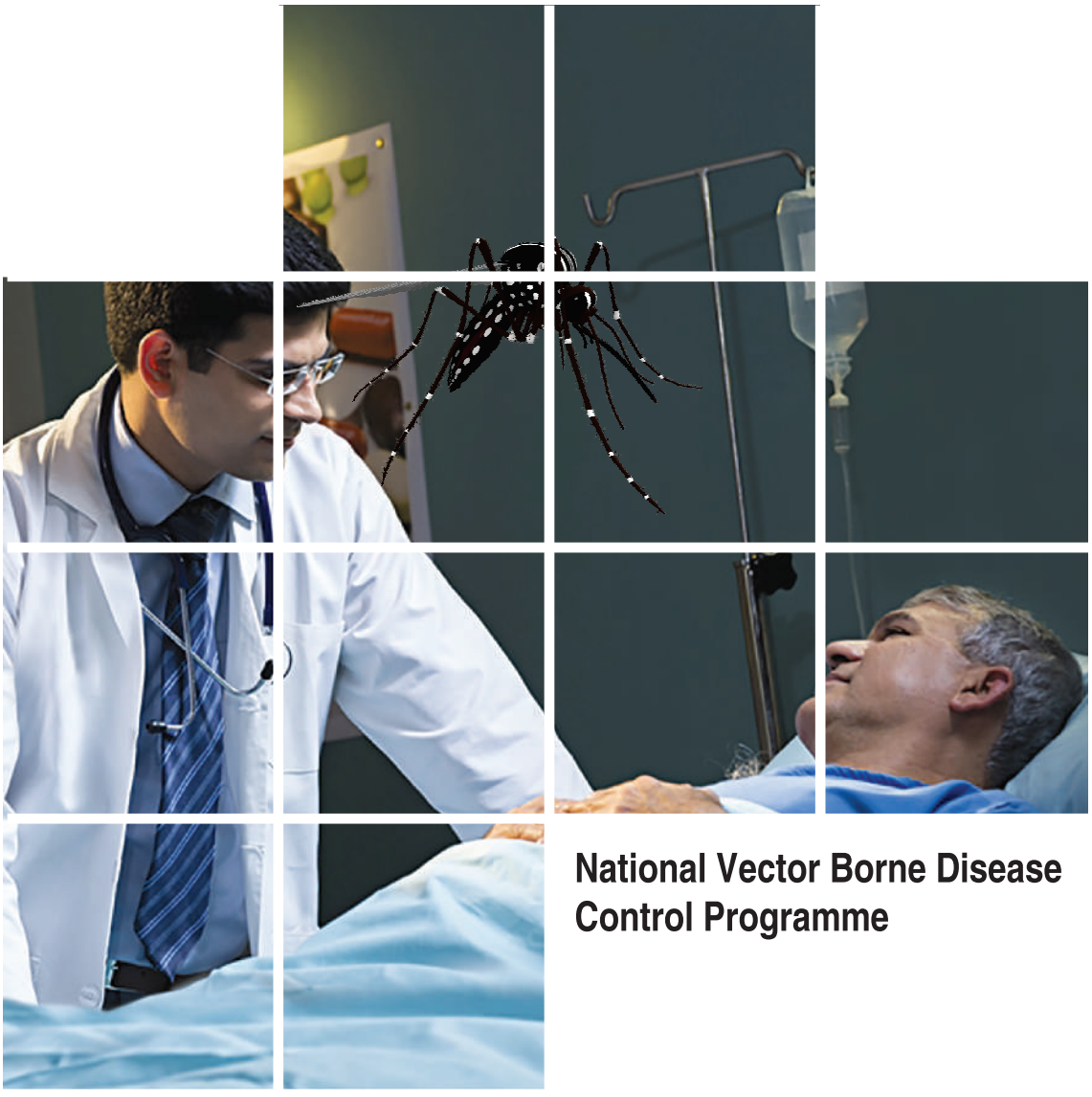
सत्यमेव जयते

Government of India

National Guidelines for Clinical Management of Dengue Fever



National Vector Borne Disease Control Programme

World Health Organization

COUNTRY OFFICE FOR India

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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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.

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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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 usually becomes evident on 3rd to 7th day of illness and patients may be afebrile during this time. It is likely that both dengue virus 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 heparin 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

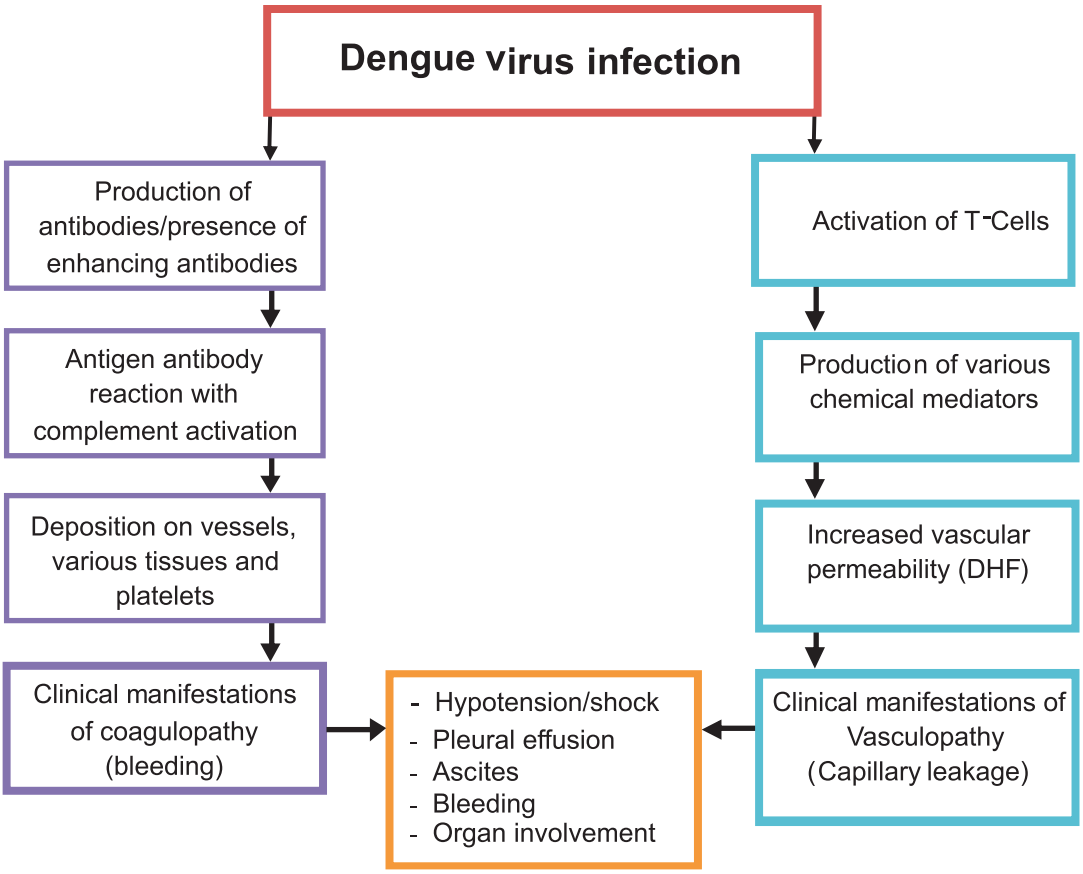


Fig. 4. Patho-physiology of DF/DHF

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.

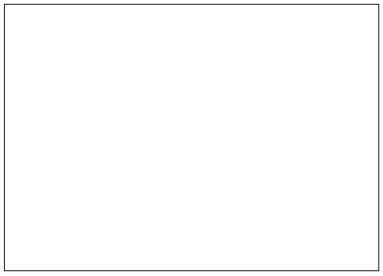


Figure 5: Dengue patient with Maculopapular rash

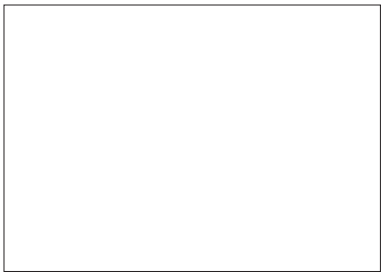


Figure 6A : Finger impression on skin of a dengue patient

Figure 6B : Rounded stetho impression 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.

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 Specificity 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.

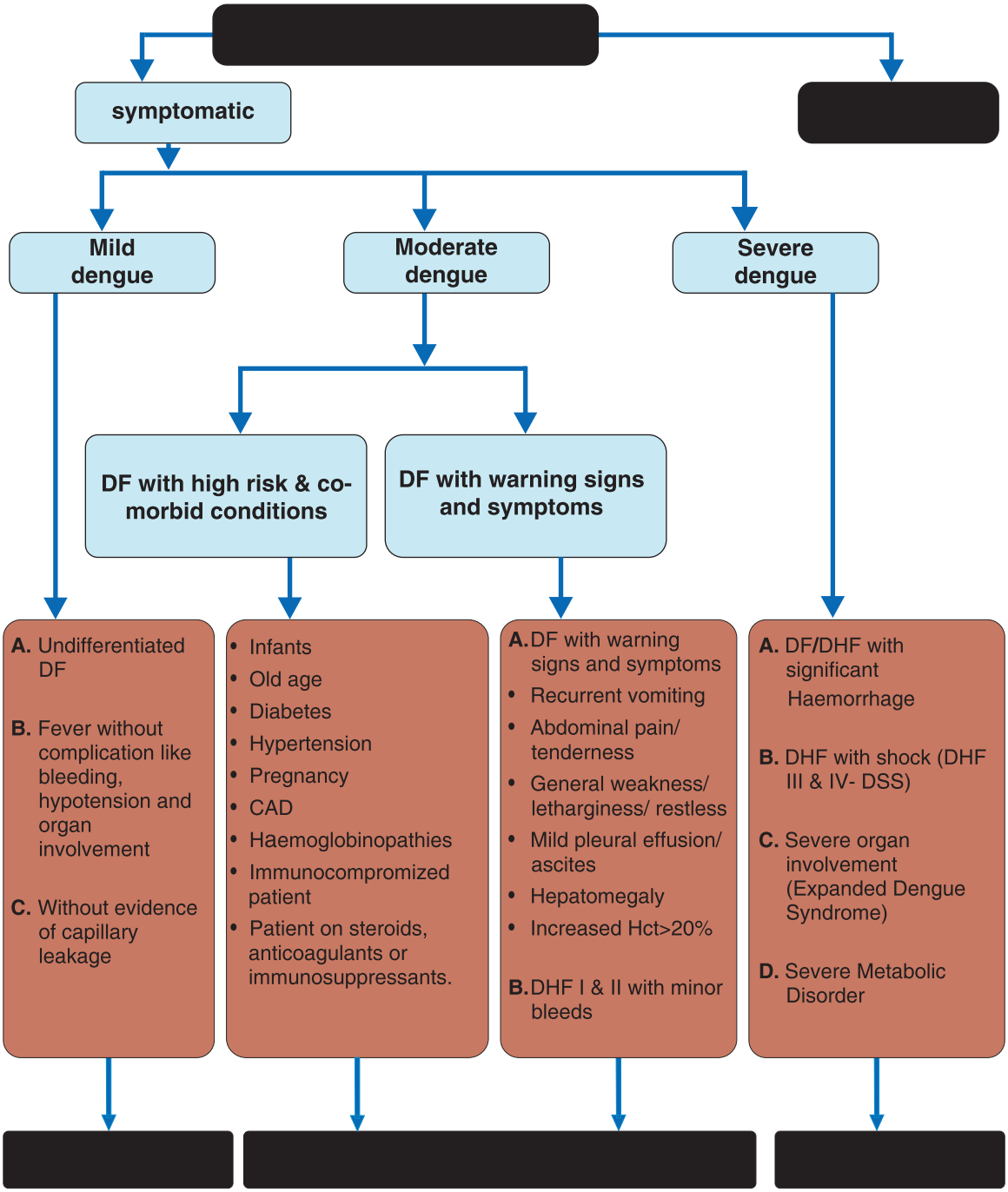
3.5.3 Convalescent phase (recovery phase)

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

3.7 Dengue Case classification



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

3.8 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.
DHFI: 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.

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

DHFIII (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.

DHFIV (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.

CHAPTER 4

LABORATORY DIAGNOSIS

In endemic areas, early symptoms of dengue fever mimic many other prevalent diseases such as chikungunya, malaria, viral infection, urinary tract infection, typhoid, leptospirosis, etc. For proper management exclusion of these conditions is hence very crucial.

4.1 Laboratory diagnosis tests

Laboratory diagnosis can be carried out by one or more of the following tests.

4.1.1 ELISA-based NS1 antigen tests

Dengue NS1 antigen, a highly conserved glycoprotein which is produced in both membrane-associated and secretion forms, is abundant in the serum of patients during the early stages of DENV infection. It has been found to be useful as a tool for the diagnosis of acute dengue infections. It is a simple test that is more specific and shows high sensitivity.

NS1 enables detection of the cases early, i.e. in the viremic stage, which has epidemiological significance for containing the transmission.The NS1 ELISA-based antigen assay is commercially available for DENV and many investigators have evaluated this assay for sensitivity and specificity. The NS1 assay may also be useful for differential diagnostics between flaviviruses because of the specificity of the assay.

4.1.2 IgM-capture enzyme-linked immunosorbent assay (MAC-ELISA)

MAC-ELISA has been widely used in the past few years. It is a simple test that requires very little sophisticated equipment. MAC-ELISA is based on detecting the dengue-specific IgM antibodies in the test serum by capturing them using anti-human IgM that was previously bound to the solid phase. This is followed by addition of dengue antigen if the IgM antibody from the patient's serum is anti-dengue, it will bind to the dengue antigen. An enzyme-substrate is added to give a colour reaction for easy detection.

The anti-dengue IgM antibody develops a little faster than IgG and is usually detectable by day 5 of the illness. However, the rapidity with which IgM develops varies considerably among patients. Some patients have detectable IgM on days 2 to 4 after the onset of illness, while others may not develop IgM for seven to eight days after the onset. In some primary infections, detectable IgM may persist for more than 90 days, but in most patients it wanes to an undetectable level by 60 days. It is reasonably certain, however, that the person had a dengue infection sometime in the past two to three months. MAC-ELISA has become an invaluable tool for surveillance of DF/DHF. In areas where dengue is not endemic, it can be used in clinical surveillance for viral illness or for random, population-based serosurveys, with the certainty that any positives detected are recent infections. It is especially useful for hospitalized patients, who are generally admitted late in the illness after detectable IgM is already present in the blood.

4.1.3 Isolation of dengue virus

Isolation of most strains of dengue virus from clinical specimens can be accomplished in the majority of cases, provided that the sample is taken in the first five days of illness and processed without delay. Specimens that may be suitable for virus isolation include acute phase serum, plasma or washed buffy coat from the patient, autopsy tissues from fatal cases, especially liver, spleen, lymph nodes and thymus and mosquitoes collected in nature. Isolation of the virus takes 7–10 days, hence it may not be very useful for starting the management of patients with DF/DHF.

4.1.4 Polymerase chain reaction (PCR)

Molecular diagnosis based on reverse transcription polymerase chain reaction (RT-PCR), such as one-step or nested RT-PCR, nucleic acid sequence-based amplification (NASBA) or real-time RT-PCR has gradually replaced the virus isolation method as the new standard for the detection of dengue virus in acute-phase serum samples.

4.1.5 IgG-ELISA

An IgG-ELISA has been developed that compares well to the hemagglutination-inhibition (HI) test. This test can also be used to differentiate primary and secondary dengue infections. The test is simple and easy to perform but not considered as a diagnostic test as it indicates past infections only.

4.1.6 Serological tests

Besides MAC-ELISA and IgG-ELISA, there are a few serological tests available for the diagnosis of dengue infection such as HI, complement fixation (CF) and neutralization test (NT). These are not commonly used due to various technical problems.

4.1.7 RDTs

A number of commercial RDT kits for anti-dengue IgM/IgG antibodies and NS1 antigen are commercially available, which give the results within 15 to 25 minutes. However, the accuracy of most of these tests is not known since they have not yet been properly validated. Some of the RDTs have been independently evaluated. The results showed a high rate of false positives compared to standard tests, while some others have agreed closely with standard tests. The sensitivity and specificity of some RDTs are also found to vary from batch to batch. According to WHO guidelines, these kits should not be used in clinical settings to guide management of DF/DHF cases because many serum samples taken in the first five days after the onset of illness will not have detectable IgM antibodies. The tests would thus give a false negative result. Reliance on such tests to guide clinical management could, therefore, result in an increase in the case–fatality ratio. Hence, use of RDT is not recommended under the programme.

4.2 Collection of samples

Laboratory diagnosis of dengue depends on proper collection, processing, storage and shipment of the specimens. While collecting blood for serological studies from suspected DF/DHF cases, all universal precautions should taken.

While sending the samples for lab confirmation, the day of onset of fever and day of sample collection should be mentioned to guide the laboratory for the type of test to be performed (NS1 for samples collected from day 1 to day 5 and IgM after day 5).

4.3 NVBDCP-recommended tests for laboratory diagnosis

– For confirmation of dengue infection, Government of India (GoI) recommends use of ELISA-based antigen detection test (NS1) for diagnosing the cases from the first day onwards and antibody detection test IgM capture ELISA (MAC-ELISA) for diagnosing the cases after the fifth day of onset of disease.[19]

– Directorate of National Vector Borne Disease Control Programme (NVBDCP), GoI has identified a network of laboratories (sentinel surveillance hospitals and apex referral laboratories) for surveillance of dengue fever cases across the country since 2007. These laboratories are also meant to augment the diagnostic facilities in all endemic areas. They are linked with Apex Referral Laboratories (ARLs) with advanced diagnostic facilities for backup support and serotyping of dengue samples. For details, please refer to NVBDCP website www.nvbdcp.gov.in.

– These laboratories receive the samples, diagnose and send the report (line list) regularly to districts/municipal health authorities for implementation of preventive measures to interrupt the transmission.

– NS1 antigen tests – GoI introduced ELISA-based NS1 antigen test in 2010 in addition to MAC-ELISA tests which can detect the case during day 1 to day 5 of illness.

4.4 Supply of kits

– IgM ELISA test kits (1 kit = 96 tests) are being provided to the identified laboratories through the National Institute of Virology (NIV), Pune since 2007. The cost is borne by GoI. Buffer stock is also maintained at NIV, Pune.

– For procurement of dengue NS1 antigen test kits, fund has been provided to the states. States are suppose to procure it as per GoI guidelines and provide the same to sentinel surveillance hospitals (SSHs) every year as per their technical requirement.

CHAPTER 5

CLINICAL MANAGEMENT

5.1 Management

Approach to clinical management of dengue Fever may vary depending on severity of illness. The patients who have simple fever without any danger signs or complications may be managed with symptomatic approach. Those who have warning signs and symptoms should be closely monitored for progression of disease. The patients with grade III and IV of DHF, significant bleeding or involvement of various organs require aggressive management to reduce morbidity and mortality. Patient may develop complications during later stage of fever (defervescence) or afebrile phase, where clinician should be careful to look for danger signs and signs of fluid overload.

5.1.1 Management of dengue Fever (DF)

Management of dengue fever is symptomatic and supportive

ii. Bed rest is advisable during the acute phase.
iii. Use cold/tepid sponging to keep temperature below 38.5^0 C.
iiii. Antipyretics may be used to lower the body temperature. Aspirin/NSAIDS like Ibuprofen, etc should be avoided since it may cause gastritis, vomiting, acidosis, platelet dysfunction and severe bleeding. Paracetamol is preferable in the doses given below:

- 1-2 years: 60 -120 mg/dose
- 3-6 years: 120 mg/dose
- 7-12 years: 240 mg/dose
- Adult : 500 mg/dose

Note: In children the dose of paracetamol is calculated as per 10 mg/Kg body weight per dose. Paracetamol dose can be repeated at the intervals of 6 hrs depending upon fever and body ache.

iv. Oral fluid and electrolyte therapy is recommended for patients with excessive sweating or vomiting.
v. Patients should be monitored for 24 to 48 hours after they become afebrile for development of complications.

5.1.2 Management during Febrile Phase

Paracetamol is recommended to keep the temperature below 39°C. Adequate fluid should be advised orally to the extent the patient tolerates. Oral rehydration solution (ORS), such as those used for the treatment of diarrhoeal diseases and / or fruit juices are preferable to plain water. Intravenous fluid should be administered if the patient is vomiting persistently or

refusing to feed.
Patients should be closely monitored for the initial signs of shock. The critical period is during the transition from the febrile to the afebrile stage and usually occurs after the third day of illness. Sometimes serial haematocrit determinations are essential to guide treatment plan, since they reflect the degree of plasma leakage and need for intravenous administration of fluids. Haematocrit should be determined daily specially from the third day until the temperature remains normal for one or two days.

5.1.3 Management of DHF Grade I and II

Any person who has dengue fever with thrombocytopenia, high haemoconcentration and presents with abdominal pain, black tarry stools, epistaxis, bleeding from the gums etc. needs to be hospitalized. All these patients should be observed for signs of shock. The critical period for development of shock is during transition from febrile to abferile phase of illness, which usually occurs after third day of illness. Rise of haemoconcentration indicates plasma leakage and loss of volume for which proper fluid management plays an important role. Despite the treatment, if the patient develops fall in BP, decrease in urine output or other features of shock, the management for Grade III/IV DHF/DSS should be instituted.

Oral rehydration should be given along with antipyretics like Paracetamol, sponging, etc. as described above. The algorithm for fluid replacement therapy in case of DHF Grade I and II is given in Chart 1.

5.1.4 Management of Shock (DHF Grade III / IV)

Immediately after hospitalization, the haematocrit, platelet count and vital signs should be examined to assess the patient's condition and intravenous fluid therapy should be started. The patient requires regular and continuous monitoring. If the patient has already received about 1000 ml of intravenous fluid, it should be changed to colloidal solution preferably Dextran40 or if haematocrit further decreases fresh whole blood transfusion 10-20ml/kg/dose should be given.

However, in case of persistent shock even after initial fluid replacement and resuscitation with plasma or plasma expanders, the haematocrit continues to decline, internal bleeding should be suspected. It may be difficult to recognize and estimate the degree of internal blood loss in the presence of haemoconcentration. It is thus recommended to give whole blood in small volumes of 10ml/kg/hour for all patients in shock as a routine precaution. Oxygen should be given to all patients in shock. Treatment algorithm for patients with DHF Grades III and IV is given in Chart 2 and 3.

5.2 Management of severe bleeding

In case of severe bleeding, patient should be admitted in the hospital and investigated to look for the cause and site of bleeding and immediately attempt should be made to stop the bleeding. Internal bleeding like GI bleeding may be sometime severe and difficult to locate. Patients may also have severe epistaxis and haemoptysis and may present with profound shock. Urgent blood transfusion is life saving in this condition. However, if blood is not available shock may be managed with proper IV fluid or plasma expander.. If the patient has thrombocytopenia with active bleeding, it should be treated with blood transfusion and then if required platelet transfusion. In case of massive haemorrhage blood should be tested to

rule out coagulopathy by testing for prothrombin time (PT) and aPTT. Patients of severe bleeding may have liver dysfunction and in such case, liver function test should also be performed. In rare circumstances, intracranial bleed may also occur in some patients who have severe thrombocytopenia and abnormality in coagulation profile.

5.3 Management of DF/ DHF with co-morbid illness

Different co-morbid illness like hypertension, diabetes, thyroid diseases, hepatitis, heart diseases and renal diseases may contribute in the development of severe manifestations in DF/DHF.

5.3.1 Dengue viral hepatitis: Some patient may have impairment of liver function test due to dengue viral infection. In some DF patients the AST/ALT level may be very high and PT may be prolonged. Hepatic involvement is commonly associated with pre-existing conditions like chronic viral hepatitis, cirrhosis of liver and haepatomegaly due to some other cause. Patient may also develop hepatic encephalopathy due to acute liver failure. Liver involvement also sometimes associates with DF in pregnancy. Low albumin due to chronic liver disease may be associated with severe DHF and bleeding. GI bleeding is common in this condition and patient may go to severe DSS. These patients should be managed carefully with hepatic failure regimen with appropriate fluid and blood transfusion. If PT is prolonged intravenous vitamin K1 may be initiated in such conditions.

5.3.2 Dengue myocarditis: Dengue infection may rarely cause acute myocarditis[20] which also may contribute for the development of DSS. Cardiac complications may be seen in presence of CAD, hypertension, diabetic and valvular heart disease. Management of shock with IV fluid in such case is sometime difficult due to myocardial dysfunction. Patient may develop pulmonary oedema due to improper fluid management. Some CAD patient may be already taking Aspirin and other anti-platelet agent which may also contribute for severe bleeding unless these are stopped during dengue infection. Cardiac ischemia or electrolyte disturbances should be frequently reassessed. Patient may develop congestive or biventricular failure therefore should be treated properly for better morbidity and mortality outcome.

5.3.3 DF in Diabetes: Sometimes diabetic patients may present with severe complication in DF when target organs are involved like diabetic retinopathy, neuropathy, nephropathy, vasculopathy, cardiomyopathy and hypertension. Due to dengue infection in diabetes the blood sugar may become uncontrolled which may require sometimes insulin therapy for better management.

5.3.4 Renal involvement in DF: Acute Tubular Necrosis (ATN) may develop during DSS and may complicate to acute kidney injury (AKI) if fluid therapy is not initiated in time. Renal function may be reversible, if shock is corrected within a short span of time. If the shock persists for long time patient may develop renal complications. Urine output monitoring in dengue infection is very important to assess renal involvement. Microscopic-macroscopic Haematuria should be examined in DHF patients. Other investigations like blood urea, creatinine, electrolytes, GFR, ABG should be performed in patients with severe dengue/ DHF. Fluid intake should be closely monitored in case of AKI to avoid fluid overload and pulmonary oedema. Dengue patient may develop severe DHF in presence of diabetic nephropathy, hypertensive nephropathy, connective tissue disorders (SLE) and other pre-

existing chronic diseases.

5.3.5 CNS involvement in DF: Altered sensorium may develop in dengue patient due to various conditions like shock (DSS), electrolyte imbalance (due to persistent vomiting), fluid overload (dilutional hyponatremia or other electrolyte imbalance), hypoglycemia, hepatic enchalopathy and also due to involvement of CNS by dengue virus. Acute encephalopathy or encephalitis may be seen in some patients with severe dengue. Sometimes it may be difficult to clinically exclude cerebral Malaria and enteric encephalopathy which may also appear during same period (epidemic). Dengue serology (IgM) in CSF may help to confirm dengue encephalopathy or encephalitis.

5.4 Management of DF with co-infections

It is sometimes difficult to manage DF with co-infections like HIV, TB, malaria, chikungunya, enteric fever and leptospira as mostly clinical presentations are severe in presence of these co-infections.

5.4.1 TB: Patients may develop breathlessness and massive haemoptysis in Pulmonary Tuberculosis. These patients may also develop moderate to massive pleural effusion and ARDS. If patient has DF in presence of TB and is on ATT, then should be closely monitored for further development of respiratory/pulmonary complications to prevent morbidity and mortality.

5.4.2 HIV: Dengue patients may have severe complications like DHF, DSS, significant bleeding and organ involvement among HIV and AIDS patients. Outcome of DF is poor amongst severely immune compromised patients those who have opportunistic infection and very low CD4 count. Multi-organ involvement may be common in DF and responsible for high mortality. Management of DF with HIV and AIDS should be undertaken with HIV specialist consultation.

5.4.3 Malaria: Malaria is also a common co-infection in dengue as it is prevalent across India and transmission also coincides during the same period/season. Malaria should be excluded in the beginning without loss of much time as it has its' specific management. Antimalarial treatment should be started as soon as possible to prevent complication and better outcome during co-infection.

5.4.4 Chikungunya: It is also reported that in some geographical area both the infections are prevalent at the same time. Acute complications are sometimes severe in DF in presence of Chikungunya. In case of predominant joint involvement in a DF patient, Chikungunya should be investigated and proper management to be carried out accordingly.

5.4.5 Enteric Fever: Water borne diseases like Typhoid fever and gastroenteritis are also common during monsoon season when dengue infection is also reported in large number. In the initial phase DF patient may be more complicated with Typhoid if antibiotic treatment is started late. In high suspected cases blood culture for Typhoid fever should be sent to confirm the diagnosis as Widal test may not be positive before 2nd weeks of fever.

5.5 Management of dengue in pregnancy

DF infection in pregnancy carries the risk of more bleeding, foetal complications, low birth

weight and premature birth[13]. Risk of vertical transmission also increases during pregnancy. Pleural effusion, ascites, hypotension are commonly associated with DF in pregnancy. Involvement of lungs and liver is also common in pregnancy. Patients may have respiratory symptom due to massive pleural effusion and high SGOT/SGPT due to liver involvement. Complications of DF depend on the different stages of pregnancy like early, late, peri-partum and postpartum period.

Pregnancy is a state of hyper dynamic circulation and fluid replacement should be carefully done to prevent pulmonary oedema. Frequent platelet count and coagulation profile testing should be performed during DF in pregnancy. Regular BP monitoring should be performed during DF in pregnancy. Fulminant hepatic failure, ARDS and Acute Renal failure in pregnancy may be associated with dengue infection.

Management of dengue infection in pregnancy should be taken seriously to reduce morbidity and mortality in mother as well as foetus.

5.6 Management of neonatal dengue

After delivery, the newborn may go into shock which may be confused with septic shock or birth trauma. In this case, history of febrile illness during pregnancy is important which may help to diagnose Dengue Shock Syndrome among neonates and infants. Close observation, symptomatic and supportive treatment are the mainstay of management.

5.7 Management of dengue in infants

5.7.1 Management of dengue among infants without warning signs

Oral rehydration should be encouraged with oral rehydration solution (ORS), fruit juice and other fluids containing electrolytes and sugar, together with breastfeeding or formula feeding. Parents or caregivers should be instructed about fever control with antipyretics and tepid sponging. They should be advised to bring the infant back to the nearest hospital immediately if the infant has any of the warning signs.

5.7.2 Management of dengue among infants with warning signs

When the infant has dengue with warning signs intravenous fluid therapy is indicated. In the early stage, judicious volume replacement by intravenous fluid therapy may modify the course and severity of the illness. Initially isotonic crystalloid solutions such as Ringer's lactate (RL), Ringer's acetate (RA), or 0.9% saline solution should be used. The capillary leak resolves spontaneously after 24-48 hours in most of the patients.

5.7.3 Management of infants with severe dengue: Treatment of shock

Volume replacement in infants with dengue shock is very challenging and it should be done promptly during the period of defervescence. Each and every case should be critically analyzed separately.

5.8 Criteria for admission of a patient

If a DF patient presents with significant bleeding from any site, signs of hypotension, persistent high grade fever, rapid fall of platelet count, sudden drop in temperature should be admitted in hospital. However, those patients who have evidence of organ involvement should also be admitted for proper monitoring and management. Dengue patients with

warning signs and symptoms should be admitted and closely monitored.

5.9 Criteria for discharge of patients

The admitted patients who have recovered from acute dengue infection having no fever for atleast 24 hours, normal blood pressure, adequate urine output, no respiratory distress, persistent platelet count >50,000/cu.mm should be discharged from hospital.

5.10 Management of dengue Infection in outbreak situation

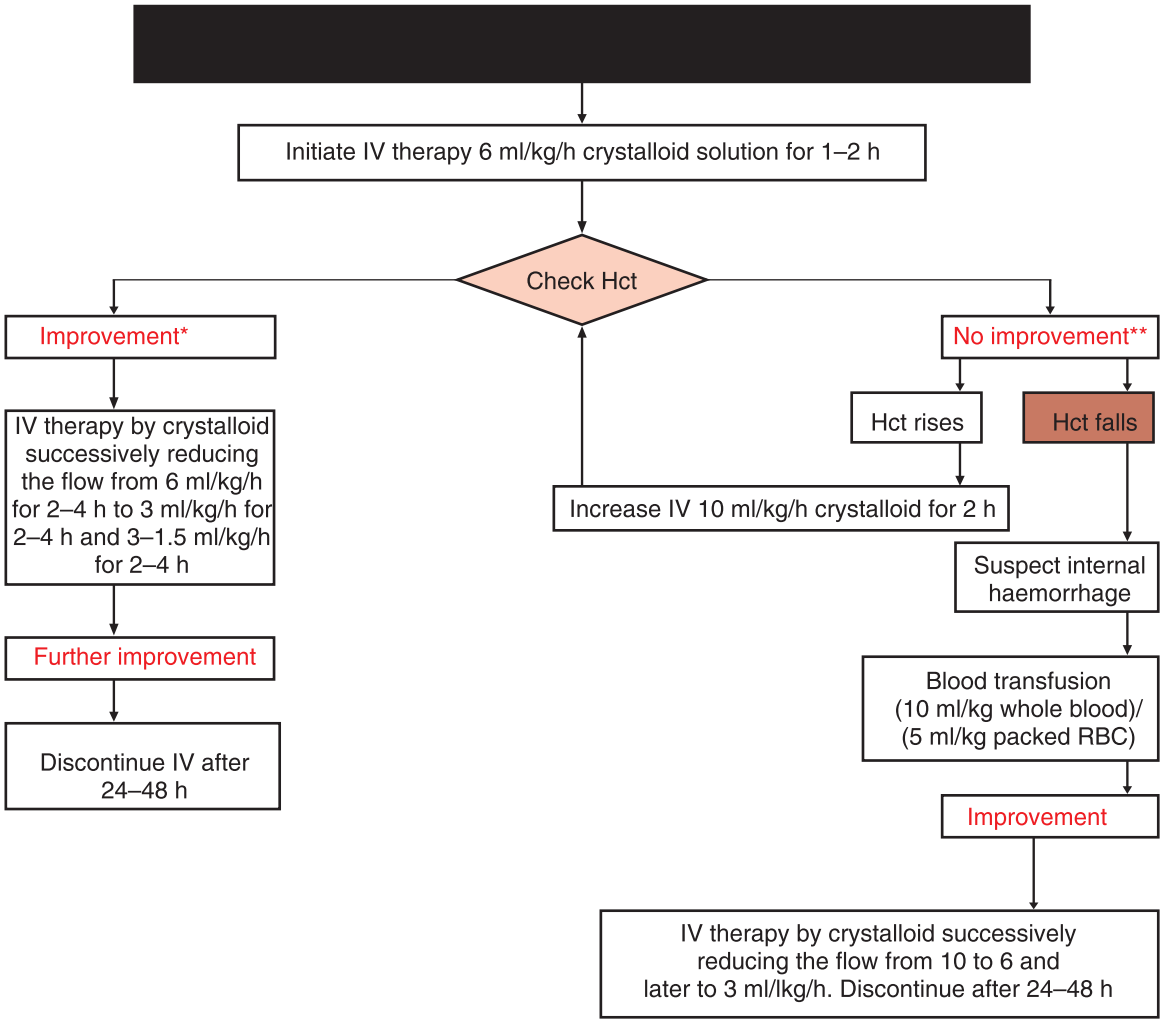
During outbreak situation dengue patient turn over may increase exceptionally. In endemic areas all the hospitals should have a plan dealing with emergency hospitalization for making the most effective use of hospital and treatment facilities in case of outbreak occurs. For epidemic management of dengue cases following issues to be considered:

- Space mobilization
- Staff mobilization
- Augmentation of Laboratory Services (Diagnosis not required in all cases in outbreak situation)
- Augmentation of blood bank services for blood and blood component
- Ensure public health measure to prevent transmission to hospital staff and other Patients by keeping *Aedes* mosquito (vector) free environment.

For Individual case management during outbreak situation following issues are crucial:

- Diagnosis
- Severity assessment
- Specific management

Chart 1. Volume replacement algorithm for patients with moderate Dengue Fever (DHF grades I & II)

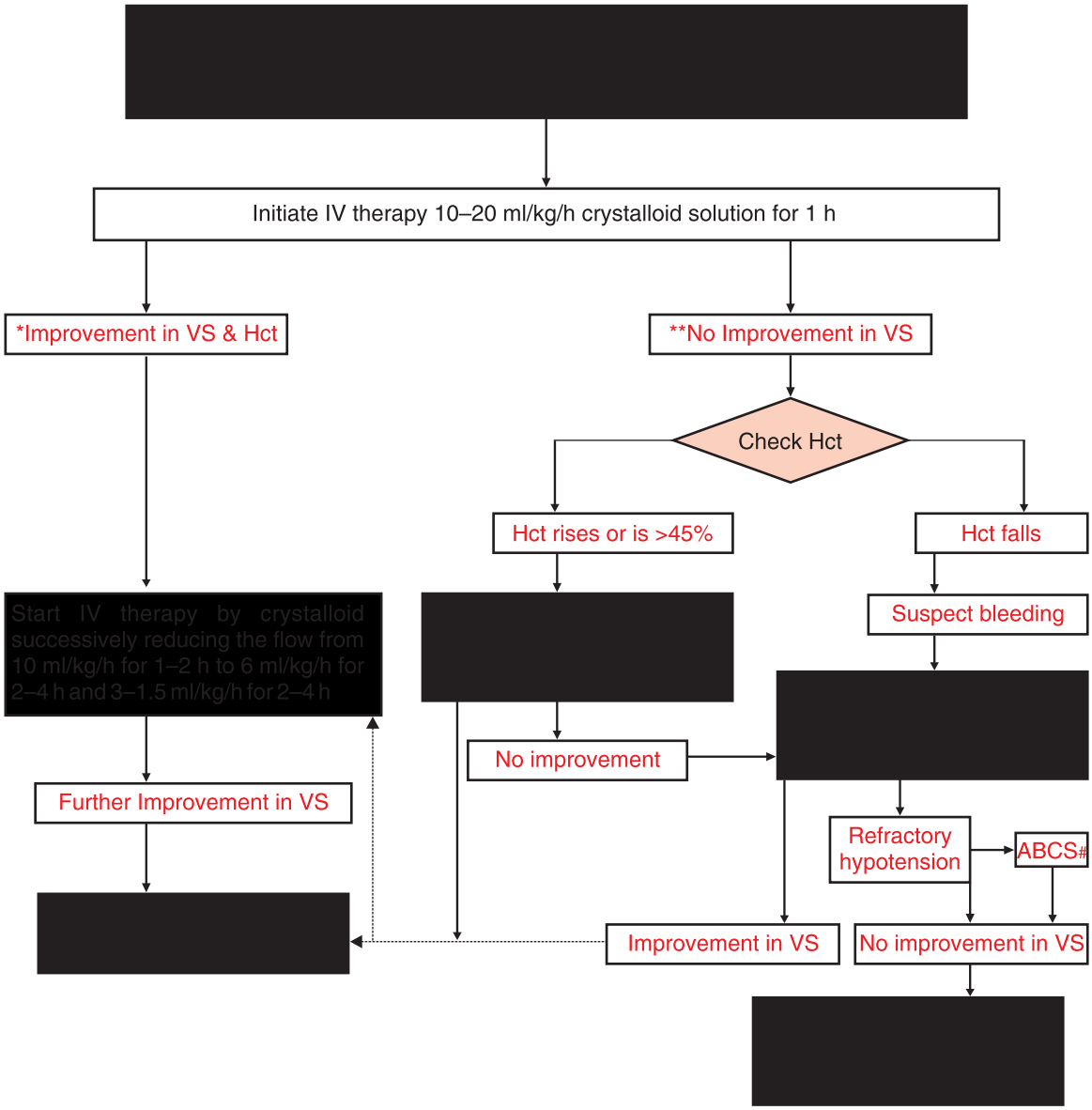


Notes:

*Improvement: Hct falls, pulse rate and blood pressure stable, urine output rises

**No Improvement: Hct or pulse rate rises, pulse pressure falls below 20 mmHg, urine output falls

Chart 2. Volume replacement algorithm for patients with seve re Dengue Fever (DHF grade III)

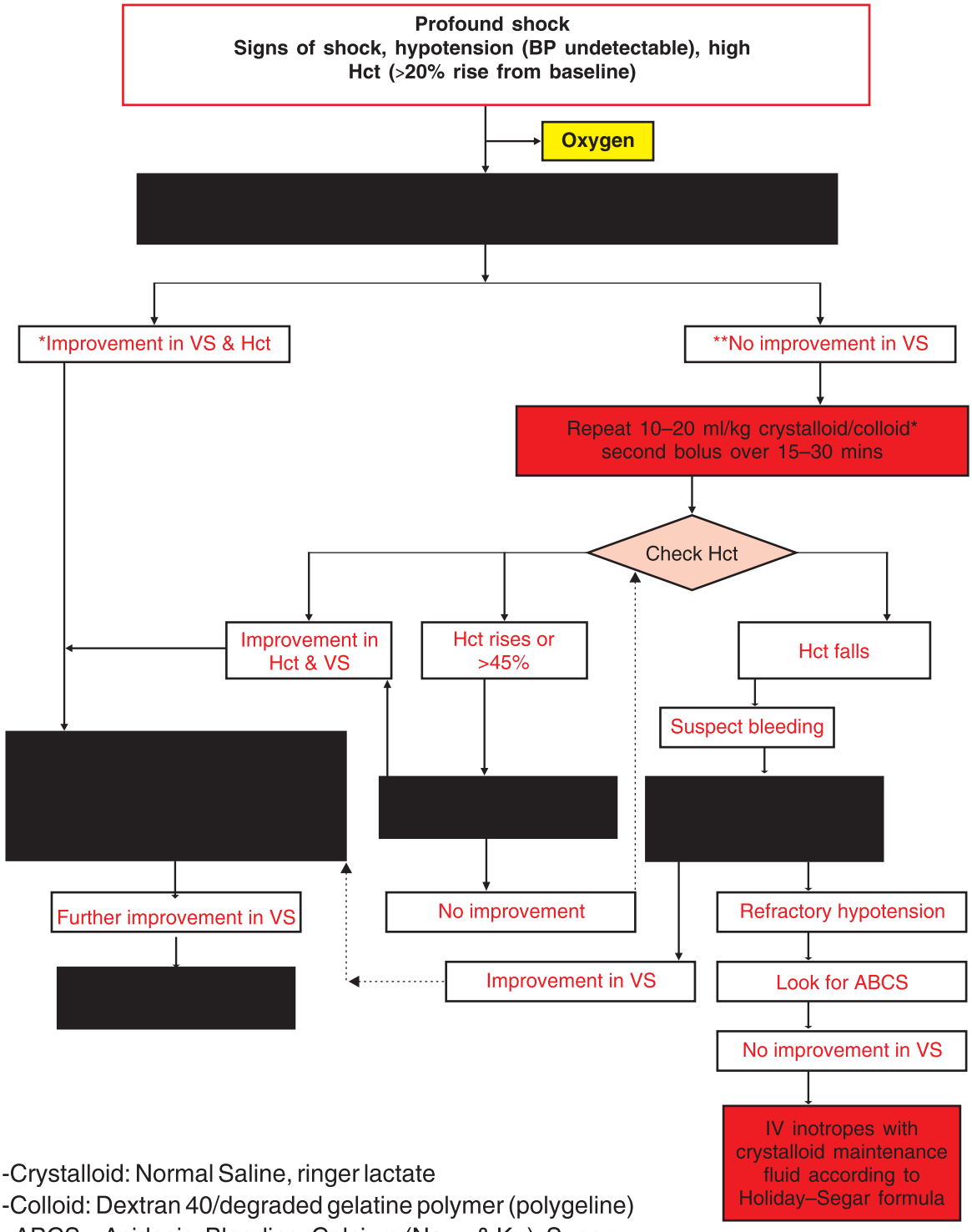


Crystalloid: Normal Saline, ringer lactate
Colloid: Dextran 40/degraded gelatine polymer (polygeline)
ABCS = Acidosis, Bleeding, Calcium (Na++ & K+), Sugar

Notes:
*Improvement: Hct falls, pulse rate and blood pressure stable, urine output rises
**No improvement: Hct or pulse rate rises, pulse pressure falls below 20 mmHg, urine output falls

- Unstable vital signs: urine output falls, signs of shock
- In cases of acidosis, hyperosmolar or Ringer's lactate solution should not be used
- Serial platelet and Hct determinations: drop in platelets and rise in Hct are essential for early diagnosis of DHF
- Cases of DHF should be observed every hour for vital signs and urine output

Chart 3. Volume replacement algorithm for patients with severe Dengue Fever (DHF IV (DSS)



-Crystalloid: Normal Saline, ringer lactate
-Colloid: Dextran 40/degraded gelatine polymer (polygeline)
- ABCS = Acidosis, Bleeding, Calcium (Na++ & K+), Sugar

Notes:

*Improvement: Hct falls, pulse rate and blood pressure stable, urine output rises

**No Improvement: Hct or pulse rate rises, pulse pressure falls below 20 mmHg, urine output falls

- Unstable vital signs: Urine output falls, signs of shock
- In cases of acidosis, hyperosmolar or Ringer's lactate solution should not be used
- Serial platelet and Hct determinations: drop in platelets and rise in Hct are essential for early diagnosis of DHF
- Cases of DHF should be observed every hour for vital signs and urine output

5.11 Calculation of fluid

Required amount of fluid should be calculated on the basis of body weight and charted on a 1-3 hourly basis, or even more frequently in the case of shock. For obese and overweight patients calculation of fluid should be done on the basis of ideal body weight. The regimen of the flow of fluid and the time of infusion are dependent on the severity of DHF. The schedule given below is recommended as a guideline. It is calculated for dehydration of about 5% deficit (plus maintenance).

The maintenance fluid should be calculated using the Holiday and Segar formula as follows:

Body weight in kg	Maintenance volume for 24 hours
<10 kg	100 ml / kg
10-20	1000+50 ml / kg body weight exceeding 10 kg
More than 20 kg	1500+20 ml / kg body weight exceeding 20 kg

For a child weighing 40 kgs, the maintenance is: 1500 + (20x20) = 1900 ml. Amount of fluid to be given in 24 hrs is calculated by adding maintenance + 5% dehydration which is equivalent to 50 ml/kg. This should be given in 24 hrs to maintain just adequate intravascular volume and circulation. Therefore for a child weighing 40 kg the fluid required will be 1900 + (40 x 50)=3900 ml in 24 hrs. For intravenous fluid therapy of patients with DHF, four regimens of flow of fluid are suggested: 1.5/ml/kg/hr, 3ml/kg/hr; 6ml/kg/hr; 10ml/kg/hr, and 20ml/kg/hr. For ready reference, the calculated fluid requirements, based on bodyweight and rate of flow of fluid volume for the Five regimens are given in Table 1.

Choice of intravenous fluids for resuscitation

There is no clear advantage to the use of colloids over crystalloids in terms of the overall outcome. However, colloids may be the preferred choice if the blood pressure has to be restored quickly. Colloids have been shown to restore the cardiac index and reduce the level of haematocrit faster than crystalloids in patients with intractable shock and pulse pressure less than 10 mm Hg.

Crystalloids

Normal plasma chloride ranges from 95 to 105 mmol/L 0.9% Saline is a suitable option for initial fluid resuscitation, but repeated large volumes of 0.9% saline may lead to hyperchloremic acidosis. Hyperchloraemic acidosis may aggravate or be confused with lactic acidosis from prolonged shock. Monitoring the chloride and lactate levels will help to identify this problem. When serum chloride level exceeds the normal range, it is advisable to change to other alternatives such as Ringer's Lactate.

Ringer's Lactate

Ringer's Lactate has lower sodium (131 mmol/L) and chloride (115 mmol/L) contents and an osmolality of 273 mOsm/L. It may not be suitable for resuscitation of patients with severe hyponatremia. However, it is a suitable solution after 0.9 Saline has been given and the serum chloride level has exceeded the normal range. Ringer's Lactate should probably be avoided in liver failure and in patients taking metformin where lactate metabolism may be impaired.

Colloids

The types of colloids are gelatin-based, dextran-based and starch-based solutions. One of the biggest concerns regarding their use is their impact on coagulation. Theoretically, dextrans bind to von Willebrand factor/Factor VIII complex and impair coagulation the most. However, this was not observed to have clinical significance in fluid resuscitation in dengue shock. Of all the colloids, gelatine has the least effect on coagulation but the highest risk of allergic reactions. Allergic reactions such as fever, chills and rigors have also been observed in Dextran 70. Dextran 40 can potentially cause an osmotic renal injury in hypovolaemic patients.

Table 1. Requirement of fluid based on bodyweight

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

Note:

- The fluid volumes mentioned are approximate.
- The fluid replacement should be just sufficient to maintain effective circulation during the period of plasma leakage.
- The recommended intravenous fluids are Normal saline, Ringers Lactate or 5% DNS.
- One should keep a watch for Urine output, liver size and signs of pulmonary oedema. Hypervolumea is a common complication.
- Normally intravenous fluids are not required beyond 36 to 48 hrs.
- Normally change should not be drastic. Do not jump from R-3 to R-5 since this can overload the patient with fluid. Similarly, reduce the volume of fluid from R-5 to R-4, from R-4 to R3, and from R-3 to R-1 in a stepwise manner.
- Remember that ONE ML is equal to 15 DROPS. In case of micro drip system, one ml is equal to 60 drops. (if needed adjust fluid speed in drops according to equipment used).
- It is advised to start with one bottle of 500 ml initially, and order more as and when required. The decision about the speed of IV fluid should be reviewed every 1-3 hours. The frequency of monitoring should be determined on the basis of the condition of the patient.

5.12 Indication of Platelet transfusion

1. Platelet count less than 10000/cu.mm in absence of bleeding manifestations (Prophylactic platelet transfusion).
2. Haemorrhage with or without thrombocytopenia.

Packed cell transfusion/FFP along with platelets may be required in cases of severe bleeding with coagulopathy. Whole fresh blood transfusion doesn't have any role in managing thrombocytopenia.

Platelets can be classified as random donor platelets (prepared by buffy coat removal method or by platelet rich plasma method), BCPP (buffy coat pooled platelet) and single donor platelets (SDP) or aphaeretic platelets (AP).

The details of the different platelet products are given at Annexure II.

5.13 Vaccine for dengue infection

Till now there is no licensed vaccine available against dengue viral infection. Several trials are ongoing in the world for the development of tetravalent dengue vaccine. So far phase III trials of a recombinant, live attenuated tetravalent dengue vaccine (CYD-TDV) has completed in Five Asian countries in children which may be promising in preventing dengue infection in near future.[21]

CHAPTER 6

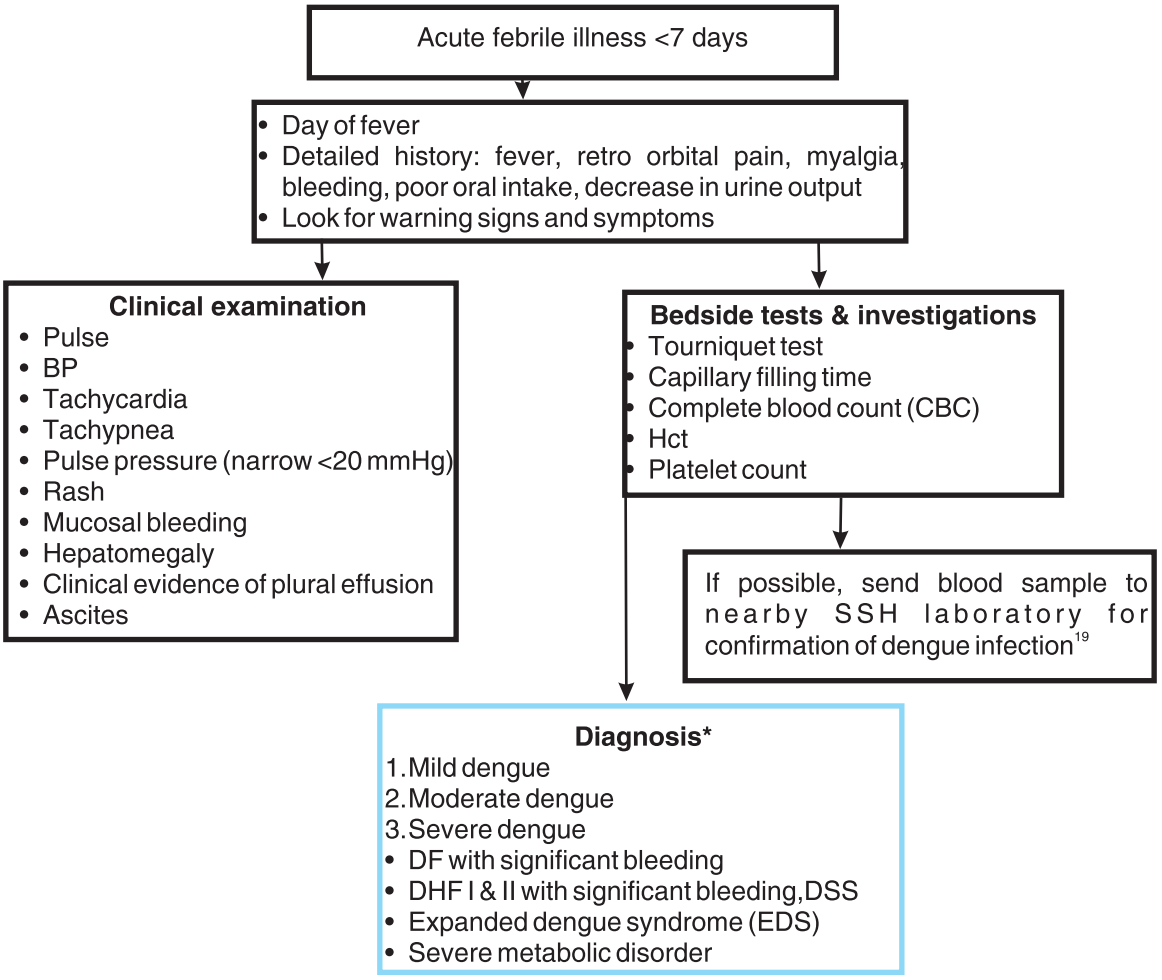
MANAGEMENT AND REFERRAL OF DENGUE CASES AT PRIMARY HEALTH-CARE LEVEL

Dengue was earlier known as an urban disease. However, due to manmade, environmental and societal changes and improper water storage practices, the vector *Ae. aegypti* has also invaded rural areas. Frequent movement of the population has also helped in introduction of the virus in rural areas, leading to rural spread of the disease.

6.1 Diagnosis of dengue cases

In the primary health centre (PHC), the guidelines to be followed for diagnosis of dengue cases are given at Figure 7.

Fig. 7. Guidelines for diagnosis of dengue cases



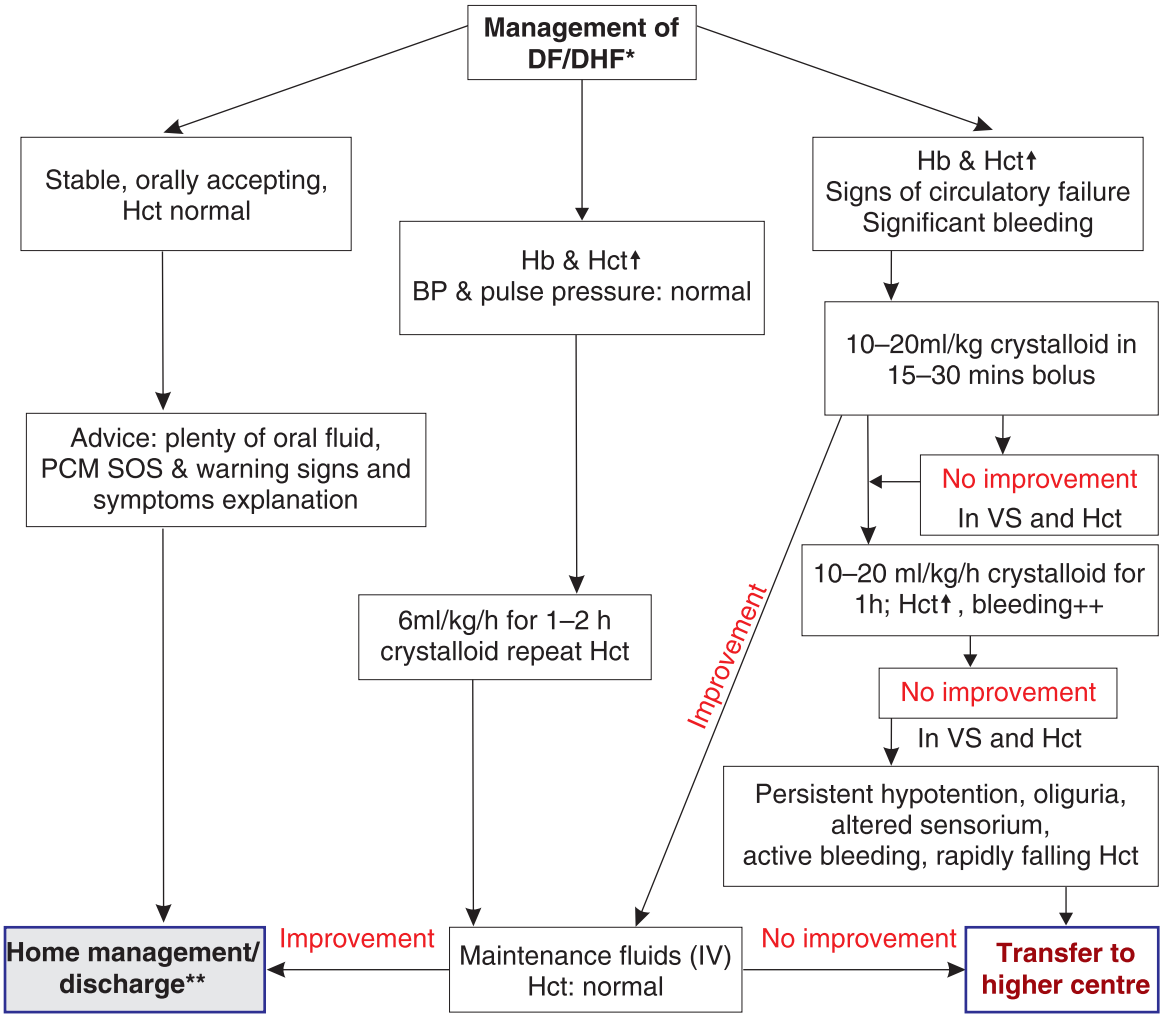
* For details, refer Dengue case classification at 3.7.

Note: Inform the District VBD Officer for taking public health measures in the affected area/s to prevent further spread of the disease.

6.2 Management and referral of dengue cases at PHC level

The guidelines to be followed in the PHC for management of dengue cases and for referral of severe/complicated cases to the higher centre are given in Figure 8.

Fig. 8. Guidelines to be followed in the PHC for management of Dengue cases



* Look for co-morbid illnesses and coinfections – refer Sections 5.3 and 5.4 for details

** Patient should be advised to come for follow-up after 24 h for evaluation. He should report to the nearest hospital immediately in case of the following complaints:

- Bleeding from any site (fresh red spots on skin, black stools, red urine, nose bleed, menorrhagia)
- Severe abdominal pain, refusal to take orally/poor intake, persistent vomiting
- Not passing urine for 12 h/decreased urinary output
- Restlessness, seizures, excessive crying (young infants), altered sensorium and behavioural changes and severe persistent headache
- Cold clammy skin
- Sudden drop in temperature

Also follow Chart 1 to 3 fir volume replacement algorithm

Notes:

– In a medical care set-up where blood transfusion facility is not available to manage thrombocytopenia of DHF, platelets can be obtained from a nearby licensed blood bank.

– Whole bood preserved at 4°C does not have much role in correcting thrombocytopenia as platelets are preserved at 22°C.

CHAPTER 7

NURSING CARE IN ADMITTED CASES

Nursing care plays an integral role in management of dengue patients admitted to hospital.[22]

7.1 Basic management

The basic management of dengue patients admitted to hospital includes the following:

– a mosquito-free environment in hospital
– close monitoring of patient vitals, input and output, oxygen saturation, sensorium
– early identification of warning signs and symptoms
– avoid NSAID and intramuscular injections
– psychological support for patient and family.

7.2 Warning signs and symptoms

Presence of the following signs and symptoms require close monitoring and management:

- respiratory distress
- oxygen desaturation
- severe abdominal pain
- excessive vomiting
- altered sensorium, confusion
- convulsions
- rapid and thready pulse
- narrowing of pulse pressure less than 20 mmHg
- urine output less than 0.5 ml/kg/h
- laboratory evidence of thrombocytopenia/coagulopathy, rising Hct, metabolic acidosis, derangement of liver/kidney function tests.

7.3 Managing common problems in dengue patients

Management of common problems in dengue patients are summed up below.

– *High-grade fever.* Tepid sponging/paracetamol. Encourage intake of plenty of oral fluids.
– *Abdominal pain.* Severe abdominal pain may be a sign of severe complication, so remain vigilant and inform the treating doctor.
– *Bleeding.* Estimate and record the amount of blood loss, monitor vitals and inform the doctor.
– Plasma leakage. Monitor vitals, Hct and input/output. Encourage oral intake if possible and start IV fluid as per instructions.
– Shock/impending shock. Monitor vitals, input/output Hct and sensorium. Start IV fluids/inotropes as per instructions.

- Decreased urine output. First rule out catheter blockade by palpating the bladder. Flush the catheter if blocked. Continue monitoring vitals, input/output and inform the doctor.
- Respiratory distress. Check oxygen saturation and administer oxygen via facemask or nasal catheter if SpO2 <90%. Look for pleural effusion, cardiac involvement and inform the doctor.
- Convulsions/encephalopathy. Pay attention to maintenance of airway, breathing and circulation (ABC). Be ready with resuscitation set for emergency intubation and mechanical ventilation.
- Fluid overload can develop during recovery phase of the illness due to fluid shifts. Closely observe for pedal oedema, neck vein engorgement and respiratory distress. Continue strict input/output monitoring during the recovery phase.

ANNEXURES

Annexure 1

READY RECKONER

In an outbreak situation where it is not possible to admit every patient, it is important to prioritize to decide who needs in-hospital care the most. The following points are important to distinguish between those patients who need hospitalization and those who can be clinically managed at home.

1. Dengue corner

Consider having a dengue corner in the hospital during the transmission season which is functional round the clock with adequate trained manpower and facilities for:

- tourniquet test
- BP cuff of all sizes
- lab investigations at least for CBC: Hb, Hct, total leukocyte count (TLC), differential leukocyte count (DLC), platelet count, peripheral blood smear.

2. Lab investigations for diagnosis and confirmation

– NS1 ELISA test to be done on patients reporting during the first five days of fever.
– Serology to be done on or after day 5 by MAC-ELISA. In an outbreak, all suspected patients of dengue need not undergo serology for purpose of clinical management.

3. Indications for domiciliary management

– If patients have none of the following conditions, they can be managed at home:

- tachycardia;
- hypotension;
- narrowing of pulse pressure;
- bleeding;
  and
- haemoconcentration.

The patient should come for follow up and evaluation after 24 hours. The patient should report to the nearest hospital immediately in case of the following complaints:

– bleeding from any site (fresh red spots on skin, black stools, red urine, nose bleed, menorrhagia);
– severe abdominal pain, not taking food orally/poor intake, persistent vomiting;
– not passing urine for 12 h/decreased urinary output;
– restlessness, seizures, excessive crying (young infants), altered sensorium and behavioural changes and severe persistent headache;
– cold clammy skin; and
– sudden drop in temperature.

4. Conditions for admission

A patient showing the following symptoms and signs should be considered for admission to hospital:
– significant bleeding from any site;
– any warning signs and symptoms;

– persistent high grade fever (38.5°C and above);
– impending circulatory failure – tachycardia, postural hypotension, narrow pulse pressure (<20 mmHg, with rising diastolic pressure, e.g. 100/90 mmHg), increased capillary refilling time > 2 secs;
– neurological abnormalities – restlessness, seizures, excessive crying (young infant), altered sensorium and behavioural changes, severe and persistent headache;
– drop in temperature and/or rapid deterioration in general condition; and
– shock – cold clammy skin, hypotension/narrow pulse pressure, tachypnoea.

It should be noted that a patient may remain fully conscious until a late stage.

5. Investigations for indoor patients

– Chest X-ray: PA view and lateral decubitus, one day after temperature drops
– USG abdomen and chest
– Blood biochemistry: serum electrolytes, kidney function test and liver function test if required

6. Indoor management of patients

(a) Indications for blood transfusion (packed red blood cells [PRBC])

– Loss of blood (overt blood) –10% or more of total blood volume
– Refractory shock despite adequate fluid administration, and declining Hct
– Replacement volume should be 10 ml/kg body weight at a time and coagulogram should be done
– If fluid overload is present, packed-cell volume (PCV) is to be given.

(b) Indications for platelet transfusion

– Platelet transfusion is not the mainstay of treatment in patients with DF. In general, there is no need to give prophylactic platelets even if at platelet count >10 000/mm^3.
– Prophylactic platelet transfusion may be given at levels of <10 000/mm^3 in the absence of bleeding manifestations
– Prolonged shock with coagulopathy and abnormal coagulogram
– In case of systemic bleeding, platelet transfusion may be needed in addition to red cell transfusion.

7. Criteria for discharge of patients

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

8. Use of whole blood/fresh frozen plasma/cryoprecipitate in coagulopathy

Use of whole blood/fresh frozen plasma/cryoprecipitate is to be done in coagulopathy with bleeding as per advice of the treating physician and the patient's condition.

Note: These are only broad guidelines to assist physicians in managing patients. Decisions should be taken as per the severity of individual cases.

Annexure 2

PLATELET PRODUCTS

1. **Random donor platelets (RDP).** The platelets are prepared from whole blood. Depending upon the method of preparation, they can be classified as PRP platelets or buffy coat reduced platelets. Either of these platelet products have a volume of 40–50 ml, platelet content of =4.5x10^2 and shelf life of 5 days. These whole-blood derived platelet concentrates are expected to raise the platelet count by 5–7 thousand in adults and 20 thousand in paediatric patients.

2. **Buffy coat pooled platelets (BCPP).** Pooled buffy coat platelet concentrates are derived from four donations of whole blood (obtained from the buffy coat of ABO identical donors re-suspended in plasma or additive solutions). BCPP has a volume of 160–200 ml, with platelet content ranging from 2.5 to 4.4x10^{11} per product.

3. **Single donor apheresis (SDP).** These are collected by a variety of apheresis systems using different protocols. A single donation procedure may yield one to three therapeutic doses and the donation may be split between two or three bags, depending on counts. SDP are leukocyte reduced; however, in some apheresis systems, filtration may be required for leucocyte depletion. For SDP collection, donors are tested for platelet count, transfusion transmitted infection (TTI) markers and blood group before collection. The average volume for SDP is 200–300 ml, yield or platelet content is 3x10^{11} per bag and is thus equal to 5–6 RDP. Thus, it also often regarded as the jumbo pack. SDPs are expected to increase a patient's platelet count by 30–50 000/ul. BCPP serves as an alternative choice of SDP in case of emergency.

a. Compatibility testing is not required for platelet concentrates. Platelet concentrates from donors of the identical ABO group and the patient can have the components of choice and should be used as far as is possible. However, administration of ABO non-identical platelet transfusions are also an acceptable transfusion practice; in particular, when platelet concentrates are in short supply.

b. Similarly, RhD-negative platelet concentrates should be given, where possible, to RhD-negative patients, particularly to women who have not reached menopause. If RhD-positive platelets are transfused to an RhD-negative woman of childbearing potential, it is recommended that anti-D should be given. A dose of 300 IU of anti-D should be sufficient to cover six SDP or 30 RDP RhD-positive platelets within a 6-week period.

c. Platelets with WBC counts of <8.3x105 in RDP and <5x106 in SDP or BCPP are regarded as leuco-reduced platelets. Leuco-reduced platelets offer the advantage of decreased CMV transmission, febrile non-haemolytic transfusion reaction and all immunization. Irradiated platelet or blood products are used for patients at risk of TA-GVHD.

d. The standard dose for adults is 5–6 units of random donor platelets or one unit of apheresis platelets or one unit of BCPP, equivalent to 3x10^{11} platelets. For neonates/infants, the dose of the platelets should be 10–15ml/kg of body weight.

REFERENCES

1. World Health Organization and Tropical Diseases Research. Dengue: Guidelines for diagnosis, treatment, prevention and control. Geneva: World Health Organization; 2009: new edition.
2. World Health Organization. First report on neglected tropical diseases: working to overcome the global impact of neglected tropical diseases. Geneva: World Health Organization; 2010.
3. World Health Organization. Global strategy for dengue prevention and control – 2012–2020. Geneva: World Health Organization; 2012..
4. Suaya JA, Shepard DS, Siqueira JB, Martelli CT, Lum LCS, Tan LH, et al. Cost of dengue cases in eight countries in the Americas and Asia: a prospective study. American Journal of Tropical Medicine and Hygiene. 2009;80:846–855.
5. World Health Organization. Comprehensive guidelines for prevention and control of dengue and dengue hemorrhagic fever. New Delhi: WHO, SEARO; 2011: revised and expanded edition.
6. Baruah K, Dhariwal AC. Epidemiology of dengue, its prevention and control in India. Journal of Indian Medical Association. 2011;109 (2):82–6.
7. Baruah K, Biswas A, Suneesh K, Dhariwal AC. Dengue fever: Epidemiology and clinical pathogenesis. Chapter 13, Major tropical diseases: Public health perspective. Goa: Broadway publishing House; 2014: 255–71.
8. Dutta AK, Biswas A, Baruah K, Dhariwal AC. National guidelines for diagnosis and management of dengue fever/dengue hemorrhagic fever and dengue shock syndrome. J Ind Med Assn. 2011;109 (1):30–35.
9. Dash AP, Bhatia R, Kalra NL. Dengue in South East Asia: An appraisal of case management and vector control. Dengue Bulletin. 2012;36:1–12.
10. Chen L, Wilson ME. Non-vector transmission of dengue and other mosquito-borne flaviviruses. Dengue Bull. 2005;29:18–30.
11. Kalayanarooj S. Clinical manifestations and management of dengue/DHF/DSS. Tropical Medicine and Health. 2011; 39 (4 suppl) 83–9.
12. Guzman MG, Halstead SB, Artsob H, Buchy P, Farrar J, Gubler DJ, et al. Dengue: A continuing global threat. Nat Rev Microbiol. 2010;8 (12 Suppl):7–16.
13. World Health Organization and Tropical Diseases Research. Handbook for clinical management of dengue. Geneva: World Health Organization; 2012.
14. Sharma S, Sharma SK, Mohan A, Wadhwa J, Dar L, Thakur S, et al. Clinical profile of dengue hemorrhagic fever in adults during 1996 outbreak in Delhi, India. Dengue Bulletin. 1998;22:20–30.
15. World Health Organization. Comprehensive guidelines for prevention and control of dengue and dengue hemorrhagic fever. New Delhi: WHO, SEARO; Revised and expanded edition.
16. Chan DPL, Teoh SCB, Tan CSH, Nah GKM, et al. Ophthalmic Complications of dengue. Emerging Infectious Diseases. 2006;12(2):285–6.
17. Juanarita J, Azmi MNR, Azhany Y, Liza-Sharmini AT. Dengue related maculopathy and foveolitis. Asian Pac J Trop Biomed. 2012; 2(9):755–6.
18. Wali J P, Biswas A, Aggarwal P, Wig N, Handa R. Validity of tourniquet test in dengue hemorrhagic fever, J Assoc Physicians India. 1999;47(2):203–204.
19. Mid term plan for prevention and control of dengue and chikungunya. New Delhi: National Vector Borne Disease Control Programme, Directorate of Health Services, Ministry of Health & Family Welfare, Govt of India; 2011.
20. Wali JP, Biswas A, Chandra S, Malhotra A, Agarwal P, Handa R, et al. Cardiac involvement in dengue hemorrhagic fever. Int J. Cardiol; 64:31-6.
21. Capeding MR, Tran NH, Hadinegoro RS, Ismail HIHJM, Chotpitayasunondh T, Chua MN, et al. Clinical efficacy and safety of a novel tetravalent dengue vaccine in healthy children in Asia: a phase 3, randomised, observer-masked, placebo-controlled trail. www.thelancet.com, published online 11 July 2014.
22. Kalayanarooj S, Nimmannitya S. Guidelines for dengue hemorrhagic fever case management. Bangkok: Bangkok Medical Publisher; 2004.

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