechiae, positive tourniquet test)
- Leucopenia

Probable Dengue:

(ICD10-A91.3)very high fever at 39-40°C of 2 to 7 days duration (usually 3-4 days), with 2 or more following signs:

- Flushed face
- Headache
- Retro-orbital pain
- Myalgia / arthralgia
- Rash cutaneous
- Haemorrhagic signs (petechiae, positive tourniquet test)
- Leucopenia

and

Antibody HI≥1/1280 or IgM/IgG positive by ELISA test in convalescence serum

or

Case occurred in the region where the dengue case has been confirmed

> Pay a particular attention to a patient with tourniquet test positive (petechiae) + leukopenia (WBC ≤ 5,000 cells per mm^3)

Confirmed Case:

Dengue fever (ICD10-A90) is a case confirmed by laboratory criteria

- Isolation of the dengue virus,
- Detection of dengue virus RNA in serum or tissues (NSI Ag),
- Detection of specific dengue virus antigen

Significant (4-folds or greater) rise in specific antibodies between acute-phase and convalescence-phase serum samples by haemagglutination-inhibition (HI), compliment fixation (CF), neutralization test (NT), IgM-capture enzyme-linked immunosorbant assay (MAC-ELISA), or indirect IgG ELISA.

3. Calculation of the amount of drops per minute

Electrolyte Solution: **Drops/minute =** $\frac{\text{V (volume to perfuse, in ml)}}{\text{3 x T (perfusion time, in hours)}}$

Macromolecule Solution: **Drops/minute =** $\frac{\text{V (volume to perfuse, in ml)}}{\text{4 x T (perfusion time, in hours)}}$

Remark

Electrolyte solution: 1 ml = 20 drops, Macromolecule solution: 1 ml = 15 drops

4. Body temperature, heart rate and respiratory rate

The relationship between body temperature, heart rate and respiratory rate in children.

- In the assessment of the hot and unwell child, to determine whether any tachycardia or tachypnoea is caused solely by fever, or whether there may be an element of concurrent shock.
- Body temperature an independent determinant of HR
- Increase of **~ 10 beats/minute/degree centigrade**.

Derivation and validation of age and temperature specific reference values and centile charts to predict lower respiratory tract infection in children with fever.

- An increase in respiratory rate of > 2.5 breaths/minute/1°C rise predicts LRTI

PARAMETERS	FEBRILE RESPONSE	DENGUE SHOCK	WARM SEPTIC SHOCK	COLD SEPTIC SHOCK
Temperature	High fever	Normal/below	High fever	High fever (Hypothermic)
Heart Rate	Tachycardia proportional to the fever	Tachycardia	More trhan temperature rise	Tachycardia (Bradycardia)
Skin Temperature	Cold	Cold	Warm	Cold
Pulse volume	**Normal**	**Small**	**Good/Bouding**	**Feeble**
Skin Colour	Mottled	Cold, mottled	Pink, flushed	Mottled
CRT	Prolonged	Prolonged	Good	Prolonged
Physiology	Peripheral vasoconstriction to conserve heat, to generate temperature	Peripheral vasoconstriction	Vasodilation in response to cytokines, high cardiac output	Vasoconstriction due to inadequate fluid resuscitation, poor cardiac output
Myocardium	Normal, hyperdynamic	Normal, decreased LV size	Increased/ Decreased LV and RV function	Poor LV and RV function

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National guideline

for Clinical Management of Dengue

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