

Guidelines for Clinical Management of Dengue Fever, Dengue Haemorrhagic Fever and Dengue Shock Syndrome



Government of India



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PREFACE

Dengue Fever/Dengue Haemorrhagic Fever is an acute viral disease having the potential of causing, large scale outbreaks. The risk of dengue has shown an increase in recent years due to rapid, urbanization, life style changes and deficient water management including improper water storage practices in urban, peri-urban and rural areas, leading to proliferation of mosquito breeding sites. In India, the first evidence about the occurrence of dengue fever was reported during 1956 from Vellore district in Tamil Nadu. The first DHF outbreak occurred in Calcutta (Kolkata, West Bengal) in 1963 with 30% of cases showing haemorrhagic manifestations. In 1996, the country had experienced an outbreak recording a total number of 16517 cases (suspected) and 545 deaths. During 2003 as well, large number of cases and deaths had been reported (12754 and 215, respectively). In the year 2006, there was again upsurge in DF/DHF cases in the country, with a total 11638 cases and 174 deaths reported by 21 states of the country. All the four serotypes i.e. Dengue 1, 2, 3 and 4 have been isolated in India.

There is no specific treatment for dengue fever. Besides, the dengue vaccine has a long way to go. As any of the four dengue viruses can cause the disease, hence the vaccine must be tetravalent i.e., it needs to protect against all four viruses.

One of the primary problems in management of dengue is misinterpretation and resultant confusion because of the term “haemorrhagic fever” implying a significant haemorrhagic component to the patho-physiology and overshadowing the increased permeability, which causes depletion of the intravascular component. The doctor managing a dengue patient has to make evaluations of the haemodynamic state to assess for judicious fluid replacement at several points of time. A broad-angled evaluation involves integration of clinical and laboratory parameters, which are in turn summation of the disease process as well as the ongoing treatment. This understanding is crucial in guiding decisions about the volume, rate and type of fluid infusion. Most, if not all, deaths due to dengue are potentially avoidable. Thus, it was essential to frame the common guidelines on Clinical Management of Dengue for the physicians across the country.

These guidelines on clinical management of DF/DHF/DSS have been developed in consultation with the leading national and international experts in the field of clinical management of DHF. I am sure these will guide the clinicians for appropriate treatment of the patients with DF/DHF /DSS and would help in reducing the case fatality rate of DHF/DSS.

These are only broad guidelines, the treating physician should consider the condition of the patient in totality and decide the course of treatment to save the life.



(Dr. G.P.S. Dhillon)

ACKNOWLEDGMENTS

In recent years Dengue cases are increasing alarmingly in various parts of the country including rural areas. The disease is now endemic in 21 states/UTs. As the disease is spreading to newer areas, not only the number of cases and deaths are increasing, but explosive outbreaks are occurring. In absence of any specific treatment or vaccine, proper management of cases is utmost crucial in dengue.

Keeping the above in mind these guidelines on clinical management of DF/DHF/DSS has been developed during a brain storming workshop held on 14th & 15th March 2007 at AIIMS in collaboration with WHO SEARO. Many national and international leading experts in the field of clinical management of DF/DHF/DSS participated in this workshop and deliberated to frame the draft guidelines. NVBDCP gratefully acknowledge contributions and technical inputs of all the experts for developing these guidelines.

Dr. P.L. Joshi, former Director, NVBDCP, is gratefully acknowledged for his keen interest in developing these guidelines for clinicians to bring about the nuances in dengue management and technical advice for undertaking the preparation of this document.

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CHAPTER 1

INTRODUCTION

1.1 Introduction

Dengue is a self limiting acute mosquito transmitted disease characterized by fever, headache, muscle, joint pains, rash, nausea and vomiting. Dengue Fever (DF) is caused by an arbovirus and spread by *Aedes* mosquitoes. Some infections result in Dengue Haemorrhagic Fever (DHF) and in its severe form Dengue Shock Syndrome (DSS) can threaten the patient's life primarily through increased vascular permeability and shock.

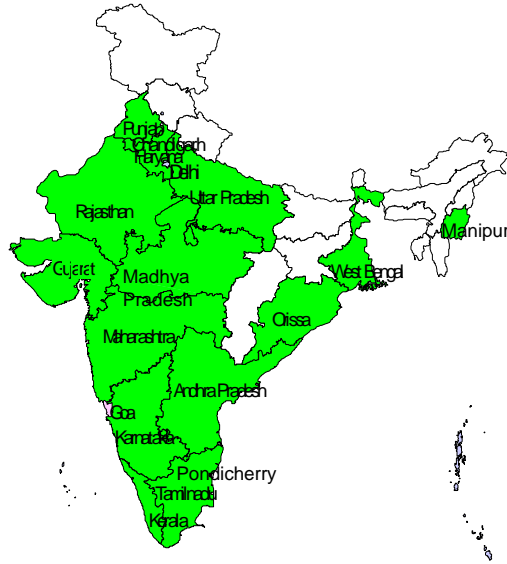
Over the past two decades, there has been global increase in the frequency of DF, DHF and its epidemics, with a concomitant increase in disease incidence. Various factors responsible for the resurgence of dengue epidemic are: (i) un-precedented human population growth; (ii) un-planned and un-controlled urbanization; (iii) inadequate waste management; (iv) water supply mismanagement; (v) increased distribution and densities of vector mosquitoes; (vi) lack of effective mosquito control has increased movement & spread of dengue viruses and development of hyper endemicity and (vii) deterioration in public health infrastructure.

1.2 Dengue in India

The first evidence of occurrence of DF in the country was reported during 1956 from Vellore district in Tamil Nadu. The first DHF outbreak occurred in Calcutta (West Bengal) in 1963 with 30% of cases showing haemorrhagic manifestations. All the four serotypes i.e. Dengue 1,2,3 and 4 have been isolated in India. As *Ae aegypti* breeding is more common in urban areas the disease was observed mostly prevalent in urban areas. However, the trend is now changing due to socio economic and man made ecological changes, It has resulted in invasion of *Ae. aegypti* mosquitoes into the rural areas, which has tremendously increased the chances of spread of the disease to rural areas.

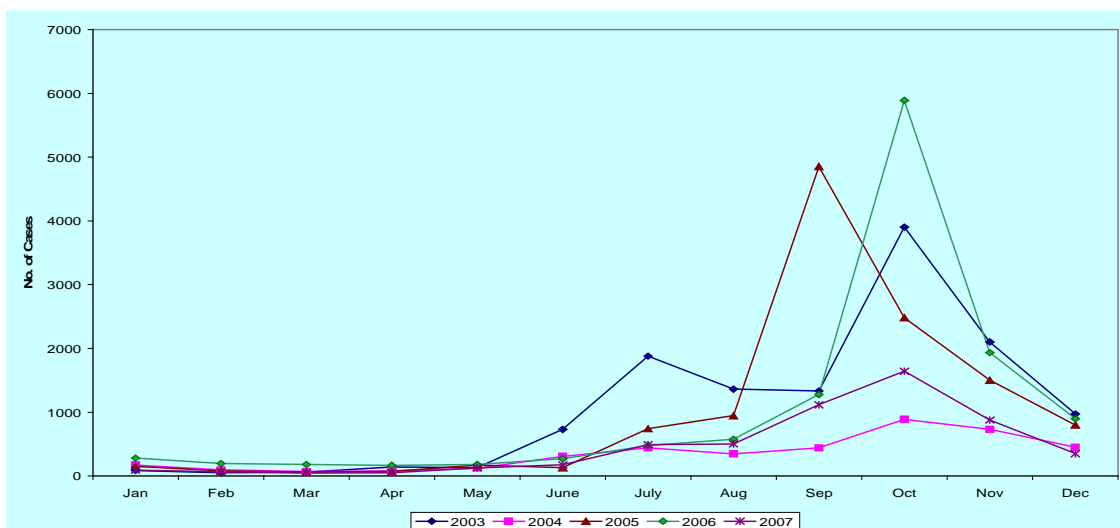
Recurring outbreaks of DF/DHF have been reported from various States/UTs namely Andhra Pradesh, Delhi, Goa, Haryana, Gujarat, Karnataka, Kerala, Maharashtra, Rajasthan, Uttar Pradesh, Pondicherry, Punjab, Tamil Nadu, West Bengal and Chandigarh. The states that reported DF/DHF in 2007 are shown in Fig. 1.

Fig. 1. Dengue endemicity map of the country (2007)



During 1996, one of the most severe outbreaks of DF/DHF occurred in Delhi where, 10,252 cases and 423 deaths occurred. In 2006, the country witnessed another outbreak of DF/DHF, total 12,317 cases and 184 deaths were reported in 21 states/UTs. However, in 2007 only 5534 cases and 69 deaths were reported from 18 states. Among the NE States Manipur has reported Dengue outbreak for the first time in 2007. Every year during the period of July-Nov there is an upsurge in the cases of Dengue/DHF. The seasonal trends for 2003-07 are depicted in Fig. 2.

Fig. 2. Seasonal trends of Dengue/DHF 2003-07



CHAPTER 2

EPIDEMIOLOGY

2.1 Epidemiology

Dengue is one of the most important emerging viral disease of humans in the world afflicting humanity in terms of morbidity and mortality. Currently the disease is endemic in all continents except Europe. The Epidemiology of dengue is a complex phenomenon that mainly depends upon an intricate relationship between the 3 epidemiological factors: the host (man and mosquito), the 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.

2.2 Agent Factor

The dengue viruses are the members of the genus flavivirus. These small (50nm) viruses contain single stranded RNA. There are four virus serotypes, which are designated as DEN-1, DEN-2, DEN-3 and DEN-4. 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. Man and mosquito are reservoirs of infection. Transovarian transmission (infection carried over to next progeny of mosquitoes through eggs) has made the control more complicated.

- At present DEN1 and DEN2 serotypes are widespread in India.

2.3 Vector

Dengue viruses are transmitted by the bite of female *Aedes (Ae)* mosquitoes. *Ae. aegypti* is the most potential vector (Fig.3) but other species such as *Ae albopictus*, *Ae. polynesiensis* and *Ae. niveus* have also been incriminated as secondary vectors. In India *Ae. aegypti* is the main vector in most urban areas; however, *Ae albopictus* is also found as vector in few areas of southern India.

- Dengue is transmitted by the bite of female *Aedes* mosquito

Female *Aedes* mosquito deposits eggs singly on damp surfaces just above the water line. Under optimal conditions the life cycle of aquatic stage of *Ae. aegypti* (the time taken from hatching to adult emergence) can be as short as seven days.

The eggs can survive one year without water. At low temperature, however, it may take several weeks to emerge. *Ae. aegypti* has an average adult survival of fifteen days. During the rainy season, when survival is longer, the risk of virus transmission is greater. It is a day time feeder and can fly up to a limited distance of 400 meters. To get one full blood meal the mosquito has to feed on several persons, infecting all of them.

Fig. 3. A female *Ae. aegypti* mosquito



2.4 Environmental Factors

The population of *Ae. aegypti* fluctuates with rainfall and water storage. Its life span is influenced by temperature and humidity, survives best between 16°-30° C and a relative humidity of 60-80%. *Ae. aegypti* breeds in the containers, in and around the houses. Altitude is an important factor in limiting the distribution of *Ae. aegypti*, it is distributed 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 development of rural water supply schemes, improved transport systems, scarcity of water and like style changes.

Ae. aegypti breeds almost entirely in domestic man-made water receptacles found in and around households, construction sites and factories; natural larval habitats are tree holes, leaf axils and coconut shells. In hot and dry regions, overhead tanks and ground water storage tanks become primary habitats. Unused tyres, flower pots and desert coolers are among the most common domestic breeding sites of *Ae. aegypti* (Fig. 4).

Fig. 4. Few common and favoured breeding places/sites of *Ae. aegypti*



Desert cooler



Water storage pots



Tyres



Unused tyres



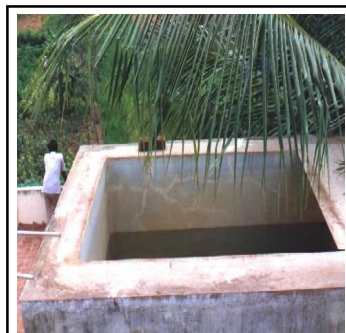
Coconut shells



Disposable cups



Open overhead tank



Water reservoir



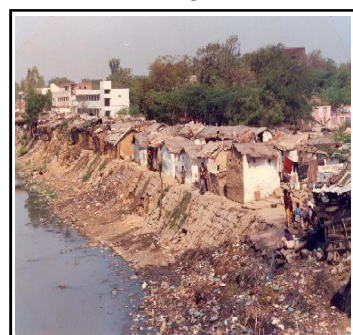
Grinding stone



Construction sites



Coolers in Multi- Storied buildings in urban areas



Suburban slums

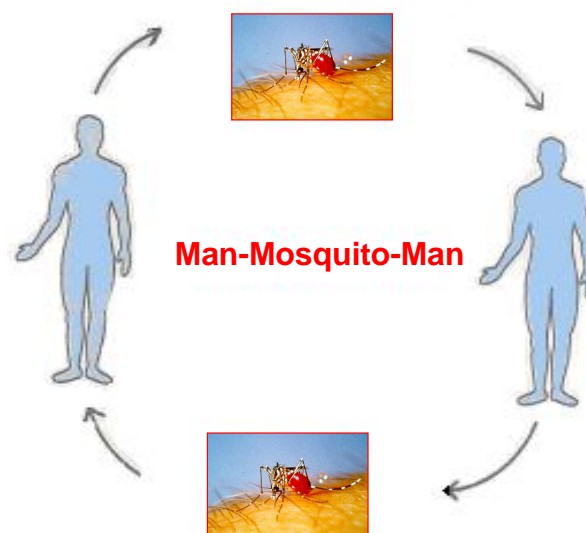
2.5 Host Factor

Dengue virus infects humans and several species of lower primates but in India man is the only natural reservoir of infection. All ages and both sexes are susceptible to dengue fever. Secondary dengue infection is a risk factor for DHF including passively acquired antibodies in infants. Travel to dengue endemic area is an important risk factor, if the patient develops fever more than 2 weeks after travel, dengue is unlikely. Migration of patient during viremia to a non endemic area may introduce it into the area.

2.6 Transmission cycle

The female *Ae. aegypti* usually becomes infected with dengue virus when it takes blood meal from a person during the acute febrile (viraemia) phase of dengue illness. After an extrinsic incubation period of 8 to 10 days, the mosquito becomes infected and virus is transmitted when the infective mosquito bites and injects the saliva into the wound of the person (Fig 5). There is evidence that vertical transmission of dengue virus from infected female mosquitoes to the next generation occurs through eggs, which is known as transovarian transmission.

Fig. 5. Transmission Cycle



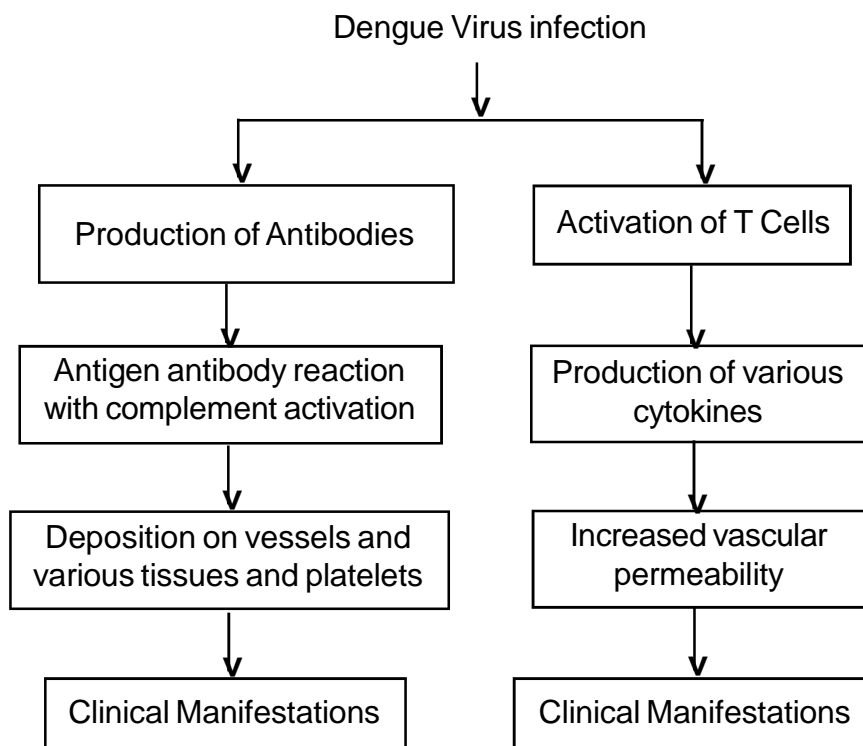
CHAPTER 3

CLINICAL DIAGNOSIS OF DHF/DSS

3.1 Immuno-pathogenesis

Primary or first infection in non immune persons usually causes Dengue fever. Subsequent dengue infection by different serotype causes more severe illness like DHF/DSS. The key manifestations of the DHF/DSS are sudden onset of shock, capillary leakage, haemorrhagic diathesis/ thrombocytopenia occurring at the time of defervescence of fever. Pathogenesis is not well defined but it is suggested that it is mediated through soluble mediators, compliment activation and cytokines that are responsible for various manifestations. Fig. 6 illustrates the patho-physiology of DHF.

Fig. 6. Patho-physiology of DHF



3.2 Clinical manifestations of DF/ DHF/DSS

Clinical manifestations vary from undifferentiated fever to florid haemorrhage and shock. The clinical presentations depend on age, immune status of the host and the virus strain. Under NVBDCP the case definitions recommended by WHO are being followed, which is as under:

Dengue Fever : Clinical description

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.

Criteria for Dengue Haemorrhagic Fever and Dengue Shock Syndrome **Dengue Haemorrhagic Fever :**

a). A probable or confirmed case of dengue

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
4. Haematemesis or malena

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, ascitis, hypoproteinaemia)

Dengue Shock Syndrome :

All the above criteria for DHF plus evidence of circulatory failure manifested by rapid and weak pulse and narrow pulse pressure (≤ 20 mm Hg) or hypotension for age, cold and clammy skin and restlessness.

Case classification

Suspected : A case compatible with the clinical description

Probable : A case compatible with the clinical description with **one or more** of the following:

- Supportive serology (reciprocal haemagglutination - inhibition titre, comparable IgG ELISA titre or positive IgM antibody test in late acute or convalescent-phase serum specimens)
- Occurrence at same location and time as other confirmed cases of dengue fever

Confirmed : A case compatible with the clinical description that is laboratory confirmed

Laboratory criteria for diagnosis

One or more of the following:

- Isolation of the dengue virus from serum, plasma, leucocytes or autopsy samples
- Demonstration of a fourfold or greater change in reciprocal IgG or IgM antibody titres to one or more dengue virus antigen in paired serum samples.
- Demonstration of dengue virus antigen in autopsy tissue by immunohistochemistry or immunofluorescence or in serum samples by ELISA.
- Detection of viral genomic sequences in autopsy tissue, serum or CSF samples by polymerase chain reaction (PCR).

CHAPTER 4

LABORATORY DIAGNOSIS OF DENGUE

4.1 Laboratory diagnosis

Early symptoms of dengue fever mimic other diseases often prevalent in areas where it is endemic, such as chikungunya, malaria and leptospirosis. Hence for proper management rapid differential diagnosis is very crucial. Laboratory diagnosis can be carried out by one or more of the following tests:

- Isolation of Dengue virus from serum, plasma, leucocytes or autopsy samples.
- Demonstration of a fourfold or greater rise in reciprocal IgG antibody titres to one or more dengue virus antigen in paired sera samples.
- Demonstration of dengue virus antigen in autopsy tissue by immunohistochemistry or immunofluorescence or in serum samples by EIA
- Detection of viral genomic sequences in autopsy tissue, serum or CSF sample by PCR (Polymerase Chain Reaction)

4.1.1 Isolation of Dengue Virus

Isolation of most strains of dengue virus from clinical specimens can be accomplished in a majority of cases provided the sample is taken in the first few 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. This method is suitable for research or for other academic purpose not for patient care.

4.1.2 Serological Tests

Following tests are available for the diagnosis of dengue infection

- Haemagglutination-Inhibition (HI),
- Complement Fixation (CF),
- Neutralization test (NT),
- IgM capture enzyme-linked immunosorbent assay (MAC-ELISA), and
- Indirect IgG ELISA.

4.1.2.1 Haemagglutination inhibition (HI) test

Of the above, HI assay has been the most widely used method for the serological diagnosis of dengue in the past. However, due to the extensive cross-reaction encountered and time consuming due to the requirement of both acute and convalescent sera collected at least seven days apart have limited the general applicability of this assay.

4.1.2.2 Compliment Fixation Test (CFT)

The testing procedure is cumbersome and require highly trained personnel the reagents are thermolabile. Due to these, currently it is not used for routine diagnosis.

4.1.2.3 Neutralization test (NT)

Though this is most specific and sensitive serological test for dengue infections, due to time involved in the testing procedure coupled with technical difficulty has limited the use of this test.

4.1.2.4 IgM-capture Enzyme-Linked Immunosorbent Assay (MAC-ELISA)

MAC-ELISA has become widely used test in the past few years. It is a simple, rapid test that requires very little sophisticated equipment. MAC-ELISA is based on detection of the dengue-specific IgM antibodies in the test serum by capturing them out of solution using anti-human IgM that was previously bound to the solid phase. 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 five of the illness. However, the rapidity with which IgM develops varies considerably among patients. Some patients have detectable IgM on days two to four 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 previous two to three months. MAC-ELISA has become an invaluable tool for surveillance of Dengue. 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.

4.1.2.5 IgG-ELISA

An indirect IgG-ELISA has been developed that compares well to the HI test. This test can also be used in comparison with Igm to differentiate primary and secondary dengue infections. The test is simple and easy to perform and is thus useful for high-volume testing. The IgG-ELISA is nonspecific and exhibits the same broad cross-reactivity among flaviviruses as the HI test thus cannot be used to identify the infecting dengue serotype.

4.1.2.6 Rapid Diagnostic tests

A number of commercial Rapid Diagnostic Test (RDT) kits for anti-dengue IgM and IgG antibodies are at present commercially available, which produces the results within 15 to 20 minutes. However, the sensitivity/specificity of most of these tests is not known since they have not yet been properly validated. Though some of the RDTs have been independently evaluated, the results showed a high rate of false positive compared to standard tests, while others have agreed closely with standard tests. The sensitivity and specificity of some RDTs also found to vary from lot to lot. According to WHO guidelines, these kits should not be used in the 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 case fatality rate.

4.2 Collection of Specimens

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 be taken. Samples could be collected

- as soon as possible after the onset of illness, hospital admission or attendance at a clinic (acute serum, S1).
- shortly before discharge from the hospital or, in the event of a fatality, at the time of death (convalescent serum, S2).
- in the event if hospital discharge occurs within 1-2 days of the subsidence of fever collect a third specimen 7-21 days after the acute serum (S1) was drawn (late convalescent serum, S3).

The optimal interval between the acute (S1) and the convalescent (S2 or S3) serum is 10 days. The above recommendations allow for the collection of at least two serum samples for comparison and ideally will provide for an adequate interval between sera. Serological diagnoses are on the identification of changes in antibody levels over time. Serial (paired) specimens are required to confirm or refute a diagnosis of acute flavivirus or dengue infection.

4.3 NVBDCP strategy for laboratory diagnosis

The dengue IgM antibody appears quite early in the course of illness. Its detection requires only a single but properly timed blood sample. IgM responses are also usually less cross-reactive to other flaviviruses. The procedure involved is comparatively easier than other methods available for diagnosis of dengue infections due to which NVBDCP is currently following IgM Antibody Capture ELISA (MAC-ELISA) for diagnosis of dengue infection in the network of sentinel surveillance laboratories it has established/ identified across the country. For details of these laboratories refer **Annexure II**.

Available literature suggests that whichever the test, the complexity of flavivirus diagnosis cannot be disregarded. Hence, a diagnosis of a particular flavivirus should always be made taking into account the clinical presentation of the patient, the performance characteristics of the serological test employed and the knowledge of the flaviviruses circulating in that particular geographical region.

CHAPTER 5

CLINICAL MANAGEMENT

5.1 Grading the severity of Dengue infection

To decide where to treat the patient, it is important to classify the severity of dengue infection as given in the Table 1. The presence of thrombocytopenia with concurrent haemoconcentration differentiates Grade I and Grade II DHF from DF.

Table1: Grading the severity of Dengue infection

DF/ DHF	Grade	Symptoms/signs	Laboratory findings
DF		Fever with two or more of following - Headache - Retro-orbital pain - Myalgia - Arthralgia	Leucopenia, thrombocytopenia
DHF	I	Above criteria for DF plus positive tourniquet test, evidence of plasma leakage	Thrombocytopenia : Platelet count less than 100,000/cu.mm. Haematocrit rise 20% or more
DHF	II	Above signs and symptoms plus some evidence of spontaneous bleeding in skin or other organs (black tarry stools, epistaxis, bleeding from gums, etc) and abdominal pain	Thrombocytopenia platelet count less than 100,000/cumm Haematocrit rise 20% or more
DHF	III	Above signs and symptoms plus circulating failure (weak rapid pulse, pulse pressure \leq 20 mm Hg or high diastolic pressure, hypotension with the presence of cold clammy skin and restlessness)	Thrombocytopenia: Platelet count less than 100,000/cumm Haematocrit rise more than 20%
DHF	IV	Profound shock with undetectable blood pressure or pulse Haematocrit rise more than 20%	Thrombocytopenia : Platelet count less than 100,000/cumm Haemotocrit rise more than 20%

Note:

- DF may sometimes present with bleeding manifestation but without evidence of haemoconcentration/ plasma leakage. It should not be confused with DHF.
- In addition pain and/or tenderness in upper abdomen have been commonly observed as prominent clinical feature.

A patient showing Petechiae in legs.



Tourniquet test : The tourniquet test is performed by inflating a blood pressure cuff to a mid point between the systolic and diastolic pressure for five minutes. The test is considered positive when 10 or more petechiae per 2.5 cm² are observed. 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).**

If tourniquet test is found negative it should be repeated. Early diagnosis of disease and admission of DHF patients in hospitals are important in order to reduce case fatality rates. Treatment can be initiated on clinical suspicion and on the basis of interpretation of platelet count and haematocrit, confirmation by laboratory diagnosis is not required.

5.2 MANAGEMENT

5.2.1 Management of Dengue Fever (DF)

Management of Dengue fever is symptomatic and supportive

- i. Bed rest is advisable during the acute phase.
- ii. Use cold sponging to keep temperature below 39°C.
- iii. Antipyretics may be used to lower the body temperature. Aspirin/NSAID like Ibuprofen etc should be avoided since it may cause gastritis, vomiting, acidosis and platelet dysfunction. Paracetamol is preferable in the doses as follows:

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

Note : In children the dose is calculated as per 10mg/KG Body Weight per dose which can be repeated at the interval of 6hrs

- iv. Oral fluid and electrolyte therapy are recommended for patients with excessive sweating or vomiting.
- v. Patients should be monitored in DHF endemic area until they become afebrile for one day without the use of antipyretics and after platelet and haematocrit determinations are stable, platelet count is >50,000/ cumm.

5.2.2 Management of DHF (Febrile Phase)

The management of febrile phase is similar to that of DF. Paracetamol is recommended to keep the temperature below 39° C. Copious amount of fluid should be given orally, to the extent the patient tolerates, oral hydration solution (ORS), such as those used for the treatment of diarrhoeal diseases and/or fruit juices are preferable to plain water. IV fluid may 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. Serial haematocrit determinations are essential guide for treatment, since they reflect the degree of plasma leakage and need for intravenous administration of fluids. Haematocrit should be determined daily from the third day until the temperature has remained normal for one or two days. If haematocrit determination is not possible, haemoglobin determination may be carried out as an alternative. The details of IV treatment when required for patients are given in Chart 1.

5.2.3 Management of DHF Grade I and II

Any person who has dengue fever with thrombocytopenia and haemoconcentration and presents with abdominal pain, black tarry stools, epistaxis, bleeding from the gums and infection etc needs to be hospitalized. All these patients should be observed for signs of shock. The critical period for development of shock is transition from febrile to abferile phase of illness, which usually occurs after third

day of illness. A rise of haemococoncentration indicates need for IV fluid therapy. If despite the treatment, 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 detailed treatment for patients with DHF Grade I and II is given at Chart 1.

5.2.4 Management of DHF Grade III and IV

Common signs of complications are observed during the afebrile phase of DHF. 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 sustained monitoring. If the patient has already received about 1000 ml of intravenous fluid, it should be changed to colloidal solution preferably Dextran40/ haemaccele or if haematocrit is decreasing, fresh whole blood transfusion 10ml/kg/dose should be given.

However, in case of persistent shock when, 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 haemococoncentration. It is thus recommended to give fresh 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. The detailed graphical presentation of the treatment for patients with DHF Grades III and IV is given at Chart 2.



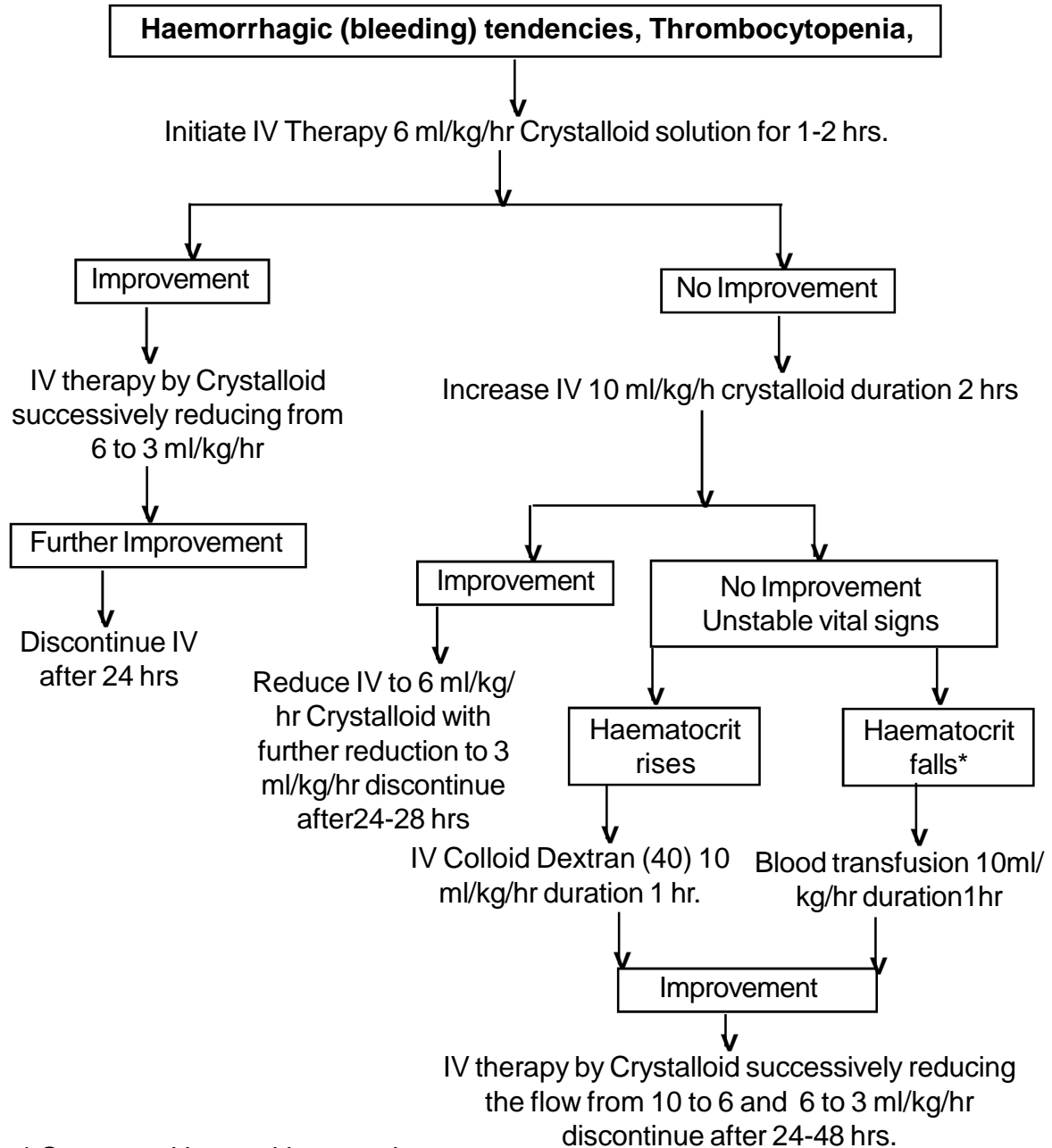
Subconjunctival Haemorrhage with Ecchymosis in a patient with DHF



Chemosis and subconjunctival haemorrhage in a patient with DSS

CHART 1

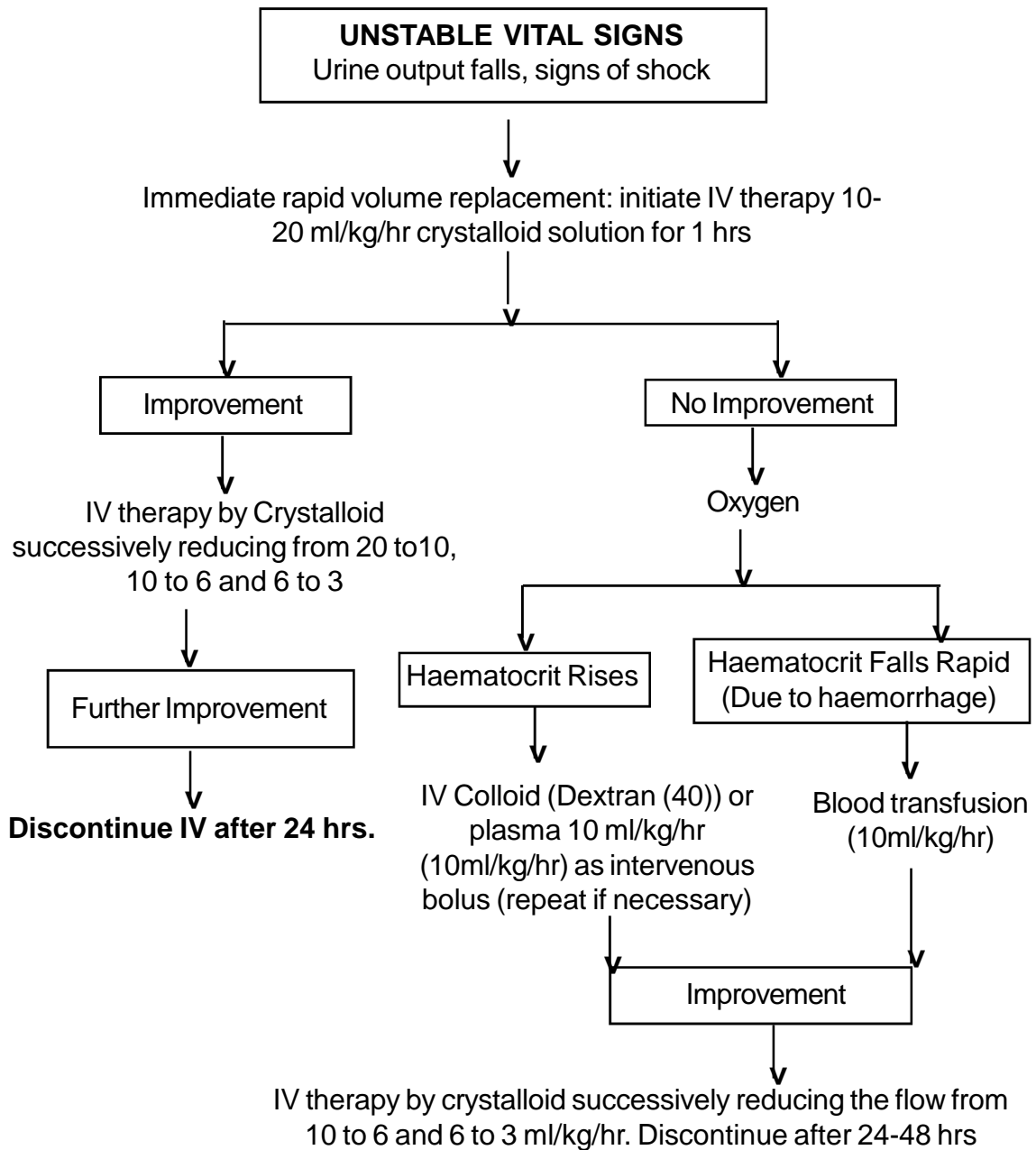
Volume Replacement Flow Chart for Patients with DHF Grades I & II



* Suspected internal haemorrhage

- Improvement** : Haematocrit falls, pulse rate and blood pressure stable, urine output rises
- No Improvement** : Haematocrit or pulse rate rises, pulse pressure falls below 20 mmHg, Urine output falls
- Unstable Vital signs** : Urine output falls, signs of shock

Chart 2. Volume Replacement Flow Chart for Patients With DHF Grades III & IV



- Serial platelet and haematocrit determinations: drop in platelets and rise in haematocrit are essential for early diagnosis of DHF.
- Cases of DHF should be observed every hour for vital signs and urinary output.

5.2.5 Criteria for discharge of patients

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

Checklist of diagnostics and therapeutics necessary for management of dengue is given at **Annexure I**.

5.3 Requirement of fluid

The volume of fluid required to be replaced should be just sufficient to maintain effective circulation during the period of plasma leakage. To ensure adequate fluid replacement and avoid over-fluid infusion, the rate of intravenous fluid should be adjusted throughout the 24 to 48 hour period of plasma leakage by periodic haematocrit determinations and frequent assessment of vital signs.

The require regimen 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. 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 moderate dehydration of about 6% deficit (plus maintenance).

ml/lb bodyweight/day	Weight on admission		ml/kg Body weight/day
	Lbs	Kgs	
100	<15	<7	220
75	16-25	7-11	165
60	26-40	12-18	130
40	>40	>18	90

In older children who weigh more than 40 kgs, the volume needed for 24 hours should be calculated as twice that required for maintenance (using the Holiday

and Segar formula). The maintenance fluid should be calculated as follows:

Holiday and Segar formula

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

For a child weighing 40 kgs, the maintenance is: $1500 + (20 \times 20) = 1900$ ml. This means that the child requires 3800 ml IV fluid during 24 hours.

For intravenous fluid therapy of patients with DHF, four regimens of flow of fluid are suggested: 3ml/kg/hr; 6ml/kg/hr; 10ml/kg/hr, and 20ml/kg/hr.

For ready reference, the calculated or fluid requirements, based on bodyweight and rate of flow of fluid volume for the four regimens are given in Table 2.

Table 2: Requirement of fluid based on bodyweight

Body weight (In kgs)	Volume of fluid to be given in 24 hrs	Rate of fluid (ml/hours)			
		R*1	R*2	R*3	R*4
10	1500	30	60	100	200
15	2000	45	60	150	300
20	2500	60	90	200	400
25	2800	75	120	250	500
30	3200	90	150	300	600
35	3500	105	180	350	700
40	3800	120	210	400	800
45	4000	135	240	450	900
50	4200	150	270	500	1000
55	4400	165	300	550	1100
60	4600	180	360	600	1200

*Regimen 1 – 3ml/kg/hr; 2 – 6ml/kg/hr; 3 – 10ml/kg/hr, and 4 – 20ml/kg/hr

➤ The fluid volumes mentioned are approximations.

- Normally change should not be drastic. Do not jump from R-2 to R-4 since this can overload the patient with fluid. Similarly, reduce the volume of fluid from R-4 to R-3, from R-3 to R2, and from R-2 to R-1 in a stepwise manner.
- Remember that ONE ML is equal to 20 DROPS. In case of MACRO system, one ml is equal to 15 drops. (if needed adjust fluid speed in drops according to equipment used)
- It is advised to procure only a 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.

5.4 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 most. Following points are a guide to distinguish various situations and the action to be taken:

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

- tourniquet test
- BP cuff of all sizes
- Blood counter for complete blood count and haematocrit

5.4.2 Indications for domiciliary management:

- No tachycardia
- No hypotension
- No narrowing of pulse pressure
- No bleeding
- Platelet count > 100,000/cumm

Patient should come for follow up after 24 hours for evaluation. In case of the following complaints patient should report to nearest hospital immediately

- 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 hrs / decreased urinary output
- restlessness, seizures, excessive crying (young infant), altered sensorium

and behavioral changes and severe persistent headache

- cold clammy skin
- sudden drop in temperature

5.4.3 Consider admission of patient showing the following symptoms and signs

- Bleeding from any site

Warning signs:

- Persistent high grade fever(40° C and above)
- Severe Abdominal pain, refusal to take orally/ poor intake, persistent vomiting, any signs of dehydration
- Impending circulatory failure – tachycardia, postural hypotension, narrow pulse pressure(<20 mmHg, with rising diastolic pressure eg 100/90 mmHg), increased capillary refilling time → 3secs (paediatric age group)
- Neurological abnormalities - restlessness, seizures, excessive crying (young infant), altered sensorium and behavioral changes, severe and persistent headache.
- Drop in temperature and/or rapid deterioration in General Condition
- Shock- cold clammy skin, hypotension/ narrow pulse pressure, tachypnoea

However a patient may remain fully conscious until late stage

5.4.4 Lab investigations for all patient assessment

- CBC: Hb, Hct, TLC, DLC, Platelet count, Peripheral blood smear

5.4.5 Lab investigations for diagnosis

- 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.)
- While sending the sample to the Laboratory fill the lab. requisition form at Annexure IV and send with the sample.

5.4.6 Investigations for indoor patients

- Chest X Ray : Rt lateral decubitus one day after temperature drops
- USG abdomen and Chest
- Blood Biochemistry: Serum electrolytes , KIDNEY FUNCTION TEST AND LIVER FUNCTION TEST IF REQUIRED

- Stool examination for occult blood, pleural fluid tapping and Blood culture for excluding other causes may be done.

5.4.7 Indoor management of Patients

5.4.7.1 Indications of red cell transfusion

- Loss of blood(overt blood) -10% or more of total blood volume – Preferably whole blood/ component to be used
- Refractory shock despite adequate fluid administration and declining haematocrit
- Replacement volume should be 10 ml/kg body wt at a time and coagulogram should be done
- If fluid overload is present PCV is to be given

5.4.7.2 Indications of platelet transfusion

In general there is no need to give prophylactic platelets even at < 20,000/ cumm

- Prophylactic platelet transfusion may be given at level of <10,000/ cumm in absence of bleeding manifestations
- Prolonged shock; with coagulopathy and abnormal coagulogram
- In case of Systemic massive bleeding, platelet transfusion may be needed in addition to red cell transfusion.

5.4.7.3 Use of fresh frozen plasma/ cryoprecipitate in coagulopathy with bleeding as per advise of Physician and patients condition.

These are only broad guidelines. The treating physician should consider the condition of the patient in totality and decide

Annexure 1

Checklist of diagnostic and therapeutic material for dengue case management

1. Minimum of diagnostic materials should be:

- Blood pressure cuffs (adult and paediatric)
- Thermometers
- Haematocrit centrifuge
- Haematocrit supplies (lancets, capillary tubes, reader)
- Compound microscope and materials for white blood cell and platelet counts
- Vacutainers or syringes/needles for obtaining dengue and diagnostic test samples

2. Minimum of diagnostic therapeutics:

- Paracetamol
- WHO oral rehydration solution
- Lactate Ringer's solution; 0.9% saline; 5% glucose
- Tubes and needles for intravenous therapy

3. Additional facilities for in-patients:

- Laboratory test equipment and supplies for blood typing and cross-matching for measuring arterial blood gases and pH and for measuring serum electrolytes
- Portable X-ray and ultrasound equipment
- Central venous pressure monitoring kits
- Intake-output monitoring charts

4. Therapeutic materials will be same as that of outpatient department plus:

- Intravascular volume expanders (Dextran 40, plasmanate, platelet concentrates, fresh frozen plasma, whole blood)
- 7.5% sodium bicarbonate for injection
- Chloral hydrate
- Oxygen

Annexure II

To facilitate the diagnostic facilities Government of India (GOI) has identified/established 110 Sentinel Surveillance Hospitals (SSHs) and linked them to 13 Apex Referral Laboratories (ARLs) for advanced diagnosis, capacity building, quality assurance and backup support. In addition to the existing network of 110 SSHs, 27 more are proposed in different endemic areas. Dengue IgM ELISA test kits are being provided to these institutes as per the technical requirement of the states based on the previous epidemiological situations by National Institute of Virology (NIV), Pune. Test kits production capacity of NIV, Pune has been enhanced and the cost of the kits is reimbursed by GOI. These SSHs and ARLs will maintain the line list of the cases (confirmed and suspected) and send the report to the respective health authorities for implementation of remedial vector control measure to interrupt the transmission. Report should be submitted at the earliest and in the proforma given at Annexure-III. List of the Sentinel Surveillance Hospitals and Apex Referral Laboratories are as follows:

LIST OF THE SENTINEL HOSPITALS FOR DENGUE AND CHIKUNGUNYA

Name of the States	Sentinel Hospitals/Institutes
1. Andhra Pradesh	<ol style="list-style-type: none"> 1. MGM Hospital, Warangal, 2. Ruya Hospital, Tirupathi, 3. Govt. Hospital, Guntur, 4. Govt. Hospital, Vijayawada, 5. Govt. Hospital, Karimnagar, 6. Govt. Hospital, Nizamabad, 7. Govt. Hospital, Annanthpur, 8. VBRI, Hyderabad, 9. Medical Collage, Kurnool, 10. Medical Collage, Mahboobnagar.
2. Goa	<ol style="list-style-type: none"> 1. Hospicio Hospital, Margo, South Goa, 2. Goa Medical College, Goa.
3. Maharashtra	<ol style="list-style-type: none"> 1. Govt. Medical Vollege, Nagpur, 2. B.J. Medical College, Pune, 3. Govt. Medical College, Aurangabad, 4. District Hospital, Akola, 5. District Hospital, Nashik, 6. Govt. Medical College, Nanded, 7. J.J. Hospital, Mumbai, 8. District Hospital, Chandrapur,

	<ul style="list-style-type: none"> 9. Govt. Medical College, Yavatmal, 10. District Hospital, Beed, 11. Govt. Medical College, Kolhapur, 12. Govt. Medical College, Dhule, 13. K.E.M. Hospital, Mumbai, 14. Sion Hospital, Mumbai, 15. District Hospital, Thane.
4. Gujarat	<ul style="list-style-type: none"> 1. N.H. Municipal Med. College, Ahmedabad, 2. Govt. Medical College, Vadodara, 3. Govt. Medical College, Surat, 4. Municipal Medical College, Surat, 5. M.P. Shah Medical College, Jamnagar, 6. Govt. Medical College, Rajkot, 7. Govt. Medical College, Bhavnagar, 8. General Hospital, Palanpur, 9. General Hospital, Dahod, 10. General Hospital, Bhuj.
5. Madhya Pradesh	<ul style="list-style-type: none"> 1. Gandhi Medical College, Bhopal, 2. G.R. Medical College, Gwalior, 3. S.S. Medical College, Rewa, 4. N. S.C.B Medical college Jabbalpur, 5. M.G.M. Medical College, Indore.
6. Haryana	<ul style="list-style-type: none"> 1. B.K. Hospital, Faridabad, 2. General Hospital, Ambala, 3. State Bacteriological Laboratory, Karnal, 4. General Hospital, Gurgaon, 5. General Hospital, Panchkula.
7. Delhi	<ul style="list-style-type: none"> 1. Swami Daya Nand Hospital, Shahadra, Delhi, 2. Raja Harish Chand Hospital, Narela, Delhi, 3. Hindu Rao Hospital, Delhi, 4. Sanjay Gandhi Memorial Hospital, Mangol Puri, Delhi, 5. BSA Hospital, Rohini, Delhi, 6. Safdarjung Hospital, New Delhi, 7. Malviya Nagar Hospital, Malviya Nagar, Delhi, 8. SVB Patel Hospital Patel Nagar, New Delhi, 9. ABG Hospital, Moti Nagar, Delhi, 10. Ram Manohar Lohia Hospital, New Delhi, 11. Lok Nayak Hospital, Jawahar Lal Nehru Marg, Delhi, 12. Deen Dayal Upadhyay Hospital, Hari Nagar, Delhi, 13. GTB Hospital, Dilshad Garden, Delhi,

7. Delhi	<p>14. Chacha Nehru Children Hospital, Geeta Colony, Delhi, 15. Lal Bahadur Shastri Hospital, Khichirpur, Delhi, 16. Maharishi Balmiki Hospital, Pooth Khurd, Delhi, 17. Dr. Hedgewar Arogya Sansthan, Karkardooma, Delhi, 18. Lady Hardinge Medical College and Smt. Sucheeta Kriplani, New Delhi, Hospital, Panchkuin Road, New Delhi, 19. Army Base Hospital, New Delhi, 20. Agersen Sen Jain Hospital, 21. Guru Govind Singh Govt.Hospital, Raghuvir Ngr, Delhi, 22. Babu Jagjivan Ram Memorial Hosp., Jahangirpuri, Delhi 23. Bhagwan Mahavir Hospital, Pitampura, Delhi, 24. Shastri Park Hospital, Delhi, 25. N.C. Joshi Memorial Hospital, Karolbagh, New Delhi, 26. Kasturbha Hospital, Near Jama Masjid, Delhi, 27. Aruna Asaf Ali Hospital, Rajpur Road, Delhi, 28. NDMC Charak Palika Hospital, Moti Bagh, New Delhi, 29. Rao Tula Ram Memorial Hospital, Jaffarpur, Delhi, 30. G.B. Pant Hospital, Jawahar Lal Nehru Marg, Delhi,</p>
8 . Punjab	1. Civil Hospital, Ludhiyana.
9. Rajasthan	<p>1. S.M.S. Hospital, 2. J.K. Lone Hospital, 3. Umaid Hospital, Jodhpur, 4. SMDM, Jaipur, 5. M.B. Hospital, Kota, 6. S.P. Medical College, Bikaner, 7. R.N.T. Medical College, Udaipur, 8. J.L.N. Medical College, Ajmer.</p>
10. Kerala	<p>1. Govt. Medical College, Kozhikode, 2. Medical College, Kottayam, 3. Medical college, Thiruvanthapuram, 4. Public Health lab, Thiruvanthapuram, 5. District Hospital, Kollam, 6. THQHThodupuzha, Dist. Idukki, 7. Public Health lab. Ernakulam, 8. District Hospital, Palakkad, 9. District Hospital, Manjeri, Malappuram, 10. District Hospital, Mananthavady, Wyanad,</p>
11. West Bengal	<p>1. Burdwan Medical College Hospital. 2. School of Tropical Medicine, Calcutta</p>
	1. Central Laboratory (Hqrs), Bangalore

12. Karnataka	<ol style="list-style-type: none"> 2. Virus Giagnostic Laboratory, Shimoga 3. Vijay Nagar Institute of Medical Science, Bellary 4. District Surveillance Unit, SNR hospital, Kollar 5. District Surveillance Unit, Belgaum 6. District Surveillance Unit, Mangalore, D Kanada 7. NIV, Pune, Field Unit, Bangalore
13. Tamil Nadu	<ol style="list-style-type: none"> 1. Kanniyakumari Medical College, 2. Tirunelveli Medical College, 3. Thoothukudi Medical College, 4. Thanjavur Medical College, 5. Mohan Kumaramangalam Medical College, Salem, 6. Coimbatore Medical College, 7. K.A.P.Viswanathan Medical College, Trichy, 8. Theni Medical College, 9. Chengalpattu Medical College, 10. Madurai Medical College, 11. Vellore Medical College, 12. Madras Medical College, 13. Institute of Vector Control and Zoonoses, Hosur,
14. Bihar	<ol style="list-style-type: none"> 1. Patna Medical College & Hospital.
15. Uttar Pradesh	<ol style="list-style-type: none"> 1. Regional Laboratory Swasthya Bhawan, Lucknow, 2. District Hospital, Ghaziabad, 3. L.L.R.M., Medical College, Meerut, 4. M.L.B. Medical College, Jhansi, 5. M.L.N., Medical College, Allahabad, 6. Institute of Medical Sciences, B.H.U., Varanasi, 7. S.N., Medical College, Agra, 8. G.S.B.M., Medical College, Kanpur, 9. K.G.M.U., Lucknow, 10. Authority Hospital Noida.
16. Orissa	<ol style="list-style-type: none"> 1. S.C.B. Medical College, Cuttak, 2. V.S.S. Medical College, Burla, Sambalpur, 3. MKCG, Medical College, Berhampur, Ganjam.
17. A & N Islands	<ol style="list-style-type: none"> 1. G.B. Pant Hospital, Port Blair.
18. Lakshyadweep	<ol style="list-style-type: none"> 1. Indira Gandhi Hospital, Kavaratti.
19. Manipur	<ol style="list-style-type: none"> 1. Regional Institute of Medical Sciences, Imphal.
20. Pondicherry	<ol style="list-style-type: none"> 1. JIPMER, Pondicherry, 2. General Hospital, Pondicherry

LIST OF THE APEX REFERRAL LABORATORIES

1. National Institute of Virology (ICMR), Pune.
2. National Institute of Communicable Diseases, Delhi.
3. National Institute of Mental Health & Neuro-Sciences, Bangalore.
4. Sanjay Gandhi Post-Graduate Institute of Medical Sciences, Lucknow.
5. Post- Graduate Institute of Medical Sciences, Chandigarh.
6. All India Institute of Medical Sciences, New Delhi.
7. ICMR Virus Unit, Kolkata.
8. Regional Medical Research Centre (ICMR), Dibrugarh, Assam.
9. King Institute of Preventive Medicine, Chennai.
10. Institute of Preventive Medicine, Hyderabad.
11. B J Medical College, Ahmedabad.
12. Kerala State Institute of Virology and Infections Disease, Alappuzha.
13. Defence Research Development and Establishment (DRDE) Gwalior, Madhya Pradesh.

NATIONAL VECTOR BORNE DISEASE CONTROL PROGRAMME

Proforma for line listing* of Suspected / Clinically Diagnosed Dengue cases at the regional /District Sentinel Centre

State : **Sentinel centre :** **Date :**

Sl. No.	Name of the Patient & Address & Telephone No. if any	Age/Sex	Date of onset of fever	Clinical manifestations (give numbers as indicated in the foot note)	Laboratory Investigations			IgM capture ELISA Test (+ ve or - ve)	Remarks
					Total WBC	Platelet count	Haematocrit count		

31 Foot Note:

Sign and symptoms of DHF/DSS (please fill the number in the column for clinical manifestations)

1	Positive tourniquet test	2	Petechiae, ecchymosis or purpura	3	Bleeding from mucosa, injection site or any other site (specify)
4	Haematemesis or melena	5	Thrombocytopaenia	6	Evidence of plasma leakage
7	Signs of circulatory failure	8	Rash	9	Retro-orbital pain
10	Others (please specify)	line listing should be maintained at the sentinel centre and copy sent to higher authorities (district VBD control officer) on day-to-day basis			

Name & Designation & Signature

LAB REQUISITION FORM

State / District..... Regn. No.
 PHC/Name of Institute
 Name of the patient Age/Sex.....
 Date of admission
 Addresss
 Local
 Permanent
 Telephone No.
 Clinical findings
 Fever Duration Days
 Any other finding
 Date of collection of sample

Nature of Sample

Tick the box

Serum

Whole Blood

Name and Signature of MO.....

Results

Patient ID.....

Patient of Name.....

Date of collection.....Date of reporting.....

Tick the box

Test type	Positive	Negative
IgM Mac ELISA		
IgG Paired Sera		
RDT		

Name and signature of the Investigator

References (for further information)

- (1) Suchitra Nimmannitya: Clinical Manifestations of DF/DHF - WHO Regional Publication No. 22, Monograph on Dengue/DHF, pp 48-54, WHO/SEARO, New Delhi.
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- (5) Prevention and Control of Dengue and Dengue Haemorrhagic Fever Comprehensive Guidelines WHO Regional Publications SEARO No. 29, New Delhi, 1999 .
- (6) Long Term Action Plan for prevention and control of Dengue and Chikungunya : Directorate of National Vector Borne Disease Control Programme, (Dte. General of Health Services), Ministry of Health and Family Welfare, Govt of India, 2007.