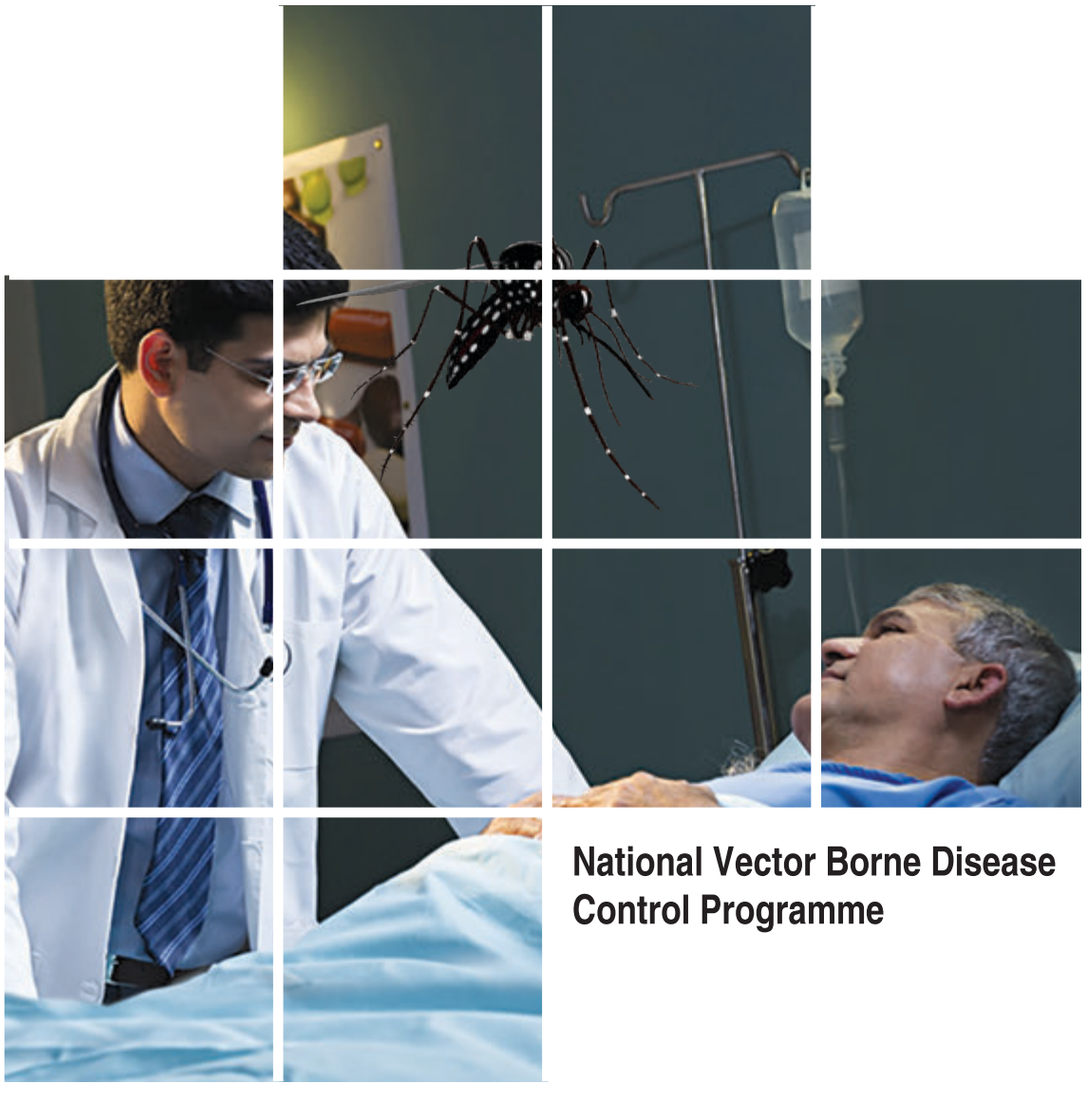
सत्यमेव जयते
Government of India

National Guidelines for Clinical Management of Dengue Fever



National Vector Borne Disease Control Programme

World Health Organization
COUNTRY OFFICE FOR India

राष्ट्रीय वैक्टर जनित रोग नियंत्रण कार्यक्रम
NVBDCP

NATIONAL HEALTH MISSION
राष्ट्रीय स्वास्थ्य मिशन

Release of the National Guidelines for Clinical Management of dengue Fever

Prof (Dr) Jagdish Prasad, Director General of Health Services, Government of India released the new Guidelines on 19 December 2014 during the National Consultation on dengue with Special Focus on Case Management held at Hotel Lalit, New Delhi in the presence of Dr Nata Manabde, WHO representative to India; Dr Mohmmad Jamsheed Ahmed, Medical Officer, Vector Borne and Neglected Diseases, WHO, SEARO; Professor Siripen Kalayanarooj, Former Director, Queen Sirikit, NICH, Bangkok, Thailand; Professor Ashutosh Biswas, Department of Medicine, AIIMS, New Delhi and Dr A.C. Dhariwal, Director NVBDCP.

National Guidelines for Clinical Management of Dengue Fever

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दिनांक/Dated.....

15th December, 2014

PREFACE

Dengue is a major public health concern throughout the tropical and subtropical regions of the world. Almost half the world's population live in countries where Dengue is endemic. World Health Organization (WHO) estimates that 50-100 million Dengue infections occur every year with 22000 deaths. It has been identified as one of the 17 neglected tropical diseases by WHO.

First isolated in India in 1945, occurrence of Dengue fever in the country was first reported during 1956 from the district of Vellore in Tamil Nadu. All the 36 states/UTs except Lakshadweep have reported Dengue cases during the last two decades. Recurring outbreaks of DF/DHF have been reported from various States/UTs namely Andhra Pradesh, Chandigarh, Delhi, Goa, Gujarat, Haryana, Karnataka, Kerala, Maharashtra, Odisha, Puducherry, Punjab, Rajasthan, Tamil Nadu, Uttar Pradesh and West Bengal. There were 50222 confirmed cases and 242 deaths in 2012. Subsequently 75808 cases and 193 deaths reported in 2013. The increasing magnitude of the problem of dengue illness together with its changing epidemiology is an important public health concern.

Guidelines for clinical management of Dengue fever, Dengue Haemorrhagic fever and Dengue Shock Syndrome was developed by National Vector Borne Disease Control Programme, India in 2008. Since then newer understanding of the pathogenesis of the disease along with change in mode of clinical presentation and severity of the illness have led to change in concept of clinical management of the disease.

In 1997 WHO SEAR introduced guidelines on dengue with the case definition of Dengue Fever (DF) and Dengue Haemorrhagic Fever (DHF) which had been adapted by all WHO Regions. The same was revised in 2011 as expanded guidelines. In 2009, WHO HQ in collaboration with TDR has published another guideline for the diagnosis, classification and management of dengue with a new classification of Dengue and severe dengue. Due to lack of uniform criteria there was a great confusion. If classification is not uniform, comparisons and aggregations between can be misleading. Besides, correct classification is important clinically, because death is associated with the more severe form of the disease. Moreover, cases of dengue can be misclassified at the time of diagnosis because of the confusion over two sets or difficulties with using the WHO classification system. The severity of dengue is also a predictor of the use of health-care services. In order to make uniformity in treatment of dengue cases it was thought prudent to harmonize the case classification of WHO-SEAR (2011) and WHO-HQ&TDR (2009). And accordingly, following a series of consultations, a new National Guidelines for Clinical Management of Dengue Fever 2014 has been developed by a team of Indian National experts.

This guideline has been prepared to make widely available the updated practical information on clinical management of dengue to health practitioners of various level available in different parts of the country. At the same time it will bring uniformity in case management of dengue illness in the country.

I express my gratitude to the Experts and congratulate NVBDCP on this major initiative. I wish all success to the Programme.

(Dr. Jagdish Prasad)

Message from WHO Representative to India

Over the last five decades, dengue has emerged globally as a critical threat to population health. The World Health Organization (WHO) estimates that 50–100 million dengue infections occur each year and that almost half the world's population lives in countries where dengue is endemic.

Today, dengue ranks as the most important mosquito-borne viral disease in the world. The emergence and spread of all four dengue viruses (serotypes) represent a global pandemic. While dengue is a global concern, currently close to 75% of the global population exposed to dengue are in the Asia-Pacific region.

Mortality from dengue can be reduced to zero by immediately implementing timely, appropriate clinical management, which involves early clinical and laboratory diagnosis, intravenous rehydration, staff training and hospital reorganization and training health personnel, along with appropriate referral systems, at primary health-care levels.

Dengue morbidity can also be reduced by implementing improved outbreak prediction and detection through coordinated epidemiological and entomological surveillance; promoting the principles of integrated vector management and deploying locally-adapted vector control measures including effective urban and household water management. Effective communication can achieve behavioral outcomes that augment prevention programmes.

In India, resurgence of epidemic dengue activity poses a major public health challenge. This upsurge has been associated with the geographical expansion of both the mosquito vectors and the viruses.

A Joint Monitoring Mission (JMM) on vector-borne diseases was conducted from 01 to 10 March 2014 in New Delhi. It clearly noted the deficiency in the competence of clinicians in clinical diagnosis and management of dengue and recommended that the capacity of health staff must be strengthened, especially to manage severe forms of the disease. The JMM also recommended focus on effective triage and case management at primary and secondary levels and adequate referral mechanisms for critical cases.

This document on the new guidelines for the clinical management of dengue will address many of these issues. I am certain it will strengthen our ability and preparedness to address this recurrent epidemic in India.

Dr Nata Menabde
WHO Representative to India

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ACKNOWLEDGMENTS

Dengue ranks as the most important, rapidly emerged mosquito-borne viral disease in recent years and is endemic in all continents. The increasing burden of dengue has been a matter of serious concern globally. Approximately 1.8 billion (more than 70%) of the population is at risk for Dengue worldwide live in WHO South-East Asia Region (SEAR) and Western Pacific Region, which bear nearly 75% of the current global disease burden. In 2012, SEAR countries reported approximately 0.29 million cases, of which India contributed 20%.

The existing National Guidelines on Clinical management of DF/DHF/DSS developed during 2007 following the WHO SEAR 1997 guidelines. The recent guidelines developed by WHO HQ & TDR in 2009 and WHO SEARO in 2011 using two different sets of classification have led to great confusion due to lack of uniform criteria. Realizing the difficulties in classifying and reporting of the cases NVBDCP has taken the initiative to make a user friendly National Guidelines for clinical management of Dengue Fever harmonizing the existing WHO and national guidelines.

NVBDCP is grateful to Prof. Ashutosh Biswas, Department of Medicine, AIIMS who has taken a lead while framing these guidelines and made enormous effort to harmonize the case classifications. NVBDCP gratefully acknowledges the valuable inputs through brain storming deliberations provided by Dr. Veena Devgan, HOD, Pediatrics, Hindu Rao Hospital; Dr. Ghanshyam Pangtey, Associate Prof. Medicine, LHMC, Prof. Ratnakar Sahoo, Department of Medicine, Dr RML Hospital and Dr. Kabita Chatterjee, Incharge Blood Bank, AIIMS through series of discussions.

I also acknowledge all the Experts who participated in the deliberations on 21st August, 2014 under the Chairmanship of DGHS for their inputs on the draft guidelines.

Valuable inputs given by Prof. Siripen Kalayanarooj, Former Director, Queen Sirikit, NICH, Bangkok, Thailand is highly acknowledged.

NVBDCP sincerely acknowledges its gratitude to Prof.(Dr) Jagdish Prasad, Director General of Health Services, Govt of India, for his valuable thought provoking suggestions and technical guidance while finalizing these guidelines.

The support of Dr Nata Menabde, WHO Representative to India for her commitment towards improving case management and helping the programme is also thankfully acknowledged. Efforts made by Dr. Asheena Khalakdina, Team Leader, Communicable Disease, and Dr Pavana Murthy, National Professional Officer - Communicable Disease, WHO Country office for India are duly acknowledged.

I would like to acknowledge the endless efforts of Dr Kalpana Baruah, Joint Director & Programme Officer for Dengue, NVBDCP for coordination with the Experts throughout the process of framing these guidelines. Also acknowledging the contribution of Dr P. K. Sen, Additional Director, Head of Arboviral Divison, NVBDCP for his technical inputs.

Secretarial Assistance rendered by Ms Nandini Arora, Technical Assistant and Shri Sachin Verma, Secretarial Assistant of dengue division while preparing this document is also acknowledged.

Dhariwal
15/12/2014

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Abbreviations

ABG	arterial blood gas
Ae.	Aedes
AKI	acute kidney injury
ALT	alanine aminotransferase
AP	aphaeretic platelet
aPTT	activated partial thromboplastin time
ARDS	acute respiratory distress syndrome
ARL	apex referral laboratory
AST	aspartate aminotransferase
ATN	acute tubular necrosis
BCPP	buffy coat pooled platelet
C	core protein
CAD	coronary artery disease
CBC	complete blood count
CF	complement fixation
CFR	case fatality ratio
CNS	central nervous system
COPD	chronic obstructive pulmonary disease
CSF	cerebrospinal fluid
DALY	disability-adjusted life year
DENV	dengue virus
DF	dengue fever
DHF	dengue haemorrhagic fever
DIC	disseminated intravascular coagulation
DLC	differential leukocyte count
DSS	dengue shock syndrome
E	envelope protein
EDS	expanded dengue syndrome
FDP	fibrinogen degradation product
FFP	fresh frozen plasma
G6PD	glucose-6-phosphate dehydrogenase
GFR	glomerular filtration rate
GoI	Government of India
Hct	haematocrit

HI	hemagglutination-inhibition
HIV	human immunodeficiency virus
NASBA	nucleic acid sequence-based amplification
NS	non-structural
NSAID	nonsteroidal anti-inflammatory drug
NT	neutralization test
NVBDP	National Vector Borne Disease Control Programme
ORS	oral rehydration solution
PCR	polymerase chain reaction
PCV	packed-cell volume
PHC	primary health centre
PRBC	packed red blood cells
PT	prothrombin time
RDP	random donor platelets
RDT	rapid diagnostic test
RT-PCR	reverse transcription polymerase chain reaction
SDP	single donor platelet
SEAR	WHO South-East Asia Region
SLE	systemic lupus erythematosus
SSH	sentinel surveillance hospital
TB	tuberculosis
TLC	total leukocyte count
TTI	transfusion transmitted infection
UDF	undifferentiated dengue fever
WHO	World Health Organization

CHAPTER 1

INTRODUCTION

Dengue is the most rapidly spreading mosquito-borne viral disease of mankind, with a 30-fold increase in global incidence over the last five decades. It is a major public health concern throughout the tropical and subtropical regions of the world. Almost half the world's population lives in countries where dengue is endemic. According to World Health Organization (WHO), about 50–100 million new dengue infections are estimated to occur annually in more than 100 endemic countries, with a steady increase in the number of countries reporting the disease.[1]

1.1 Global scenario

Dengue has been identified as one of the 17 neglected tropical diseases by WHO as mentioned in their first report on neglected tropical diseases (2010).[2] Although the full global burden of the disease is still uncertain, the patterns are alarming for both human health and the economy. Every year, hundreds of thousands of severe cases arise, of which 20 000 lead to death. The loss to the economy is 264 disability-adjusted life years (DALYs) per million population per year.[3,4]

Approximately 1.8 billion (more than 70%) of the population at risk for dengue worldwide live in Member States of the WHO South-East Asia Region (SEAR) and Western Pacific Region, which bear nearly 75% of the current global disease burden due to dengue.[5] Of the 11 countries of SEAR, 10 countries including India are endemic for dengue. The only exception is the Democratic People's Republic of Korea. In 2012, SEAR countries reported approximately 0.29 million cases, of which Thailand contributed almost 30%, Indonesia 29% and India 20%. Similarly, Western Pacific countries have reported 0.33 million cases, of which Philippines contributed almost 52%, Vietnam 24% and Cambodia 14% (source WHO).[5] The true numbers are probably far more, since severe underreporting and misclassifcation of dengue cases have been documented by the countries.[3]

1.2 National scenario

Dengue virus was isolated in India for the first time in 1945. The first evidence of occurrence of dengue fever in the country was reported in 1956 from Vellore district in Tamil Nadu. The first dengue hemorrhagic fever (DHF) outbreak occurred in Calcutta (West Bengal) in 1963.[6,7]

The states/districts that have reported DF/DHF since 1991 are shown in Figure 1.

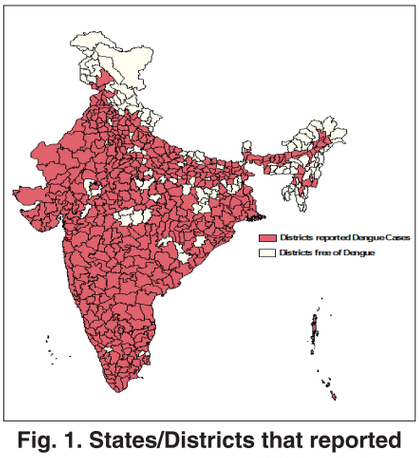


Fig. 1. States/Districts that reported dengue cases since 1991 in India

Of the 36 states/UTs, 35 (all except Lakshadweep) have reported dengue cases during the last two decades.

Recurring outbreaks of dengue fever(DF)/DHF have been reported from various states/ UTs—Andhra Pradesh, Chandigarh, Delhi, Goa, Haryana, Gujarat, Karnataka, Kerala, Maharashtra, Rajasthan, Uttar Pradesh, Puducherry, Punjab, Tamil Nadu and West Bengal.

During 1996, one of the most severe outbreaks of DF/DHF occurred in Delhi, with 10 252 cases and 423 deaths being reported (country total being 16 517 cases and 545 deaths). In 2006, the country witnessed an outbreak of DF/DHF with 12 317 cases and 184 deaths. The incidence of dengue is increasing in the last few years. During 2010, a total of 28 292 cases were reported, which increased to 50 222 in 2012 and 75 808 in 2013 – the highest since 1991. The case fatality ratio (CFR – deaths per 100 cases) has declined from 3.3% in 1996 to 0.4% in 2010 after the national guidelines on clinical management of DF/DHF/dengue shock syndrome (DSS) were developed and circulated in 2007. This further declined to 0.3% in 2013.[7,8]

Every year, during the period July–November, an upsurge in the cases of dengue/DHF has been observed. The disease has a seasonal pattern; the cases peak after the monsoons and are not uniformly distributed throughout the year. However, the states in the southern and western parts of the country report perennial transmission. The seasonal trends for 2010–13 are given in Figure 2.

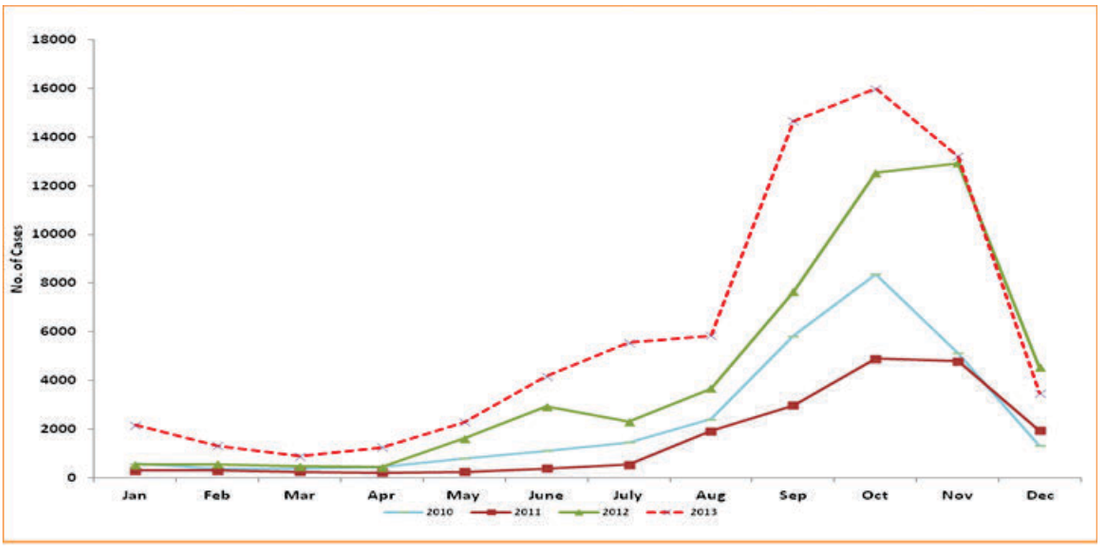


Fig. 2. Seasonal trend of dengue cases in India 2010–2013

As *Ae. aegypti* breeding was more common in urban areas, the disease was observed to be mostly prevalent in urban areas. However, the trend is now changing due to socioeconomic and man-made ecological changes that have resulted in the invasion of *Ae. aegypti* mosquitoes into the rural areas. This has significantly increased the chances of spread of the disease in rural areas.

CHAPTER 2

EPIDEMIOLOGY

Dengue ranks as the most important, rapidly emerged mosquito-borne viral disease in recent years and is endemic in all continents. It has shown an increase due to various reasons – construction activities, lifestyle changes, deficient water management, improper water storage, stagnation of rain water in containers lying outside houses and practices leading to proliferation of vector breeding sites in urban, semi-urban and rural areas.

The epidemiology of dengue is an intricate phenomenon which depends upon a complex relationship between epidemiological factors, viz. host (man and mosquito), agent (virus) and the environment (abiotic and biotic factors). The complexity of relationship among these factors eventually determines the level of endemicity in an area. During inter-epidemic periods, the transmission of dengue remains low due to extremes of temperature with low relative humidity, but during monsoons the environment becomes suitable for vectors. Temperatures in the range of 25°C ± 5°C, relative humidity around 80% and innumerable small water collections result in high vector density.

2.1 Dengue virus

The agent of dengue, i.e. dengue viruses, are categorized under the genus Flavivirus. These viruses contain single stranded RNA and are small in size (50 nm). There are four dengue virus serotypes which are designated as DENV-1, DENV-2, DENV-3 and DENV-4. These serotypes may be in circulation either singly, or more than one can be in circulation in any area at the same time. Although all four serotypes are antigenically similar, they are different enough to elicit cross-protection only for a few months after infection by any one of them. Infection with any one serotype confers lifelong immunity to the virus serotype.

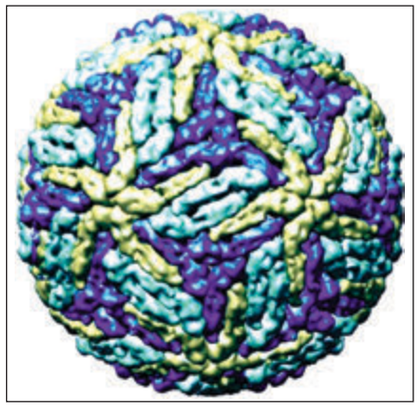


Fig. 3. Dengue virus under electron microscope

An electron microscopic view of dengue virus is given in Figure 3.

2.2 Molecular epidemiology

The four dengue virus types (DENV-1–4), called dengue virus serotypes, form a phylogenetic group and differ in nucleotide sequence from each other. These are closely related to one another rather than to other flaviviruses and form an antigenic complex of their own. The following subtypes or genotypes are also detected within each serotype, based on their phylogenetic analysis of the genomic region in the envelope gene:[7,9]

- DENV-1 : three
- DENV-2 : two (one non-human primate)
- DENV-3 : four
- DENV-4 : four (one non-human primate)

The four dengue virus serotypes can co-circulate in the endemic areas because the immunity to one serotype does not afford protection from the infection by a heterotopous serotype. Individual variations occur in antibody responses to the dengue virus. Secondary infections are associated with elevated risks of severe disease outcomes. Primary and secondary infections are distinguishable based on their antibody responses. The ability of all DENV serotypes to utilize pre-existing heterotypic flavivirus antibody to enhance infection is a unique feature of DENV which distinguishes it from all other flaviviruses and is considered to be the primary basis of DENV pathogenesis. All four serotypes are reported from India.

The dengue virus genome is composed of three structural protein genes encoding the nucleocapsid of core protein ©, a membrane associated protein (M), an envelope protein (E) and seven non-structural (NS) proteins – NS1, NS2A, NS2B, NS3, NS4A, NS4B and NS5. The functions for all the individual NS-proteins are not well characterized. However, NS1 protein has been shown to interact with the host immune system, and known to evoke T cell responses. In dengue virus infection, patients have measurable levels of NS1 protein in the blood, which are utilized as a diagnostic marker of the infection.

Dengue viral infection is mostly asymptomatic. The exact causes of severity among some patients when there is interaction between agent and host are still not clearly understood. Infected people play a major role in introducing the dengue virus by their movement to newer areas.

2.3 Vector

Dengue viruses are transmitted from an infected person to others by the bite of the female *Aedes (Ae.)* mosquito. In India, *Ae. aegypti* is the main vector in most urban areas; however, *Ae. albopictus* is also incriminated in many states. Other species like *Ae. polynesiensis* and *Ae. niveus* have also been incriminated as secondary vectors in some countries.

The female *Aedes* mosquito deposits eggs singly on damp surfaces just above the waterline. Under optimal conditions, the adult emerges in seven days (after the aquatic stages in the life cycle of *Ae. aegypti*). At low temperatures, it may take several weeks to emerge. The eggs can withstand desiccation (can remain in a viable dry condition) for more than a year and emerge within 24 hours once it comes in contact with water. This is also a major hurdle in prevention and control of dengue.

Climatic conditions, particularly temperature and rainfall, have a major impact on the life cycle, breeding and longevity of vectors and thus transmission of the disease. The average survival of *Ae. aegypti* is 30 days and Ae. albopictus is about eight weeks. During the rainy season, when survival is longer, the risk of virus transmission is greater. *Aedes* is a daytime feeder and can fly up to a limited distance of 400 metres. In the absence of any vaccine or specific drug for dengue, vector control is very significant in preventing disease transmission.

Ae. aegypti breeds almost entirely in domestic man-made water receptacles found in and around households, water storage containers, water reservoirs, overhead tanks, desert coolers, unused tyres, coconut shells, disposable cups, unused grinding stones, industrial and domestic junk, construction sites, etc. *Ae. albopictus* prefers natural larval habitats which include tree holes, latex collecting cups in rubber plantations, leaf axils, bamboo stumps, coconut shells, etc. However, *Ae. albopictus* breeding has been reported recently in domestic habitats as well.

2.4 Environmental factors

The population of *Ae. aegypti* fluctuates with rainfall and water storage. Its lifespan is influenced by temperature and humidity. It survives best between 16°C and 30°C and a relative humidity of 60–80%. Altitude is also a limiting factor for the distribution and is restricted to between sea level and 1000 ft above sea level. *Ae. aegypti* is highly anthropophilic and rests in cool shady places. The rural spread of *Ae. aegypti* is a relatively recent occurrence associated with the societal and lifestyle changes in rural areas coupled with developmental activities, improved transport systems, etc. *Ae. albopictus* has posed a serious threat of dengue transmission in certain geographical regions endowed with a sylvatic environment, particularly in peninsular and northeastern states.

2.5 Host factor

The dengue virus infects humans and several species of lower primates. People of all ages and both genders are at risk. Secondary dengue infection is a risk factor for DHF, including passively acquired antibodies in infants. Travel to dengue endemic areas is a most important risk factor. However, if the patient develops fever more than two weeks after travel, it is unlikely to be dengue infection. Migration of a patient during viremia to a non-endemic area may introduce dengue into that area. The geographical spread of dengue has been reported to occur mainly by people travelling from endemic areas to non-endemic areas.

2.6 Transmission cycle

The female *Ae. aegypti* usually becomes infected with the dengue virus when it takes a blood meal from a person during the acute febrile (viremia) phase of dengue illness. After an extrinsic incubation period of 8 to 10 days, the mosquito becomes infected. The virus is transmitted when the infected female mosquito bites and injects its saliva into the wound of the person bitten. The cycle of dengue continues by this process. Dengue begins abruptly after an intrinsic incubation period of 4 to 7 days (range 3–14 days). There is also evidence of vertical transmission of dengue virus from infected female mosquitoes to the next generation.

Though transmission primarily occurs through the bite of a vector, there are reports of dengue transmission through blood transfusion and organ transplantation.[10] There are also reports of congenital dengue infections occurring in neonates born to mothers infected very late in pregnancy.

CHAPTER 3

CLINICAL MANIFESTATION OF DF/DHF

3.1 Immuno-pathogenesis

Host immune responses play an important role in the pathogenesis of dengue Fever (DF). The exact pathogenetic mechanism for different clinical manifestations of dengue Fever is still not clearly understood. Various mechanisms are proposed to explain signs and symptoms such as complex immune mechanism, T-cell mediated antibodies cross reactivity with vascular endothelium, enhancing antibodies, complement and its products and various soluble mediators including cytokines and chemokines. The most favoured are virus strains enhancing antibodies and memory T-cells in a secondary infection resulting in "Cytokine Tsunami". Whatever the mechanisms are, these ultimately target vascular endothelium, platelets and various organs leading to vasculopathy and coagulopathy responsible for the development of haemorrhage and shock. (Figure 4)

3.1.1 Capillary leakage and shock

More commonly, hypotension is caused by plasma leakage which may be mild and transient or progress to profound shock with undetectable pulse and blood pressure. A transient disturbance in the function of the endothelial glycocalyx layer may be involved during dengue infection and alter temporarily the characteristics of the fibre matrix of the endothelium. Anti-NS1 antibody acts as autoantibodies that cross-react with platelets and noninfected endothelial cells which trigger the intracellular signaling leading to disturbances in capillary permeability. Plasma leakage is caused by diffuse increase in capillary permeability and manifest as any combination of haemoconcentration, pleural effusion or Ascites.[7,11] It usu ally becomes evident on 3rd to 7th day of illness and patients may be afebrile during this time. It is likely that both denguevirus infected monocytes and activated specific T lymphocytes are responsible for increased level of cytokines especially in DHF/DSS.

3.1.2 Coagulopathy in dengue

Coagulopathy associated with dengue Fever is well observed but unfortunately underlying mechanisms still remain unclear. An increase in activated Partial Thromboplastin Time (aPTT) and reduction in fibrinogen concentrations are fairly consistent findings. Thrombocytopenia associated with coagulopathy increases the severity of haemorrhage. Release of heparan sulphate or chondroitin sulphate (molecules similar in structure to heparin that can mimic in function as an anticoagulant) from the glycocalyx also contribute to coagulopathy.

3.1.3 Causes of Bleeding in DF/DHF

• Abnormal coagulogram • Thrombocytopenia • Platelet dysfunction • Prothombin complex deficiency secondary to Liver involvement • Endothelial injury • DIC and Prolong aPTT	• Decrease fibrinogen level • Increase level of fibrinogen degradation product (FDP) • Increase level of D-Dimer • Consumptive coagulopathy (activation of mononuclear phagocytes) • Sequestration of platelets

3.1.4 Causes of Thrombocytopenia:

- Destruction of platelet (antiplatelet antibodies)
- DIC
- Bone marrow suppression in early stage
- Peripheral sequestration of Platelets

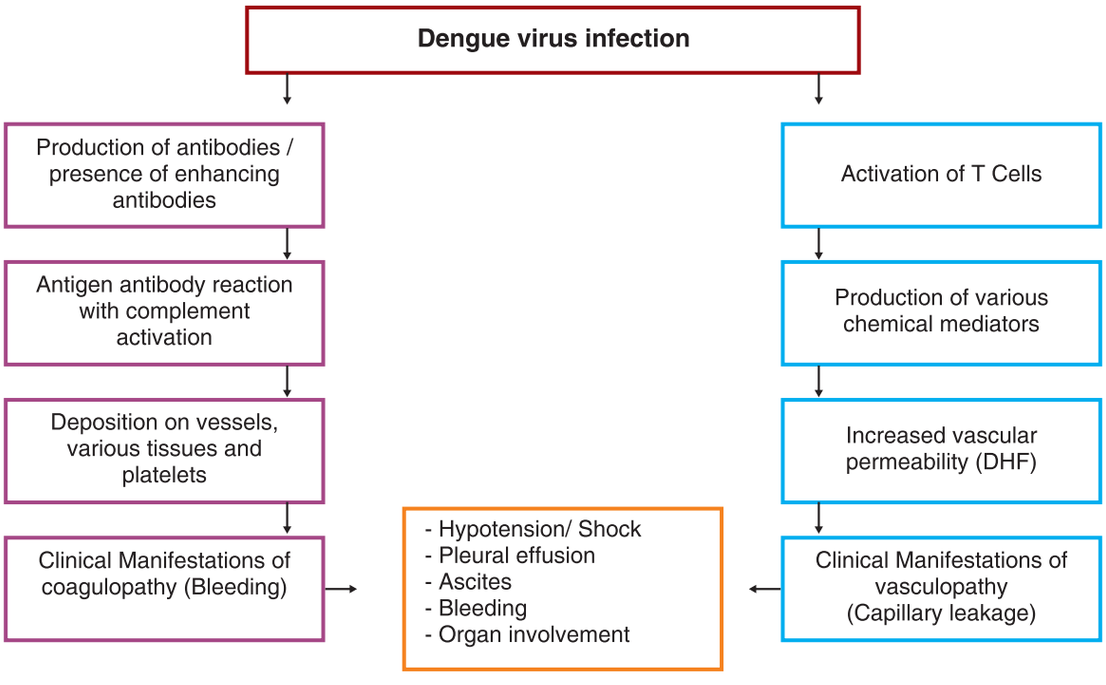


Figure 4. Patho-physiology of DF/DHF

3.2 Clinical manifestations of DF/ DHF

Dengue viral infected person may be asymptomatic or symptomatic and clinical manifestations vary from undifferentiated fever to florid haemorrhage and shock.[11,12,13,14] The clinical presentations depend on various factors such as age, immune status of the host, the virus strain and primary or secondary infection. Infection with one dengue serotype gives lifelong immunity to that particular serotype.

3.2.1 Undifferentiated dengue Fever (UDF)

In primary dengue infection patient may develop mild to moderate fever and it is often difficult to distinguish from other viral infections. Maculopapular rash may or may not appear during fever or defervescence. The symptoms of DF may not be very distinguished and signs of bleeding or capillary leakage may be absent.

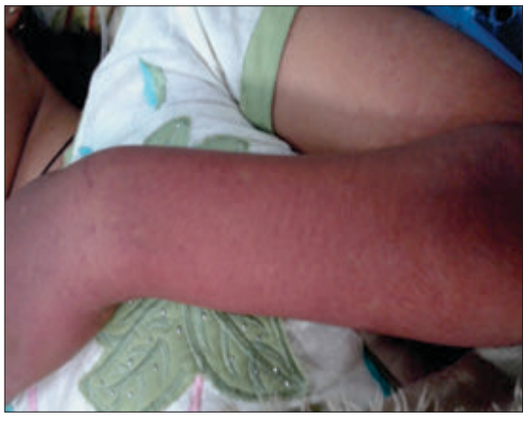


Figure 5: Dengue patient with Maculopapular rash

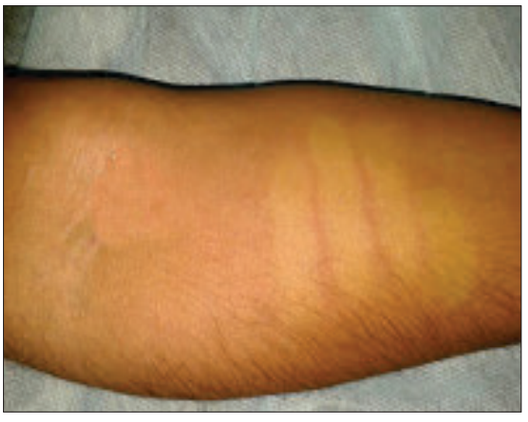


Figure 6 : Impression mark on skin of a dengue patient

3.2.2 Severe dengue Fever

Majority of the dengue virus infected persons are asymptomatic but symptomatic patients may present with undifferentiated fever, non-severe and severe manifestation. Some patients with dengue virus infection present with severe manifestations like shock, plasma leakage, bleeding and organ involvement. Based on thrombocyte count, haematocrit, evidence of capillary leakage, bleeding and hypotension. DHF has been divided into four grades.[15] Refer 3.8 Non severe cases may be DF and DHF grade I and II without significant bleeding. Severe dengue may be DHF III and IV with or without significant bleeding DHF grade I and II may be severe when they present with significant bleeding or with metabolic and electrolyte abnormalities. Sometimes DF may present with life threatening significant bleeding without evidence of capillary leakage or haemoconcentration. Some dengue Fever patients may also present with multiple organ involvement without bleeding and shock. In some patient there may be unusual atypical presentation also.

It is also reported in various literatures that high morbidity and mortality in DF/DHF is due to involvement of the following organs during illness:

- Hepatic
- Renal
- Cardiac
- Pulmonary
- CNS

3.2.3 Dengue Fever with warning signs and symptoms:

The following signs and symptoms are useful as indicators of disease progression and severity of DF/DHF/DSS:

- Recurrent vomiting
- Pleural effusion/ ascites/ gall bladder oedema on imaging

- Minor bleeding from different sites: scanty haemoptysis, haematemesis, haematuria, increase menstrual flow, gum bleeding, etc.
- Abdominal pain or discomfort
- Palpitation, breathlessness
- Hepatic dysfunction or hepatomegaly
- Decrease urinary output
- High HCT (>45%)
- Rapid fall in platelet count
- Cold clammy extremities
- Narrow pulse pressure
- Rapid pulse
- Hypotension

3.2.4 High Risk group

The following high risk groups may have severe manifestations or complications with DF/DHF, therefore this group of patients should be closely monitored for the development of severity:

- Pregnancy
- Infant
- Elderly
- Obesity
- Peptic ulcer diseases
- G6PD deficiency
- Thalassemia
- Coronary Artery Disease
- Chronic diseases: diabetes, COPD, bronchial asthma, hypertension
- Patients on steroid, antiplatelet, anticoagulant drugs
- HIV infected persons/ Immuno-compromised persons

3.2.5 Expanded dengue Syndrome (EDS)

Mild or Severe organ involvement may be found in DF/DHF. Unusual manifestations of DF/DHF are commonly associated with co-morbidities and with various other co-infections. Clinical manifestations observed in EDS are as follows:

System	Unusual or atypical manifestations
CNS involvement	Encephalopathy, encephalitis, febrile seizures, I/C bleed
G. I. involvement	Acute Hepatitis / fulminant hepatic failure, cholecystitis, cholangitis acute pancreatitis
Renal involvement	Acute renal failure, haemolytic uremic syndrome, acute tubular necrosis
Cardiac involvement	Cardiac arrhythmia, cardiomyopathy, myocarditis, pericardial effusion
Respiratory	Pulmonary oedema, ARDS, pulmonary haemorrhage. pleural effusion
Eye	Conjunctival bleed, macular haemorrhage, visual impairment, optic neuritis[16,17]

3.2.6 Dengue infection in paediatric age groups:

Dengue infection occurs in all age groups of human population and paediatric age group was found to have mostly affected. Paediatric age groups are also at high risk for morbidity and mortality. In the recent past it has been observed that there is a paradigm shift of high incidence of dengue infection from paediatric age group to adolescent and adult.

3.2.6.1 Vertical transmission and neonatal dengue infection:

Vertical dengue infection transmission from pregnant women to their foetus has been reported in different studies from 1.6 -64%.[13] Effect of dengue infection on pregnant women, foetus and new born should be carefully examined to access capillary leakage and bleeding tendency. Clinical manifestations of vertically infected neonates vary from mild illness such as fever with petechial rash, thrombocytopenia and hepatomegaly, to severe illness with pleural effusion, gastric bleeding, circulatory failure, massive intracerebral haemorrhage. Clinical presentation in the newborn infant does not appear to be associated with maternal disease severity or dengue immune status or mode of delivery. However, timing of maternal infection may be important; peripartum maternal infection may increase the likelihood of symptomatic disease in the newborn. Passive transfer of maternal dengue antibodies to the foetus influences the occurrence of a severe development of the disease. Antibodies to the dengue virus in the dengue infected mother can cross the placenta and can cause severe dengue in newborn infants. Initial presentation may be confused with bacterial sepsis, birth trauma and other neonatal illnesses.

3.2.6.2 Dengue in infants:

Dengue virus can cause a spectrum of outcomes in infants, ranging from asymptomatic infection to mild or clinically significant severe disease similar to older children and adults. The burden of severe dengue lies predominantly in infants 4–9 months of age.[13]

Manifestations of dengue in infants:

As in older children, infants with dengue typically have high fever that usually lasts 2–7 days. Compared to older children upper respiratory tract symptoms (cough, nasal congestion, runny nose, dyspnoea), gastrointestinal symptoms (vomiting, diarrhoea), and febrile convulsions are more common in infants with dengue. It is often not possible to differentiate between dengue and other common infections in infants such as pneumonia, meningoencephalitis, measles, rotavirus infections, etc. at the febrile stage. Around the time of defervescence (which usually falls on days 3–6 of illness), an increase in capillary permeability, in parallel with increasing haematocrit levels become apparent in the majority of dengue infants. The period of clinical plasma leakage lasts 24–48 hours. Clinical features and laboratory findings of infant infected with dengue become more prominent during this critical phase. Skin bleeding such as petechiae, mucosal membrane bleeding (e.g. of the nose and gums), and gastrointestinal bleeding may occur. Hepatomegaly is usually noted and Splenomegaly is seen in almost 10% of dengue infants. Shock occurs when a significant amount of volume of plasma is lost through leakage. The body temperature may be subnormal when shock occurs. However, a differential diagnosis of septic shock should be kept in mind in infants who have fever at the onset of shock. The degree of increase above the baseline haematocrit often reflects the severity of plasma leakage. However, rise of haematocrit may not be sometimes detectable because the normal value of haematocrit in infants 2-12 months of age is relatively low and may be even lower in iron deficiency

anaemia. Thrombocytopenia and leukopenia are often observed in this phase. Liver involvement is found more frequently in infants compared to children. Progression of infants with dengue is the same as that of children and adults during the recovery phase.

3.3 Clinical Criteria for DF / DHF/DSS

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

Dengue Haemorrhagic Fever (DHF):

a). A case with clinical criteria of dengue Fever

plus

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

Plus

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

plus

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

Dengue Shock Syndrome (DSS):
All the above criteria for DHF with evidence of circulatory failure manifested by rapid and weak pulse and narrow pulse pressure ($\leq$ 20% mm Hg) or hypotension for age, cold and clammy skin and restlessness.

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

Tourniquet test: The tourniquet test is performed by inflating a blood pressure cuff to a midpoint between the systolic and diastolic pressure and maintain for five minutes. The test is considered positive when 10 or more petechiae per one square inch area over forearm are observed.[18] In DHF, the test usually gives a definite positive test with 20 petechiae or more. The test may be negative or only mildly positive during the phase of profound shock (DSS).

3.4 Case Definition

Probable DF/DHF:
A case compatible with clinical description (Clinical Criteria at 3.3) of dengue Fever during outbreak.:
OR
Non-ELISA based NS1 antigen/ IgM positive.

(A positive test by RDT will be considered as probable due to poor sensitivity and sensitivity of currently available RDTs.)

Conifrmed dengue Fever:
A case compatible with the clinical description of dengue Fever with at least one of the following

- Isolation of the dengue virus (Virus culture +VE) from serum, plasma, leucocytes.
- Demonstration of IgM antibody titre by ELISA positive in single serum sample.
- Demonstration of dengue virus antigen in serum sample by NS1-ELISA.
- IgG seroconversion in paired sera after 2 weeks with Four fold increase of IgG titre.
- Detection of viral nucleic acid by polymerase chain reaction (PCR).

3.5 Natural course of dengue Infection

The clinical course of illness passes through the following three phases:

- Febrile phase
- Critical phase
- Convalescent phase

3.5.1 Febrile phase

The onset of dengue fever is usually with sudden rise in temperature which may be biphasic, lasting 2-7 days and commonly associated with headache, flushing and rash. There may be pain in retro-orbital area, muscles, joint or bone. Rash may be maculopapular or rubelliform and usually appear after 3rd or 4th day of fever and commonly seen in face, neck and other part of the body which generally fades away in the later part of the febrile phase. Localized cluster of petechiae may appear over upper and lower limbs. dengue Fever with unusual haemorrhagic manifestation may be seen rarely in case with co-morbid illness.

3.5.2 Critical phase (Leakage phase)

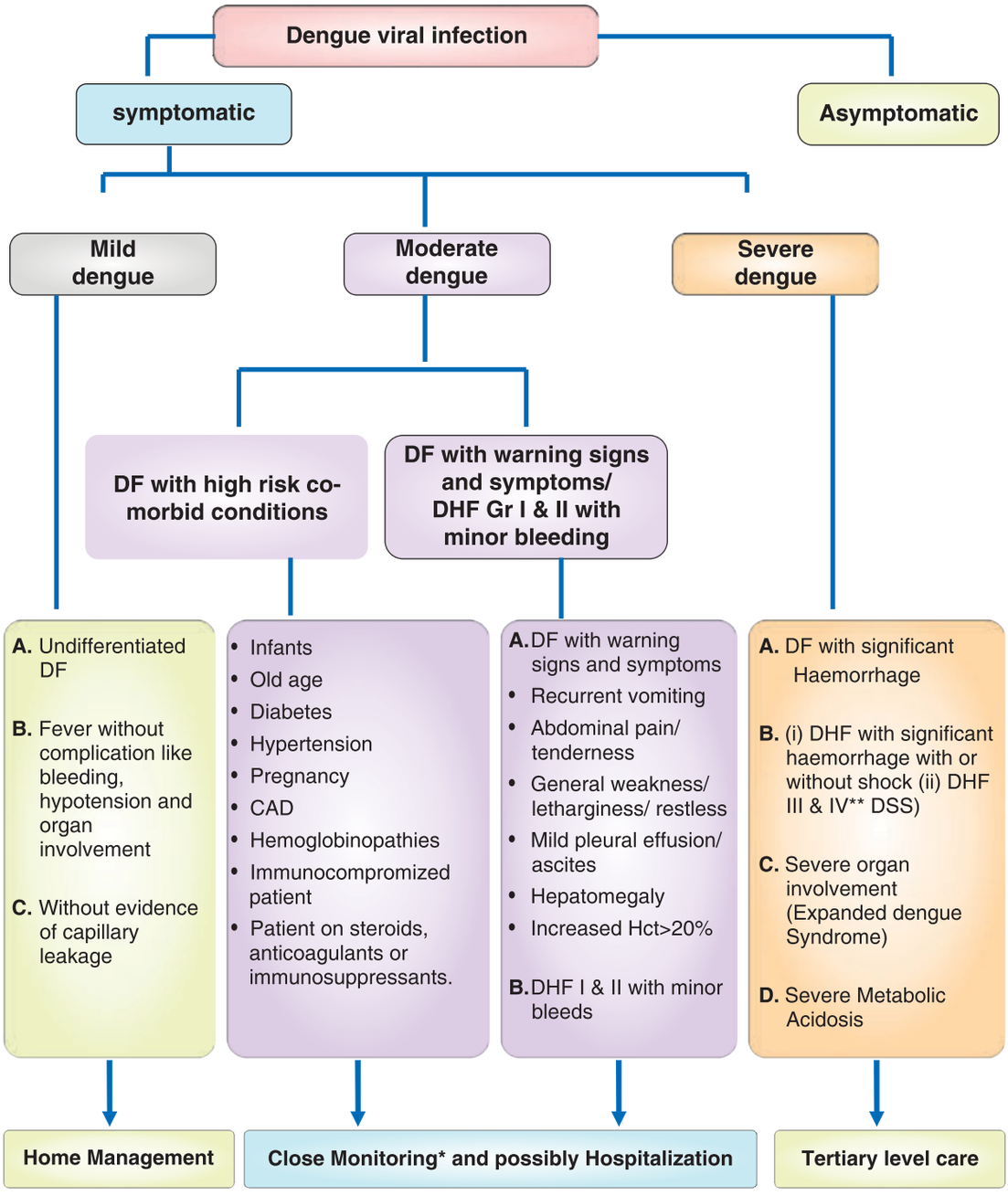
DF/DHF patients usually go to critical phase after 3 to 4 days of onset of fever. During this critical phase plasma leakage and high haemoconcentration are documented and patients may develop hypotension. Abnormal haemostasis and leakage of plasma leads to shock, bleeding, accumulation of fluid in pleural and abdominal cavity. High morbidity and mortality in DHF/DSS are commonly associated with various organ involvements and metabolic derangement. The period of plasma leakage usually persists for 36-48 hrs.

3.5.3 Convalescent phase (recovery phase)

During the recovery phase the extracellular fluid which was lost due to capillary leakage returns to the circulatory system and signs and symptoms improve. This phase usually after 6-7 days of fever and last for 2-3 days. Longer convalescence may be expected in some of the patients with severe shock, organ involvement and other complications which may require specific treatment. Patient may develop pulmonary oedema due to fluid overload if the fluid replacement is not optimized carefully.

3.6 Differential Diagnosis of DF/DHF

- Malaria
- Enteric fever
- Pharyngitis
- Tonsillitis
- Influenza
- Leptospirosis
- Meningococcal infection
- Chikungunya fever
- Epidemic typhus/ scrub typhus
- Crimean-Congo haemorrhagic fever
- Ebola haemorrhagic fever



***Close monitoring:** Hct, Plt, Hb, fluid intake/output, HR, RR, BP, Consciousness

3.7 Grading of DF/DHF

*DF: Fever of 2-7 days with two or more of following- Headache, Retro orbital pain, Myalgia, Arthralgia with or without Leukopenia thrombocytopenia and no evidence of plasma leakage.
DHF I: Above criteria plus positive tourniquet test and evidence of plasma leakage. Thrombocytopenia with platelet count less than 100000/ cu.mm and Hct rise more than 20% over baseline.

DHF II: Above plus some evidence of spontaneous bleeding in skin or other organs (black tarry stool, epistaxis, gum bleeds) & abdominal pain. Thrombocytopenia with platelet count less than 100000/ cu.mm & Hct rise more than 20% over baseline.

DHF III (DSS): Above plus circulatory failure (weak rapid pulse, narrow pulse pressure < 20 mm Hg, Hypotension, cold clammy skin, restlessness). Thrombocytopenia with platelet count less than 100000/ cu.mm and Hct rise more than 20% over baseline.

DHF IV (DSS): Profound shock with undetectable blood pressure or pulse. Thrombocytopenia with platelet count less than 100000/ cu.mm and Hct rise more than 20% over baseline.