Medical Officers' Handbook for Clinical Management of Dengue, AES/JE and Malaria

2024

Government of West Bengal
Department of Health & Family Welfare
PH & CD Branch
Swasthya Bhawan, Salt Lake, Kolkata-700091

Dr. Siddhartha Niyogi
Director of Health Services
Department of Health & Family Welfare
Government of West Bengal

Ref. No. .....

Message

Date ...10/05/2024...

Dengue and Malaria are two important Vector Borne Diseases which result in substantive numbers of morbidity & mortalityin India as well as in West Bengal. Timely diagnosis and proper intervention can save precious lives of patients infected by these diseases. In recent years, surge of dengue incidence in the rural parts, especially the peri-urban areas have been seen to take over the urban localities, necessitating the need to have management facilities even in the peripheral health units.

Acute Encephalitic Syndrome (AES) is also a group of fatal diseases, of which JE (Japanese Encephalitis) is considered to be a subset. JE, although not very common in our State, is a disease of high disability and mortality rates.

I am very glad to announce that the Medical Officers' Handbook on "Clinical Management of Dengue and Malaria" (older version) is now fine-tuned with recent inputs from experts in 2024. I think, this Handbook will be very helpful for the Medical Officers/ Clinicians to treat the cases in a uniform way both in Government & Private sectors.

A section on diagnosis & management of AES/JE is also added to cover up another important area of felt need of the frontline MO-s.

I appreciate the efforts of the Director Public Health, the Public Health & Communicable Diseases Branch, the Faculties of the Medical Colleges, and the State Coordinator, WHO (NTD) who have contributed a lot in updating the materials.

Doctors across all sectors are requested to follow the guidelines laid down in this book.

10.05.24

Director of Health Services
Department of Health & Family Welfare

Swasthya Bhavan, GN-29, Sector-V, Salt Lake City, Kolkata - 700 091
Phone : (033) 2357 7903 ; Fax : (033) 2357 7904 E-mail : dhswestbengal@gmail.com, dhs@wbhealth.gov.in

Prof. (Dr.) Kaustav Nayek
DCH, MD (Paed) FIAP
Director of Medical Education
Department of Health & Family Welfare
Government of West Bengal

Swasthya Bhaban
GN-29, Sector-V,
Salt Lake City, Kolkata - 700 091
Tel : +91 33 2333 0407
E-mail : dme.wbhealth@gmail.com

No. DME/Spl. Corresp/2024/70 Date : 10/05/2024

Message

This must be emphasized that this updated Medical Officers' Handbook on "Clinical Management of Dengue, Malaria & AES/JE" serves not only as a ready reference, but also provides the treating Physicians a working principle and uniform guidelines for early diagnosis and management of Dengue and Malaria which in some cases are not readily available in text books. Diagnosis & management of AES/JE is also added to cover up another important area. The discourse on certain special situations and controversies would help allay the confusion regarding treatment decisions the Medical Officers are sometimes faced with.

While fine tuning the older Handbook, inputs have been taken from subject experts and synchronization has been made with the existing standard guidelines.

This Handbook is a synergy of the PH & CD Branch of the Directorate, Faculties of different Medical Collages and domain experts of the private health sector. Lots of support has also come from the NTD Division of WHO.

I sincerely thank all who are behind the publication of this valuable Handbook. It would be our great pleasure if the SOPs and guidelines come to be of material help for the doctors rendering treatment at the forefront.

10/5/24

Director of Medical Education
Department of Health & Family Welfare

Foreword

In West Bengal, vector borne diseases (VBD) are a challenge in the public field of health and a substantial proportion of the VBDs are contributed by Dengue and Malaria. In recent years, beside urban locality, surge of dengue incidence was noticed also in the rural parts, especially the periurban areas. Though the case fatality rate in our state is very low, it may go up if emphasis I not given on early detection and proper management of cases,including the complication. Malaria also poses a threat nowadays by appearing in inconspicuous presentations and even vivax malaria presenting in complicated forms. So, early identification of sever malaria and averting death are the concern. Acute Encephalitis Syndrome (AES), although it is not rampant in the state, is recognized as a grave disease. Japanese Encephalitis (JE), a subset of AES, has been declining in last few years owing to a successful roll-out of the vaccination programme. However, methodical case management remains a strategy for the reduction of its morbidity & mortality.

To facilitate and bring uniformity in diagnosis & treatment of dengue and malaria, an effort was made to sensitize the doctors of govt. and private facilities through "Medical Officers' Handbook for Clinical Management of Dengue & Malaria" issued by the Health & Family Welfare Department in 2020.

Following wide usage of the Handbook in the health care system, it was further perceived that the guidelines should be more elaborate in certain aspects of the disease and its management. It was made out that focus on some thrust areas (e.g., early detection of compensated shock etc.) and more details about some special situations (e.g.,dengue wih vital organ involvement, malaria in severe forms etc.) will further helpful for the doctors in the practical field.

In view of the above, the previous handbook was updated and modified with inputs of eminent experts of different medical specialties from government and non-government sectors. A section on diagnosis and management of AES/JE has also been added.

With sincere thanks we remember the valuable contributions that were received from the following to prepare the 2020 version of the Handbook:

- Prof. Sibarjun Ghosh, Former Head, Paed Medicine, Medical College, Kolkata
- Prof. Bibhuti Saha, then Head, Dept. of Tropical Medicine, CSTM
- Dr. Subhash Todi, Critical Care Specialist, Kolkata
- Prof. Jyotirmoy Pal, then at Dept. of Medicine,RG Kar Medical College, Kol.

- Prof. Soumitra Ghosh, then at Dept. of Medicine, IPGMER, Kolkata
- Prof. Arunangshu Talukdar, Dept. of Medicine, Medical College, Kolkata
- Prof. Bhaswasti Bandyopadhyay, then Head, Virology Unit, CSTM
- Dr. Deb Kishore Gupta, Microbiologist, Kolkata
- Dr. Chandrashish Chakravarty, Critical Care Specialist, Kolkata
- Prof. Ramprasad Dey, Dept. of Gynae & Obs, Chittaranjan Seva Sadan, Kolkata
- Dr. Mihir Sarkar, then Assoc. Prof, Paed Medicine, Medical College, Kolkata
- Dr. Ritabrata Kundu, Paediatric Care Specialist, Kolkata
- Dr. Pritam Roy, State Coordinator (NTD), WHO

Now, while drafting the modified version of 2023, active inputs were received from:

- Prof. Bibhuti Saha, Head, Dept. of Infectious Diseases, CSTM
- Prof. Santasil Pain, Dept. of Medicine, IPGMER, Kolkata
- Prof. Jyotirmoy Pal, Dept. of Medicine, COM & Sagar Datta Hospital
- Prof. Mihir Sarkar, Dept. of Paediatric Medicine, Medical College, Kolkata
- Dr. Sayan Chakrabarty, Infectious Disease Specialist, Kolkata
- Dr. Yogiraj Roy, Assoc. Prof, Dept. of Infectious Diseases, IPGMER, Kolkata
- Dr. Soumendranath Halder, Assoc. Prof, Dept. of Tropical Medicine, CSTM
- Dr. Ayan Chakrabarty, Assoc. Prof, Dept. of Infectious Diseases, IPGMER, Kolkata has kindly revised the Malaria Case Management section of the book.

Contributions from all the above-named Experts have enriched the clinical aide and made it more befitting for the present day need of the practitioners. The Senior Residents and Post Graduate Trainees of the Dept. of Infectious Diseases, Calcutta STM and the Office of the State Coordinator, Neglected Tropical Diseases, WHO have helped a lot in the clinical discourse process to develop the current version. Dr. Prosun Goswami, Dr. Subhajyoti De & Dr. Mita Basu (Public Health Specialist) under H&FW Department have done the editing to give the book its final shape.

We hope, with the help of this handbook, there will be further improvement of quality of management of Dengue, Malaria and AES, and many lives will be saved in future.

State Programme Officer NVBDCP

Government of West Bengal

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DENGUE

Introduction

Dengue is a major public health concerns globally, a common cause of illness seen in primary care settings in tropical and subtropical countries. It is endemic in more than 100 countries of Africa, America, Eastern Mediterranean, South-East Asia and Western Pacific. It is the most rapidly spreading mosquito- borne viral disease of mankind, with a 30-fold increase in global incidence over the last five decades. 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.

Every year, during the period July - November, an upsurge in the cases of dengue/DHF has been observed in India. NVBDCP reported: 44585, 193245 and 233251 laboratory confirmed cases in 2020, 2021 and 2022 respectively. As per NVBDCP Report:

Overall estimated Prevalence of lab-confirmed Dengue infection among clinically suspect cases	**38.3%**
Pooled estimate of Sero-prevalence in general population	**56.9%**
Case fatality	**1.3%**
Proportion of Primary & secondary Dengue infection among lab confirmed cases	**42.9: 57.1**
Distribution of predominant and co-circulating DENV serotypes	In India, all serotypes are circulating (**DENV-2 & DENV- 3 most common).** In West Bengal, **DENV-2 & 3 are most common in the Southern part and DENV-2 in the Northern part (2022)**

The disease has a seasonal pattern; the cases peak after the monsoons. It is transmitted by *Aedes aegypti* and *Aedes albopictus*. Literature shows that case fatality in Dengue can be minimized by early treatment attention. Medical Officers play a pivotal role in the early recognition and management of dengue fever when patients progress through the different phases of illness.

Dengue Virus

The agent of dengue, dengue viruses, is categorized under the genus Flaviviridae. Dengue virus is spherical in shape. Its diameter is approximately 50 nm. This virus is composed of the following:

- **Nucleocapsid**- It is composed of following:
  1. Viral genome
  2. Capsid protein (C)
- **Viral envelope**- It surrounds the nucleocapsid. It is composed of lipid bilayer. Throughout the lipid bilayer, two types of viral proteins are present. These are envelope (E) protein and membrane (M) protein. ***These two proteins are responsible for controlling the entry of virus into the human cell.***

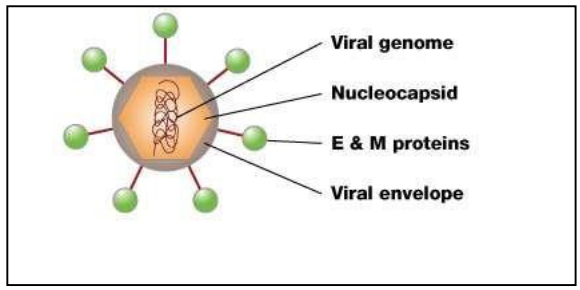


Fig 1: Structure of dengue virus

Dengue virus genome is single stranded RNA, called positive sense RNA-because it can be directly translated into protein. Viral genome is a translated single chain polypeptide which the cut into ten (10) proteins. Each protein is being encoded by a gene. These are:

Structural proteins: Capsid protein (C), Membrane protein (M), Envelope protein (E)

Seven non-structural proteins: NS1, NS2A, NS2B, NS3, NS4A, NS4B, NS5

The non-structural proteins are responsible for viral replication and viral assembly. 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 is used for diagnosis of the infection.**

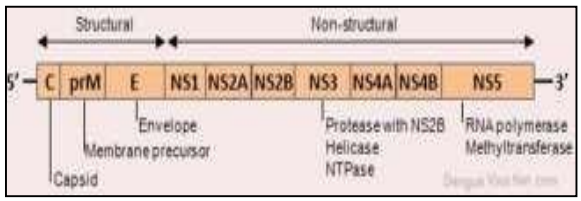


Fig 2: Genomic structure of dengue virus

Pathogenesis of Dengue fever

The pathogenesis of dengue involves a complex interaction between virus and host factors. After the DENV enters the body through the bite of the Aedes aegypti / albopictus mosquito, it proliferates in the monocyte-phagocyte system and enters the circulation, causing the first viremia, which then colonizes the reticuloendothelial system and lymphoid tissue, replicates to a certain extent in peripheral blood mononuclear cells, macrophages in tissues, and Kupffer cells in the liver, and enters the circulation again, causing a second viremia.

The DENV binds to specific antibodies produced by the body to form immune complexes that activate the complement and coagulation systems, leading to increased vascular permeability, vasodilation, congestion, extravasation of plasma proteins, and tangible blood components, causing pathophysiological changes such as hemoconcentration, hemorrhage, and shock.

Recent studies have shown that the cellular immune effect of DENV infection and the various cytokines produced mediate the immune response and affect the progression of the disease and its outcome.

The virus also inhibits leukocyte and platelet production in the bone marrow, leading to leukopenia and thrombocytopenia. The mechanism of hemorrhage may be thrombocytopenia and its dysfunction and depletion of coagulation factors.

The pathogenesis of severe dengue has not yet been fully elucidated because of the lack of ideal animal models. All four serotypes of the DENV are capable of causing severe dengue. Host and viral factors, such as ADE, cytokine storm, and viral virulence variation due to secondary DENV infection play an essential role in the pathogenesis of severe dengue.

The immune system plays a key role in disease pathogenesis. Various mechanisms of severe disease have been suggested, including:

- Antibody-dependent enhancement or ADE,
- T-cell mediated immunopathology,
- Complement activation by virus-antibody complexes and
- Cytokine abundance.

Dengue infected monocytes act as antigen presenting cells (APCs) to induce release of lymphokines and other factors from activated T cells. Tumour Necrosis Factor-α, Interleukin (IL) IL-1b, IL-2, IL-6, IL-8, Interferon gamma (IFNγ), RANTES etc. are the cytokines that are released from these cells. These cytokines along with complement breakdown products (C3a, C5a) activated in DHF/DSS increases vascular permeability of vascular endothelial cells leading to DSS. Antibody dependent enhancement and inappropriate memory T-cell response are central to the pathogenesis of DHF/DSS.

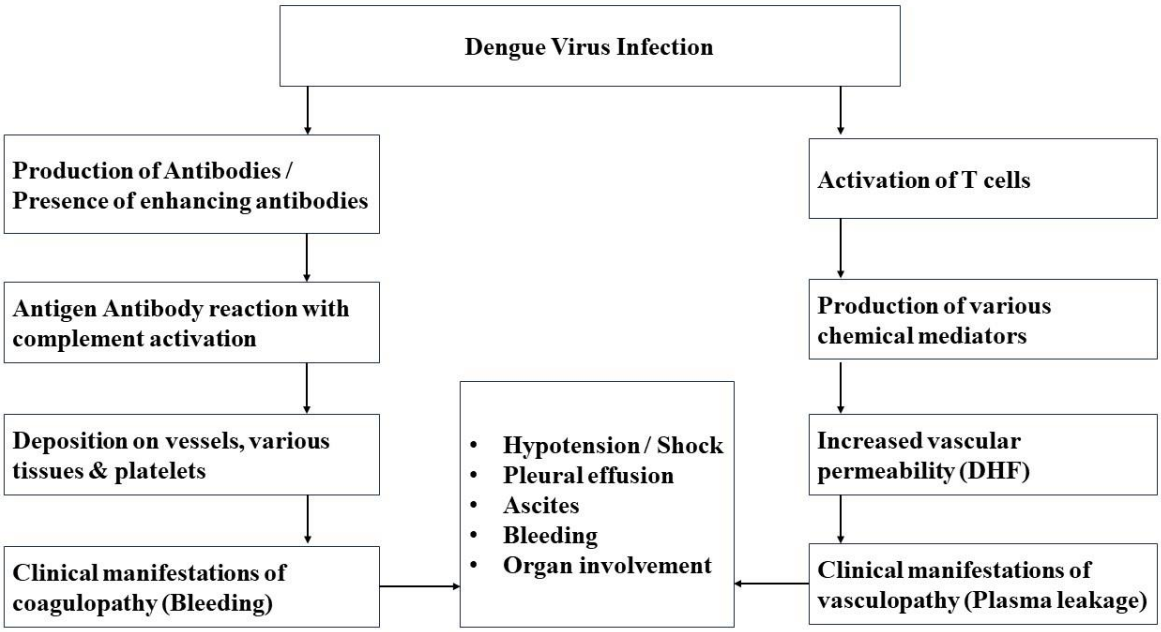


Chart 1: Dengue infection pathogenesis

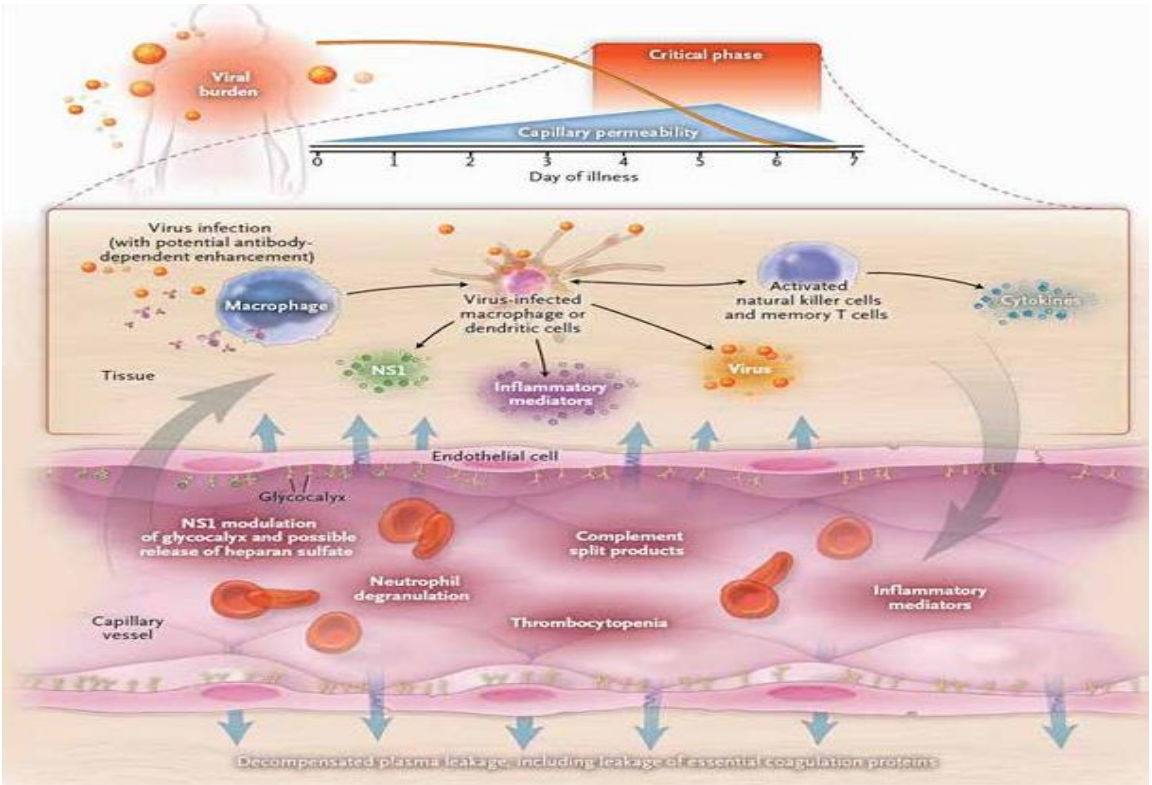


Figure 3 - Pathophysiology of dengue infection

Dengue: Review article, Simmons CP, Jeremy J. Farrar JJ, Vinh Chau NV, Wills B, N Engl J Med: April, 2012: 366: pp-1427)

Causes of Bleeding in Dengue Syndrome:

Thrombocytopenia

- Platelet dysfunction and Sequestration of platelet

Coagulopathy

- Prothrombin complex Deficiency secondary to liver involvement
- Endothelial injury
- DIC and prolonged APTT
- Decreased fibrinogen level
- Increased level of fibrinogen degradation product (FDP)
- Increase level of D-Dimer
- Consumptive coagulopathy (activation of mononuclear phagocytes)

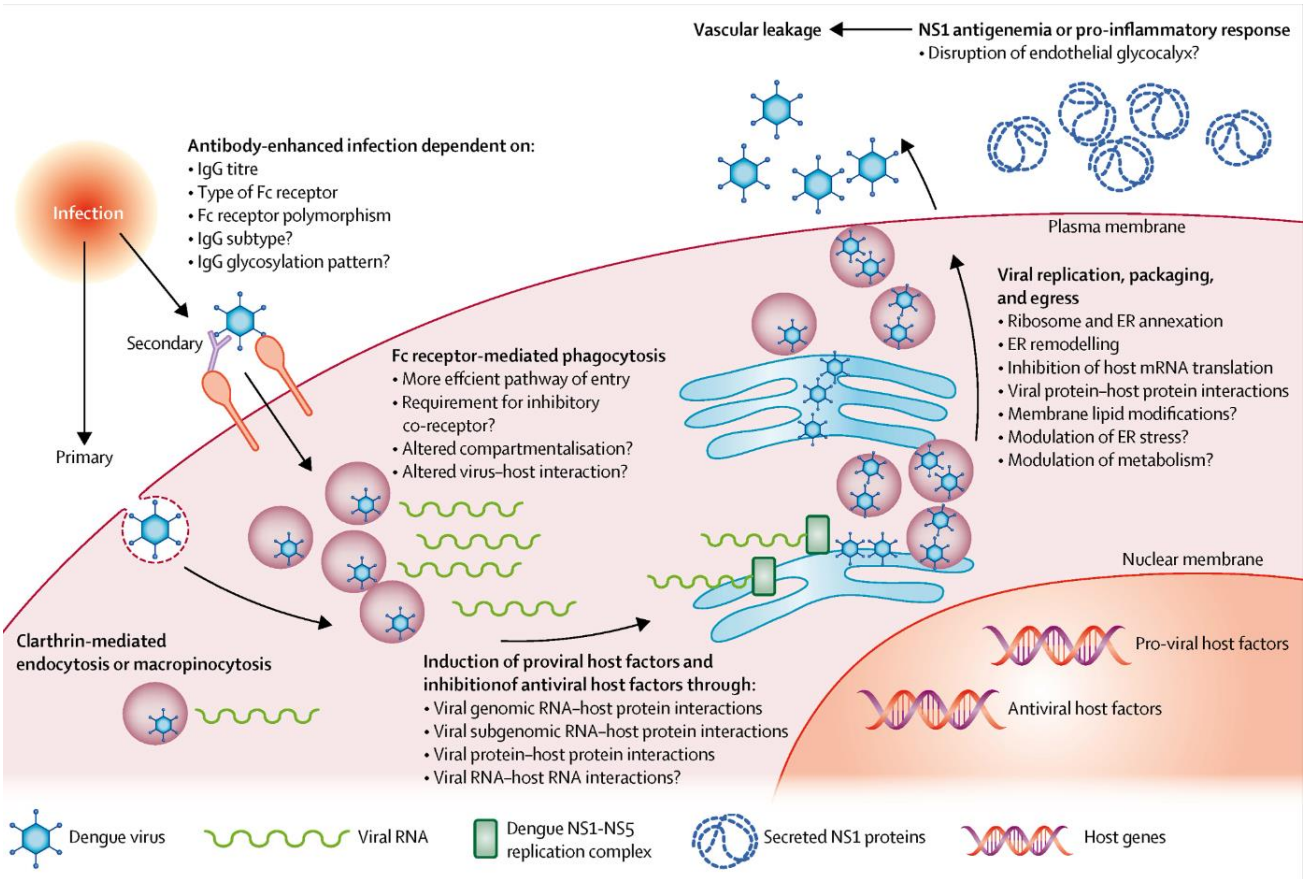


Figure 4 - Immunology of dengue infection

Dengue: Review article, Simmons CP, Jeremy J. Farrar JJ, Vinh Chau NV,Wills B, N Engl J Med: April, 2012: 366:pp-1427)

There are four dengue virus serotypes which are designated as DENV-1, DENV-2, DENV-3 and DENV- 4. The fifth variant DENV-5, not yet reported in India, has been circulating among non-human primates in the forests of South East Asia with occasional spillover into humans. These serotypes can co-exist in the endemic areas because the immunity to one serotype does not afford protection from the infection by a heterotopous serotype. 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 that virus serotype. The ability of all DENV serotypes to utilize pre-existing heterotypic flavivirus antibody to enhance antigen antibody reaction, is a unique feature of DENV and considered to be the basis of complications in Secondary Dengue**. Individual variations occur in antibody responses to the dengue virus. **Secondary infections are associated with elevated risks of severe disease outcomes.**

Understanding dengue fever / illness

- Dengue viruses cause symptomatic infections or asymptomatic seroconversion. Patients with asymptomatic infection are viremic and thus may be a source of infection.
- Symptomatic dengue infection is a systemic and dynamic disease. It has a wide clinical spectrum, which includes both severe and non-severe clinical manifestations.
- **The incubation period lasts for 5 to 7 days** and the onset of the illness is abrupt.
- Common presenting symptoms include **high-grade fever, headache, retro-orbital pain, myalgia, arthralgia, nausea, vomiting and rash**. The symptoms usually last for 2-7days.
- As the symptoms are relatively nonspecific in early stages, other differential diagnoses need to be considered in the first 72 hours. Inpatients with moderate-to-severe disease, the course of the illness follows three phases: **febrile, critical and recovery**. **The severity of the disease becomes apparent during defervescence** (transition from the febrile to the afebrile phase). This often coincides with the onset of the critical phase, usually occurs on days 3 to 8 of illness. The critical phase is distinguished by the pathophysiological phenomenon of increased capillary permeability, which lasts approximately for24 to 48 hours and is **more common in secondary dengue infections**. This phase is followed by the recovery phase. The key to achieve a good clinical outcome is to have an understanding of the different phases of the disease and be alert to the clinical problems that could arise during these phases.

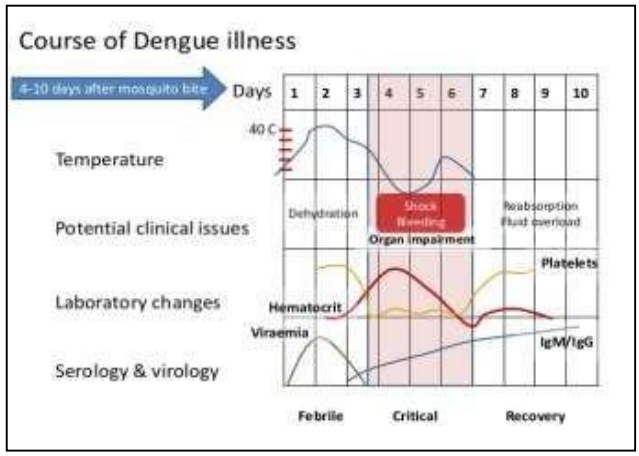


Figure 5: Course of Dengue Illness

KEY POINTS:

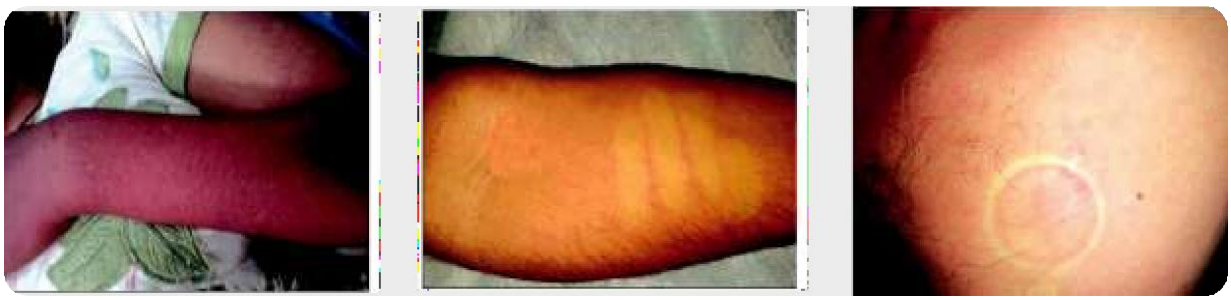
- Common presenting symptoms of dengue fever include high-grade fever, headache, retro- orbital pain, myalgia, arthralgia, nausea, vomiting and rash.
- The symptoms usually last for 2-7days.
- In patients with moderate-to-severe disease, the course of the illness follows three phases**: febrile, critical** and **recovery**.

Febrile phase of Dengue

Clinical Features:

This phase usually lasts for 2-7 days and high-grade fever develops suddenly. In this phase, it may be difficult to distinguish dengue clinically from other febrile diseases. DF is accompanied by non-specific symptoms like **facial flushing, erythematous skin rash, headache, retro-orbital pain, photophobia, generalized malaise, severe myalgia and arthralgia**, occasional sore throat, pharyngeal and conjunctival injection, anorexia, nausea, vomiting and postural dizziness. Acute and progressive weakness causes loss of ability to perform daily activities and results in anxiety or depressive mood. Mild hemorrhagic manifestation such as a petechiae and mucosal bleeding from nose (epistaxis) and gums may be seen during this phase. Easy bruising and bleeding at venepuncture sites may be present, but hematuria is rare. A ***positive tourniquet test*** in this phase indicates the increased probability of dengue. Massive bleeding like gastrointestinal bleeding and bleeding per vagina are relatively uncommon during this phase. Liver may be enlarged and tender during this phase.

The rash associated with measles and rubella has a particular distribution from the head to the trunk and extremities, but in dengue, the rash usually first appears on the trunk and later extends to the face and extremities.



Dengue patient with maculopapular rash

Finger impression on skin of a dengue patient

Rounded stethoscope impression on skin of a

Figure 6: Skin Manifestation of Dengue

****Tourniquet Test** is performed by inflating a blood pressure cuff to a point midway between the systolic and diastolic pressures for five minutes. The test is considered **positive when 10 or more petechiae per sq. inch** are observed. The test may be negative or only mildly positive in obese patients and during the phase of profound shock. Positive tourniquet test serves as an indicator of hemorrhagic tendency. The sensitivity of the test varies widely from as low as 0% to 57%, depending on the phase of illness when the test was done and how often the test was repeated, if negative. In addition, 5-21% of patients with dengue like illness had positive tourniquet test but subsequently have negative dengue serology. A recent study demonstrated that there was 95.3% positive predictive value if fever, positive tourniquet test, leucopenia / thrombocytopenia / hemoconcentration are used as screening criteria.

Critical phase of Dengue

Clinical Features:

KEY POINTS:

- Febrile or viraemia phase usually lasts for 2 to 7days.
- Headache, myalgia, arthralgia and retro-orbital pain are the frequently associated symptoms.
- Children with dengue more likely to report anorexia, nausea and vomiting
- Progressive decrease in white blood cell& platelet count +/- mild hemorrhagic manifestations should alert the physician about high probability of dengue.

The transition from febrile to afebrile usually phase takes place **after the day 3 to day 7 of onset of fever**. Patients having no increase in capillary permeability generally improve without going through the critical phase. Their appetite improves and they feel better. However, patients with increased capillary permeability, experience worsening of symptoms with the subsidence of high fever.

- Warning signs, which are mostly due to plasma leakage, usually precede the onset of shock and appear towards the end of the febrile phase.
- Pleural effusion and ascites may occur; usually clinically detectable only after an intravenous fluid therapy unless the plasma leakage is significant. It seems i.v. fluid is causing a harm here!!
- Hemorrhagic manifestations such as easy bruising and bleeding at venepuncture sites occur frequently.
- Shock occurs when a critical volume of plasma is lost through leakage. Some patients progress to the critical phase of shock before defervescence. In these patients, a rising hematocrit and rapid onset of thrombocytopenia or the warning signs indicate the onset of plasma leakage.
- Most patients with dengue having warning signs recover with intravenous rehydration, although some may deteriorate to severe dengue.

Warning signs in dengue fever

- Bleeding: epistaxis, scanty haemoptysis, hematemesis, gum bleeding, black coloured stools, excessive menstrual bleeding, dark-coloured urine or haematuria.
- Lethargy and/or restlessness
- Sudden behavioural changes
- Convulsions.
- Difficulty in breathing or palpitation or breathlessness.
- Persistent vomiting >3 times a day.
- Severe abdominal pain
- Postural hypotension - dizziness.
- Pale, cold clammy extremities.
- Not able to drink and no urine output for 4-6 h or urine output less than 0.5ml/kg/h.

Additional danger signs for clinicians

- Enlarged and/or tender liver
- Rising haematocrit together with rapid fall in platelet count.
- Metabolic acidosis.

KEY POINTS:

- Be vigilant about Warning Signs between days 3 and 7 of illness.
- Increased capillary permeability causing plasma leakage is the main pathophysiology.
- A rising hematocrit is the earliest sign of plasma leakage

The period of clinically significant plasma leakage usually lasts 24-48 h. The degree of hemoconcentration above the baseline hematocrit reflects the severity of plasma leakage; however, this can be masked by early intravenous fluid therapy.

- A rising HCT by ≥ 20% from the baseline (e.g., from HCT of 35% to 42%) is an objective evidence of plasma leakage.
- FREQUENCY OF TEST- - at least every 12 hours, or 6 hours if possible. If repeated boluses of IV fluid are required, HCT should be repeated as frequently as necessary to fine tune the fluid plan.
- In the absence of a baseline HCT level, a HCT value of >38% in female adults and children aged<12 years, and >42% in male adults should raise the suspicion of plasma leakage.

Recovery phase of Dengue

Clinical Features:

As the patient survives the 24 to 48 hours critical phase, a gradual reabsorption of extravascular compartment fluid takes place in the following 48 to 72 hours. During this time, patient's general well- being improves, appetite returns, gastrointestinal symptoms abate, hemodynamic status stabilizes and diuresis ensues. Some patients may exhibit a confluent erythematous or petechial rash with small areas of normal skin in between described as **"isles of white in the sea of red"**. Some may experience generalized pruritus. Bradycardia and electrocardiographic changes are common during this stage. The hematocrit stabilizes or may become lower due to the dilutional effect of reabsorbed fluid. The white blood cell count usually starts to rise soon after defervescence but the recovery of the platelet count is typically later than that of the white blood cell count. Respiratory distress from massive pleural effusion and ascites, pulmonary edema or congestive heart failure may occur during the critical and/or recovery phases if excessive intravenous fluids have been administered.

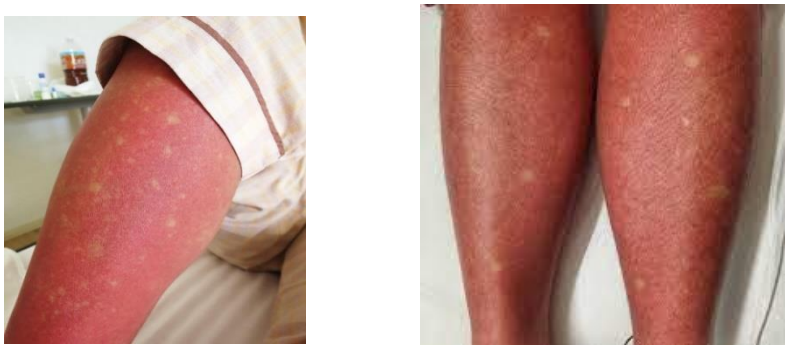


Figure 7: Skin Manifestation of Dengue infection

KEY POINTS:

- Gradual reabsorption of ECF & general wellbeing of the patient seen in this phase
- Hematocrit stabilizes or become lower
- Some patients may exhibit petechial rash

Table 1: Complication of Dengue infection

Phase	Complication
Febrile phase	Dehydration: Also, high fever may cause neurological disturbances and febrile seizures in young children
Critical phase	Shock from plasma leakage; severe hemorrhage and organ impairment
Recovery phase	Hypervolemia (only if intravenous fluid therapy has been excessive and/or has extended into this period) and acute pulmonary oedema

Shock in Dengue

It may take a few hours for patients to progress from warning signs to compensated shock and another few hours for compensated shock to progress to hypotensive shock, but only minutes from hypotensive shock to cardio-respiratory collapse.

Compensated shock:

- Systolic BP is normal but there are tachycardia & tachypnoea without increased effort.
- Extremities cold and capillary refill time (CRT) delayed (Normal value ≤ 2 seconds in adults)
- Pulse pressure is < 20 mm Hg.
- Hematocrit value is increased due to plasma leakage.

1. Normal SBP and/or Narrowed Pulse Pressure alongside Delayed CRT & Increased Hematocrit: Prompt action warranted

2. Prevention or Correction of Dehydration at the compensated shock stage avoids many of the dengue complications

Hypotensive shock:

Results from worsening of compensated shock.

- Increasing tachycardia and peripheral vasoconstriction.
- Not only are the extremities cold and cyanosed but the limbs become mottled, cold and clammy.
- Breathing becomes more rapid and increases in depth, a compensation for the metabolic acidosis (Kussmaul's breathing).
- Finally, there is decompensation, when both systolic and diastolic BPs decrease suddenly and dramatically.
- One key sign of this deterioration is a change in mental state as brain perfusion declines. However, children and young adults have been known to have a clear mental status even in profound shock.

Hypotension is a late finding and it signals an imminent total cardio-respiratory collapse and hence requires urgent intervention to prevent mortality.

Prolonged hypotensive shock and hypoxia lead to severe metabolic acidosis and multiple organ failure. **When major bleeding occurs, it is almost always associated with profound shock and can lead to multiple organ failure and advanced disseminated intravascular coagulation.** Massive bleeding may occur without prolonged shock in instances when **NSAID or corticosteroids have been taken**.

Acute liver and renal failure, encephalopathy and cardiomyopathy may be present in severe shock; or even in the absence of shock. **However, most deaths from dengue occur in patients with profound and prolonged shock resulting from plasma leakage and complicated by bleeding and/or fluid imbalance**.

Various presentations of Dengue

A majority of the dengue virus infected persons are asymptomatic but symptomatic patients may present with undifferentiated fever, non-severe and severe manifestation.

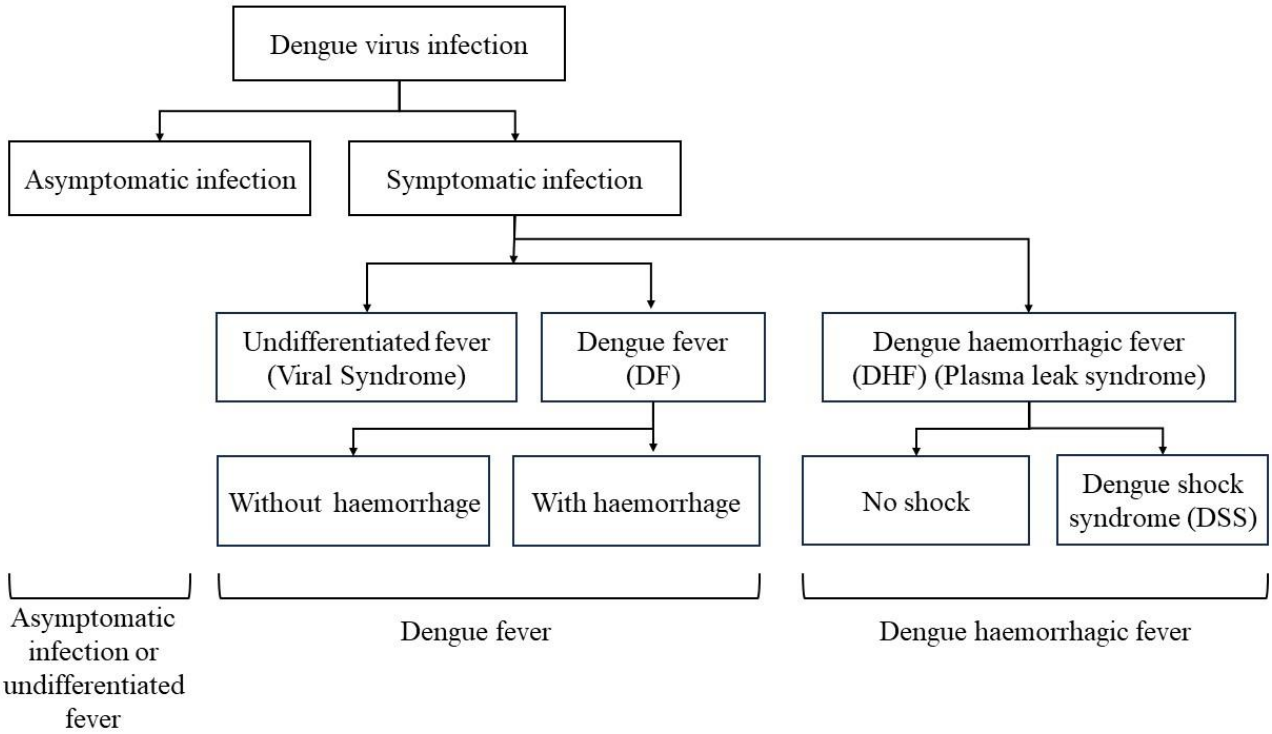


Chart 2: Spectrum of Dengue infection

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.

Dengue Fever (DF)

Clinical case definition:

Fever with any two (2) of the following:

- Nausea, vomiting
- Rash resembling measles
- Generalized aches (headache, retro-orbital pain, myalgias, arthralgias)
- Benign mucocutaneous bleeding (petechiae, positive tourniquet test, epistaxis, gingival bleeding)
- Leucopenia

Dengue Hemorrhagic Fever / Dengue Shock Syndrome (DHF/DSS)

DHF and DSS are aggravation of the pathological process of Dengue Fever (DF). They present with severe manifestations like plasma leakage, shock, bleeding and organ involvement.

Dengue Hemorrhagic Fever (DHF) has been divided into **four** grades based on –

- **Platelet count**
- **Hematocrit**
- **Evidence of capillary leakage**
- **Bleeding and hypotension**

The shock of DSS may be due to capillary leakage of plasma and/or haemorrhage. The haemorrhage may be overt (visible) or concealed.

Expanded Dengue Syndrome (EDS)

Patients with dengue illness can sometimes develop unusual manifestations such as involvement of liver, kidneys, brain or heart with or without evidence of fluid leakage and therefore do not necessarily fall into the category of DHF. These conditions are not so common and management is symptomatic. Such unusual manifestations may be associated with coinfections and comorbidities. However, these manifestations, if seen in DHF patients are mostly a result of prolonged shock leading to organ failure.

Table 2: Atypical Manifestation of Dengue

System	Unusual or Atypical Manifestation
Neurological	Febrile seizures in young children.
	Encephalopathy.
	Encephalitis/aseptic meningitis.
	Intracranial hemorrhage/thrombosis.
	Subdural effusions. Mononeuropathies/polyneuropathies/Guillain-Barre Syndrome. Transverse myelitis

Gastrointestinal	Hepatitis/fulminant hepatic failure. Acalculous cholecystitis. Acute pancreatitis.
	Hyperplasia of Peyer's patches. Acute parotitis.
Renal	Acute renal failure.
	Hemolytic uremic syndrome
Cardiac	Conduction abnormalities.
	Myocarditis, Pericarditis
Respiratory	Acute respiratory distress syndrome.
	Pulmonary hemorrhage.
Musculoskeletal	Myositis with raised creatine phosphokinase (CPK).
	Rhabdomyolysis
Lymphoreticular	Infection associated hemophagocytic syndrome (IAHS) or Hemophagocytic lymphohistiocytosis (HLH).
	Idiopathic thrombocytopenic purpura (ITP).
	Spontaneous splenic rupture.
	Lymph node infarction
Eye	Macular hemorrhage. Impaired visual acuity.
	Optic neuritis.
Others	Post-infectious fatigue syndrome, depression, hallucinations, psychosis, alopecia

Various risk factors associated with severe dengue fever

Age group: Infant, Young children, Pregnant women, old person

Comorbidities: Obesity, Hypertension, Diabetes mellitus, Immunocompromised persons, Haemolytic condition, Chronic liver or kidney disease & Hb-pathies such as sickle cell disease & autoimmune disease

Classification of Dengue Fever according to severity

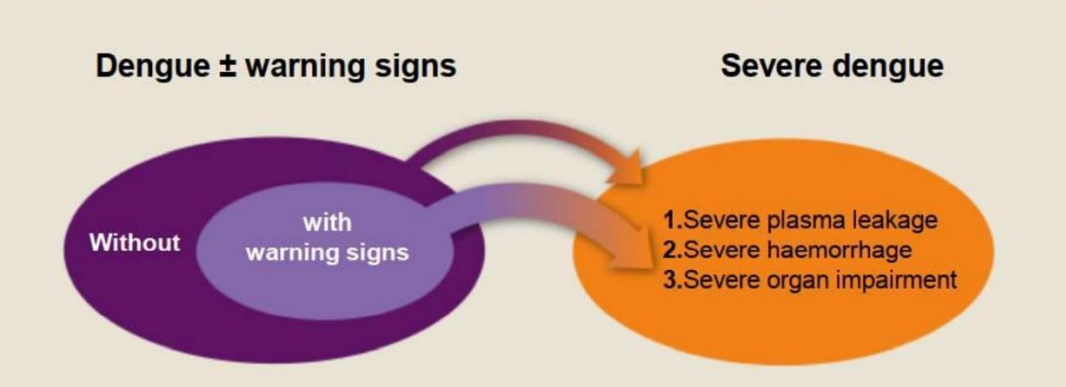


Table 3: Signs & Symptoms of Dengue infection (for classification)

Dengue without warning signs (Mild Dengue)	Fever + 2 of the following symptoms: • Nausea, vomiting • Rash resembling measles • Generalized aches (headache, retro-orbital pain, myalgias, arthralgias) • Benign mucocutaneous bleeding (petechiae, positive tourniquet test, epistaxis, gingival bleeding) • Leucopenia
Dengue with warning signs (Moderate Dengue)	Presence of at least one of these symptoms: • Intense abdominal pain • Persistent vomiting • Fluid accumulation (ascites, pleural effusion) • Mucosal bleeding • Hepatomegaly (> 2 cm) • Postural hypotension • Agitation or lethargy • Increasing haematocrit
Severe dengue	• Severe fluid accumulation (ascites, pleural effusion) with respiratory distress and/or shock • Severe mucocutaneous bleeding • Severe organ involvement (e.g.: transaminases > 1000 IU/litre, myocarditis, altered mental status)

Clinical evaluation of Dengue fever

Step 1: History taking

a. Date of onset of fever (date is preferable to the number of days of fever)
b. A history of dengue fever among households and neighbor, living in or recent travel to a dengue endemic region
c. History of chills, rash and facial flush
d. Retro-orbital headache, arthralgia, malaise
e. Persistent vomiting/diarrhea, pain abdomen
f. Reduced urine output, cold peripheries
g. Shortness of breath
h. Bleeding from any orifice, any bleeding spot on skin/mucosa
i. Profuse sweating, postural dizziness, blurring of vision
j. Yellowish discoloration of skin and mucosa, altered sensorium

Assess hydration status from history [These questions, though not specific to dengue, give a good indication of patient's hydration status and how well the patient copes with his illness]	**Ask 3 golden questions**
	Oral fluid intake-quantity and types of fluids
	Urine output-quantify in terms of frequency and estimated volume and time of most recent voiding
	Types of activities performed during this illness (e.g., can the patient go to school, work, market, etc.)

Other Relevant History	Other fluid losses-such as vomiting or diarrhea Presence of warning signs, particularly after the first 72 hours of fever
	Medications (including non-prescription or traditional medicine) in use List of medications and the time they were last taken
	Risk factors

Step 2: Clinical examination – Assessment & "Top Sheet" monitoring

Top sheet for Monitoring of Dengue/ Suspected Dengue Cases								
..... **Hospital** Patient Regn. No.-								
Name		Age (y/m)		Sex	M/ F/ O	Ward		Bed no.	
Parameters on admission: Admission date - ...../...../2022								
Fever since: _____(date)	Co-morbidity:		Bleeding: Y / N		Shock: Y / N		Tourniquet Test: Pos / Neg	

Lab test for Dengue: NS1 ELISA/ IgM ELISA Result – Positive/ Negative	Date of sample:	Date of test: .....

Body weight (kg)		Height (cm)		Ideal body wt, if obese (kg)		**Urine output: minm target** for 24 hrs (body wt x 12)	..... ml

Day-1 : Date-											**Sig. of BIC/ MO/SR**	
	6 am	10 am	4 pm	10 pm			10 am	4 pm	10 pm		M	
Pulse						Temp.					E	
BP						RR					**Sig. of SN**	
Urine (ml)					Total (ml)		Morn.	Eve.	Any other imp. finding		M	
Ur. scanty	Y / N	Y / N	Y / N	Y / N	.....	Pain abd.					E	
	Morning sample		Evening sample			L. motion					N	
PCV (Hct)						Vomiting					M:Sr I/C	
Platelet						Bleeding					E:Sr I/C	

Day-2 : Date-											**Sig. of BIC/ MO/SR**	
	6 am	10 am	4 pm	10 pm			10 am	4 pm	10 pm		M	
Pulse						Temp.					E	
BP						RR					**Sig. of SN**	
Urine (ml)					Total (ml)		Morn.	Eve.	Any other imp. finding		M	
Ur. scanty	Y / N	Y / N	Y / N	Y / N	.....	Pain abd.					E	
	Morning sample		Evening sample			L. motion					N	
PCV (Hct)						Vomiting					M:Sr I/C	
Platelet						Bleeding					E:Sr I/C	

Day-3 : Date-											**Sig. of BIC/ MO/SR**	
	6 am	10 am	4 pm	10 pm			10 am	4 pm	10 pm		M	
Pulse						Temp.					E	
BP						RR					**Sig. of SN**	
Urine (ml)					Total (ml)		Morn.	Eve.	Any other imp. finding		M	
Ur. scanty	Y / N	Y / N	Y / N	Y / N	.....	Pain abd.					E	
	Morning sample		Evening sample			L. motion					N	
PCV (Hct)						Vomiting					M:Sr I/C	
Platelet						Bleeding					E:Sr I/C	

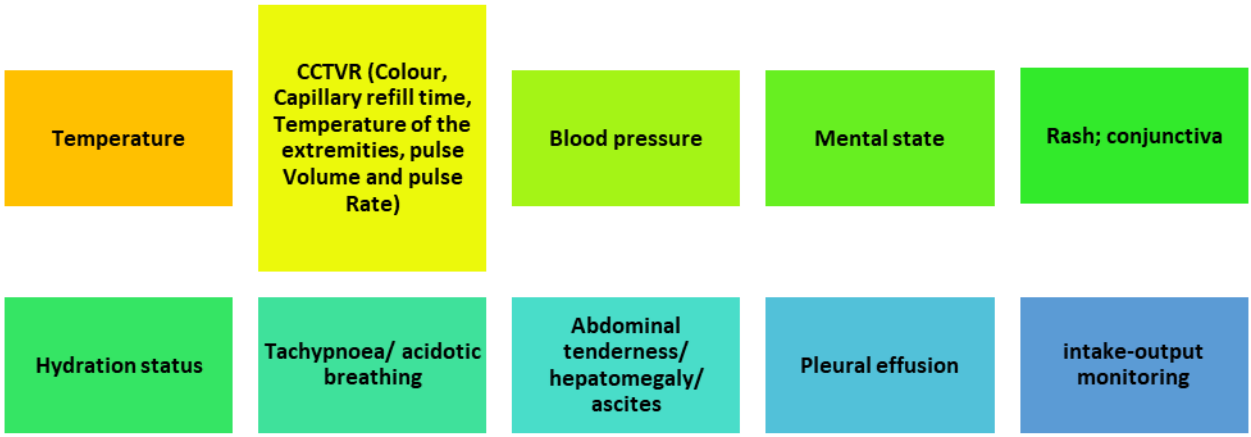
Day-4 : Date-											Sig. of BIC/ MO/SR	
	6 am	10 am	4 pm	10 pm			10 am	4 pm	10 pm		M	
Pulse						Temp.					E	
BP						RR					Sig. of SN	
Urine (ml)					Total (ml)		Morn.	Eve.	Any other imp. finding		M	
Ur. scanty	Y / N	Y / N	Y / N	Y / N	.....	Pain abd.					E	
	Morning sample		Evening sample			L. motion					N	
PCV (Hct)						Vomiting					M:Sr I/C	
Platelet						Bleeding					E:Sr I/C	

Day-5 : Date-											Sig. of BIC/ MO/SR	
	6 am	10 am	4 pm	10 pm			10 am	4 pm	10 pm		M	
Pulse						Temp.					E	
BP						RR					Sig. of SN	
Urine (ml)					Total (ml)		Morn.	Eve.	Any other imp. finding		M	
Ur. scanty	Y / N	Y / N	Y / N	Y / N	.....	Pain abd.					E	
	Morning sample		Evening sample			L. motion					N	
PCV (Hct)						Vomiting					M:Sr I/C	
Platelet						Bleeding					E:Sr I/C	

Day-6 : Date-											Sig. of BIC/ MO/SR	
	6 am	10 am	4 pm	10 pm			10 am	4 pm	10 pm		M	
Pulse						Temp.					E	
BP						RR					Sig. of SN	
Urine (ml)					Total (ml)		Morn.	Eve.	Any other imp. finding		M	
Ur. scanty	Y / N	Y / N	Y / N	Y / N	.....	Pain abd.					E	
	Morning sample		Evening sample			L. motion					N	
PCV (Hct)						Vomiting					M:Sr I/C	
Platelet						Bleeding					E:Sr I/C	

Day-7 : Date-											Sig. of BIC/ MO/SR	
	6 am	10 am	4 pm	10 pm			10 am	4 pm	10 pm		M	
Pulse						Temp.					E	
BP						RR					Sig. of SN	
Urine (ml)					Total (ml)		Morn.	Eve.	Any other imp. finding		M	
Ur. scanty	Y / N	Y / N	Y / N	Y / N	.....	Pain abd.					E	
	Morning sample		Evening sample			L. motion					N	
PCV (Hct)						Vomiting					M:Sr I/C	
Platelet						Bleeding					E:Sr I/C	

Step 2: Clinical examination – Assessment & "Top Sheet" monitoring



Observing clinical parameters for admitted dengue patient:

- Top Sheet to be maintained in I.P.D. for every dengue case and suspected dengue case.
- Urine output to be recorded (not eye estimation) in each shift and finally totaled for 24 hours. - Use means to measure urine. As Volume and frequency both has importance.

Importance of Top Sheet:

- MO, Staff Nurse and Sister in Charge to sign the Top Sheets.
- Top Sheet to be utilized
    - monitor the cases
    - identify cases at risk
    - to generate alert (call the Doctor).
- Doctors should see the Top Sheet during ward round.

Lab Investigation for Dengue Diagnosis and Management

A. For Dengue Confirmation:

Dengue diagnosis can be performed through Antigen based detection assays, detection of viral RNA by rRT PCR methods, virus isolation, and serological studies. **Serology is currently the most widely applied method in routine diagnosis.**

Dengue is said to be confirmed if any one of the ELISA-based antigen detection tests (NS1) and lgM capture ELISA (MAC-ELISA) is positive for Dengue.

For confirmation of dengue infection, Government of India (GOI) recommends use of ELISA-based antigen detection test (NS1) for diagnosing the cases from the 1st day of fever to 5th day. onwards and antibody detection test lgM capture ELISA (MAC-ELISA) for diagnosing the cases from 6th day of onset of disease.

From ***onset of Illness to 5 days*** of fever ⇩	From **6*th* *Day*** onwards ⇩
Virus detected in serum, plasma, circulating blood cells and tissues Virus isolation (up to 4th day) Nucleic Acid Detection (up to 4th day) **NS1 Antigen Detection** (up to 5th day)	**Antibody Detection** First antibody to appear –**IgM** Next to appear – IgG

IgM antibody may be detectable in blood till about 3 months of infection. Hence an IgM positive result should be interpreted with clinical correlation.

Presence of IgG antibody indicates past infection of dengue. It can persist lifelong. It has no role in diagnosis of current infection except in differentiation of secondary infection. Since a dengue case may be complicated irrespective of primary or secondary infection and the management does not essentially differ, the necessity of IgG testing should not be over stressed.

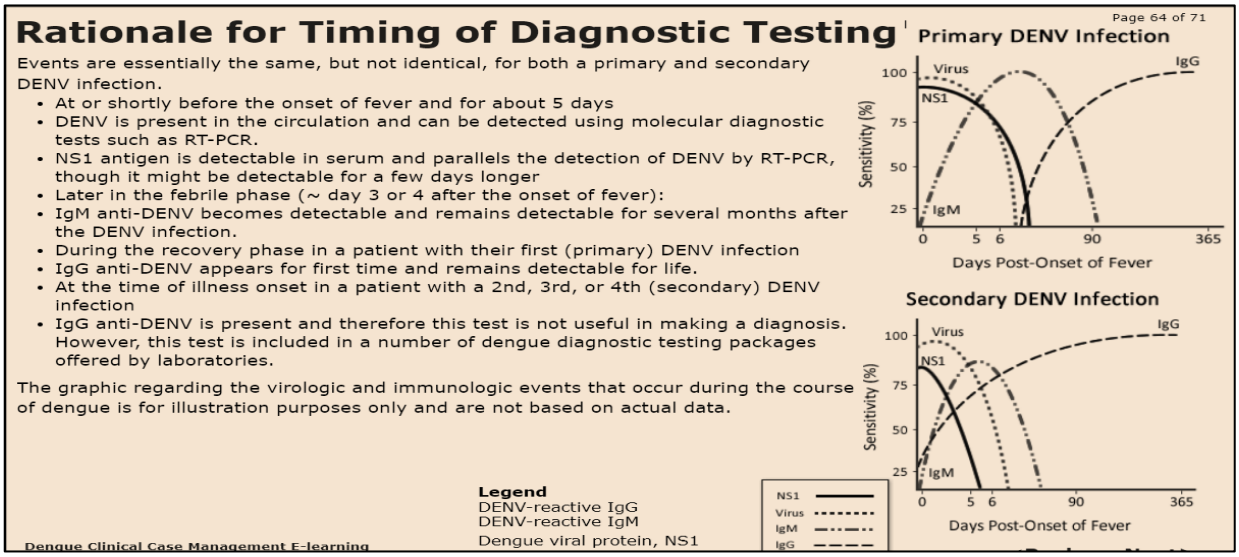


Figure 8: Timing of Dengue diagnostic testing

B. Laboratory Investigations for monitoring

1. First visit within 5 days – CBC (including WBC count, platelets), Haematocrit/ PCV

Baseline tests other than CBC in dengue

Additional baseline tests should be done in the following conditions:

(a) Patient having comorbidity
(b) Patient having warning sign(s)
(c) Preferably in all admitted dengue cases.
(d) These tests should be done during first consultation to get the baseline characteristics like Haematocrit and Complete blood count if the patient presented within 5days of fever. Follow up testing may be done on 1st afebrile day, but should be done daily once if DHF is suspected or warning signs are present.
(e) A regular haematocrit is more important for management than the thrombocytopenia. Even in severe dengue especially with shock hourly haematocrit is crucial for management.

The additional baseline tests include:**

- FBS
- Liver function test
- Kidney function test – serum urea & creatinine
- Coagulation profile (Prothrombin Time, INR etc.) – around Day 5 of illness (if facility exists).

Such investigation facilities may not be available in the govt. health facility itself at a peripheral level. **Service of PPP laboratory or hub & spoke model of lab support may be availed of in that case. Mere absence of these baseline investigations should not be a reason for referring out a dengue case.

Timing: The tests should be done on around Day-5 of the illness, if not required earlier due to the presence of any particular indication. As example, LFT would be indicated even in early stage of the disease if a patient reports with frequent vomiting.
The tests may be repeated as & when necessary.

Coagulation profile would be specially indicated if liver enzymes are highly elevated (say, >5 times the UNL), or haemorrhage is noticed or suspected.

Estimation of serum electrolytes:
Would be required especially in the following conditions –

- Repeated vomiting or diarrhoea
- Repeated boluses of i.v. fluid is required to manage DSS
- Dengue shock is not corrected even after prolonged i.v. fluid therapy as per guideline
- Patient is fully on parenteral fluids
- Metabolic acidosis is suspected
- Patient needs CCU/ITU care.

Patients with co-morbidities or clinically severe disease:

Additional tests to be considered as indicated -Liver function test, serum amylase & lipase, ABG, Blood Glucose, Serum Electrolytes, Urea and Creatinine, Bicarbonate or Lactate, Cardiac enzymes, Electrocardiogram (ECG) and Urine-R/E.

- **ABG**-A single ABG analysis estimates serum lactate and base excess both of which are very good indicators of intravascular fluid status and are easily available. Done sequentially, ABG can predict progression.
- **Aspartate aminotransferase** (AST) level is usually > alanine amino transferase (ALT) level in dengue. The degree of rise of AST and ALT is significantly more in DHF and DSS, as compared to DF. AST and ALT Levels are significantly higher (5 to 15 times the upper limit of normal) in patients with DHF. Commonly AST is more than ALT in these cases.
- **Urine RE**: Albuminuria.

Important Radiological Examination:

- **Ultrasonography**- Ultrasonography is used to look for third space fluid accumulation as a plasma leakage sign. It can be also used to measure the inferior vena cava (IVC) collapsibility to assess hydration status. A value >50% indicates hypovolemia and non-collapsing IVC indicates hypervolemic status).

- **Chest X-ray**: Should be done in a dengue patient on an urgent basis if shortness of breath is complained or SpO2 shows under-saturation. Chest X-Ray to detect pleural effusion and rule out pneumonia. A **lateral decubitus chest X-ray** demonstrating pleural effusion, mostly on the right side, is a common finding and the extent of pleural effusion is positively correlated with disease severity. Bilateral pleural effusions are common in patients with dengue shock syndrome.

Investigations to rule out other infections should be undertaken.

Malaria (MP/ICT), Enteric fever (Blood culture) or ruling out scrub typhus may be required for patients with compatible clinical syndromes

Table 4: Interpretation of common laboratory findings:

Complete Blood Count (CBC): Preferably be done at the first visit to establish the patient's own baseline hematocrit & platelet count Normal CBC during the first 72 hours of illness does not exclude dengue infection CBC should be repeated after the 3rd day of illness or in those with warning signs and with risk factors for severe disease. Platelet counts are usually normal along with other components of clotting factors. Mild thrombocytopenia (100,000 to 150,000/mm3) is common and 50% of DF patients have platelet count < 100,000/mm3; but severe thrombocytopenia (<50,000/mm3) is rare.
In the absence of the patient's baseline hematocrit: Age-specific population haematocrit levels to be used as a surrogate during the critical phase. HCT value of **>38%** in female adults and children aged <12 years and **>42%** in male adults should raise the suspicion of plasma leakage A slight increase may be due to high fever, anorexia and vomiting (10%). A sudden rise in haematocrit is observed simultaneously or shortly after the drop in platelet count. Rapid decrease in platelet count, with concomitant rising haematocrit (compared to the baseline) is suggestive of progress in the plasma leakage/critical phase of the disease
Leucopenia usually precedes the critical phase. A progressive decrease in total white cell count is the earliest abnormality in the full blood count Plasma leakage/critical phase of the disease are usually preceded by leucopenia(<5000/mm3) and ratio of neutrophils to lymphocyte (neutrophils <lymphocytes)
A decreasing WBC and platelet count makes the diagnosis of dengue very likely.
Rapid IgM-based dengue diagnostic tests: -Are a quick and easy method for use at point of care or bed -Usually lower and variable sensitivity in comparison to ELISA based tests -False-positive results found in patients with malaria, leptospiral infections, COVID, immune disorders such as rheumatoid and lupus or previous dengue infections **Hence, rapid diagnostic tests are not recommended**

Table 5: Interpretation of Hematocrit Value:

Interpretation of Haematocrit: Haemodynamic state should be the principal driver of IV fluid therapy. Haematocrit level should only be a guide.

Interpretation of rising or persistently high haematocrit					
Haematocrit		**Vitals**		**Interpretation**	**Action**
A rising or persistently high Hct	+	Unstable vital signs	=	Active plasma leakage	Need for further fluid replacement
A rising or persistently high Hct	+	Stable vital signs	=	Does not require	Continue to monitor closely. Hct should start to fall within next 24 hours as plasma leakage stops.

Table 6: Differential diagnosis of Dengue fever

Disease	Classical signs and symptoms	Differentiating feature of Dengue
Influenza	Fever, headache, myalgia, malaise, RTI	Upper respiratory symptoms such as rhinitis and cough may sometimes be present in dengue. Patients with dengue usually have gastrointestinal symptoms (i.e. abdominal discomfort, vomiting and sometimes diarrhea) during the febrile phase.
Malaria	High fever with chill and rigor, hepatosplenomegaly, features of complication are seen sometimes	Splenomegaly and prolonged fever should prompt the consideration of malaria in the differential diagnoses. Thrombocytopenia may be present in both, further diagnostic studies are needed.

Typhoid fever	Fever, headache, malaise, anorexia, abdominal pain, rose spots, hepatosplenomeg aly, altered mental status	Splenomegaly and prolonged fever should prompt the consideration of typhoid in the differential diagnoses. Severe break bone features are usually absent. Sometime very difficult to differentiate complicated typhoid fever from DSS; diagnostic studies are needed.
Scrub Typhus	Fever, chill, myalgia, headache lymphadenopathy, rash - usually maculopapular. Vital organ involvement in complicated stage.	Eschar, if present, is a characteristic feature. History of living at a high endemic place can provide a clue. Some degree of thrombocytopenia may occur in scrub typhus. However, leukocytosis is common (unlike leucopoenia in dengue). Spleen & liver may enlarge. Dry cough & pneumonitis may develop. Encephalitis is more common, as compared to dengue. IgM ELISA is confirmatory after 5 days of illness.
Leptospirosis	chill, myalgia, transient rash & non-purulent conjunctival discharge Second phase-meningitis, renal disease, liver failure	Jaundice is more often associated with leptospirosis, but ocular pain, arthralgia and diarrhea could be present as well, whereas dengue is usually associated with elevated liver enzymes and mild jaundice. In icteric leptospirosis, liver function tests (LFT) generally show a significant rise in bilirubin, with lesser increase in transaminases and marginal increase in alkaline phosphatase levels. Pulmonary hemorrhage is a particular form of leptospirosis without jaundice may be confused with severe dengue. Pulmonary hemorrhage is uncommon in dengue; evidence of plasma leakage such as pleural effusion or ascites would suggest the diagnosis of dengue. Fever, thrombocytopenia, raised liver enzyme, renal involvement is common feature of both conditions.

Meningococcemia	Fever, chills, malaise, prostration, rash (macular, maculopapular, petechial), can progress to fulminant with DIC, purpura, shock & death	DHF and shock due to dengue is sometimes undistinguishable from meningococcemia. Diagnostic studies are needed.
Chikungunya	Fever, rash, arthralgia, arthritis, headache	While fever, arthralgia, rash, malaise and leucopenia are common in both chikungunya and dengue, symmetric arthritis of small joints is pathognomonic of the former and bleeding.

General management of Dengue Fever (DF):

- Management is symptomatic and supportive
- Bed rest during the acute phase.
- Cold/ tepid sponging to keep temperature below 38.5° C.
- Paracetamol preferable as antipyretic & analgesic:
- Encourage oral intake of at least 5 glasses of other fluids (with electrolytes) in addition to normal daily intake of plain fluid. Small frequent sips for those with nausea and anorexia.
- Monitor for development of complications till 48 hours after being afebrile.

Table 7: Oral Fluid of Choice for Dengue Patient:

Fluids to be taken	Fluids to be avoided
• Fruit juices • Coconut juice • Rice water • Barley water • Oral rehydration solution • Soup	• Commercial carbonated drinks (Cold drinks) • Drinks exceeding the isotonic level (5% sugar)

Laboratory Facility for dengue patient:

- For all admitted dengue cases and suspected dengue cases – check PCV and Platelet Count at least twice a day i.e. one morning sample and another sample in evening/ late afternoon.
- Complete Blood Count test for the fever cases in O.P.D. – as suggested under Basic Lab Investigation. Utilize cell counter if available.

- Dengue Test Report and PCV & Platelet Report must reach the I.P.D. at earliest after test is done. Local level innovation is necessary for fast tracking dengue patient sample.

What should be done	What should not be done
• Adequate bed rest • Adequate fluid intake • Take paracetamol • Tepid sponging	• Do not take NSAIDs like aspirin or steroids • Do not take combination of paracetamol with NSAIDs • Antibiotics not necessary unless there is bacterial infection
• Look for mosquito breeding places in & around the home & eliminate them	

Table 8: Admission Criteria for Dengue patient

Admission criteria	
Warning signs	Persistent high-grade fever (≥ 38.5-degree Celsius). Any of the warning signs including sudden drop of temperature
Signs & symptoms related to hypotension (possible plasma leakage)	• Dehydrated patient, unable to tolerate oral fluids • Dizziness or postural hypotension • Profuse perspiration, fainting, prostration during defervescence • Hypotension or cold extremities • Difficulty in breathing or deep signing breaths
Bleeding organ impairment	• Spontaneous bleeding, independent of the platelet count • Renal, hepatic, neurological or cardiac dysfunction • Enlarged, tender liver, although not yet in shock • Chest pain or respiratory distress, cyanosis
Findings through other investigations	• Rising haematocrit • Pleural effusion • Ascites or asymptomatic gall bladder thickening (in USG)
Co-existing condition / Co-morbidities	• Pregnancy • Co-morbid conditions e.g., diabetes mellitus, hypertension, peptic ulcer, haemolytic anaemias & others • Overweight or obese (Rapid venous access difficult in emergency) • Infancy or old age
Social circumstances	• Living alone • Living far from health facility • No reliable means of transport

Table 9: Maintenance Fluid Calculation for Dengue Hemorrhagic Fever

Maintenance fluid should be calculated using Holliday-Segar formula as follows:	
Body weight in Kg	**Maintenance volume for 24 hours**
<10	100 ml/Kg
10-20	1000 + 50 ml / Kg body weight exceeding 10 Kg 1000 + 50 X (body weight in Kg – 10) ml
>20	1500 + 20 ml / Kg body weight exceeding 20 Kg 1500 + 20(body weight in Kg – 20) ml
• Fluid infusion should be just sufficient to maintain effective circulation during the period of plasma leakage • One should keep a watch for urine output, Liver size & signs of pulmonary oedema. Hypervolaemia is a common complication • Normally intra venous fluids are not required beyond 36 to 48 hours • Normally change should not be drastic. During any changes, look for signs of under & over hydration • One ml equals to 15 drops. In case of micro dip system, one ml equals to 60 drops	

Calculation of Ideal Body weight:

It is important in the case of obese patient for calculating proper fluid.

Female	Male
45.5 Kg + 0.91(Height – 152.4 cm) or	50 Kg + 0.91(Height – 152.4 cm) or
45.5 Kg + 2.3 Kg for each inch over 5 ft	50 Kg + 2.3 Kg for each inch over 5 ft

When an advice for IV fluid is given for a dengue patient, the following should be mentioned:

- What type of fluid to be given
- How much quantity of fluid
- Within how much time
- The calculation how the quantity is derived should be shown in the BHT
- After an initial phase, the patient to be re-evaluated and fresh advice for fluid to be given
- If the patient improves, de-escalation of IV fluid should be advised accordingly.

Chart 3: Principle for guiding intravenous fluid therapy in Dengue

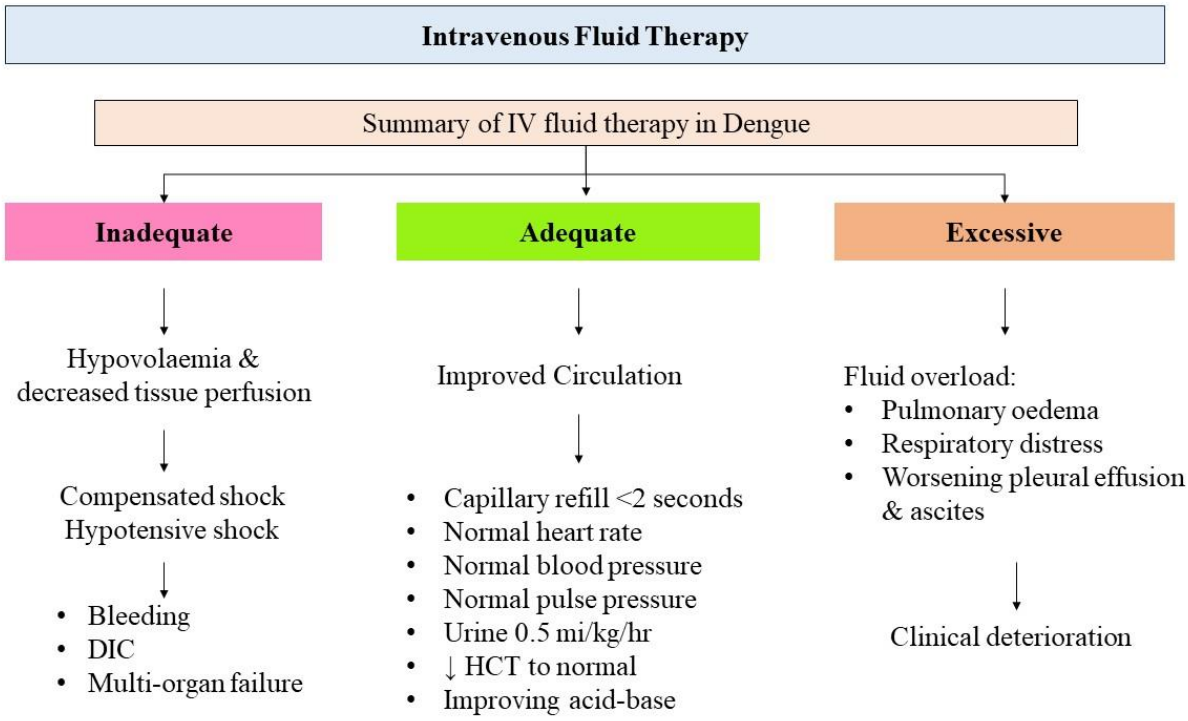


Table 10: Guiding principle for Intravenous fluid

When to start and stop intravenous fluid therapy
Febrile Phase • Limit IV fluids • Early IV therapy may lead to fluid overload especially with non-isotonic IV fluid
Critical Phase • IV fluids are usually required for 24-48 hours Note: For patients who present with shock, IV therapy should be < 48 hours
Recovery Phase • IV fluids should be stopped so that extravasated fluids can be reabsorbed

Table 11: Intravenous fluid of choice

Choice of IV Fluid	
IV Fluids to be given	**IV Fluids to be avoided**
• Use isotonic iso-osmolar solutions (normal saline, Ringer's lactate, balanced crystalloid) • Colloids are preferred if the blood pressure has to be restored urgently	• Hypotonic solution, e.g. 0.45% saline, even during the febrile phase • Dextrose containing solutions, but may be used in hypoglycaemia with close blood glucose monitoring
Colloids are used in case of: • Hypotensive Shock • Repeated shock- 2nd or 3rd shock and onwards • After > 20 to 30 ml/kg of crystalloids • If HCT does not decrease after crystalloid administration in shock **DOSE: Limited to 30 to 50 ml/kg/day**	

Chart 4: Management of Compensated Shock (DHF Grade I/II)

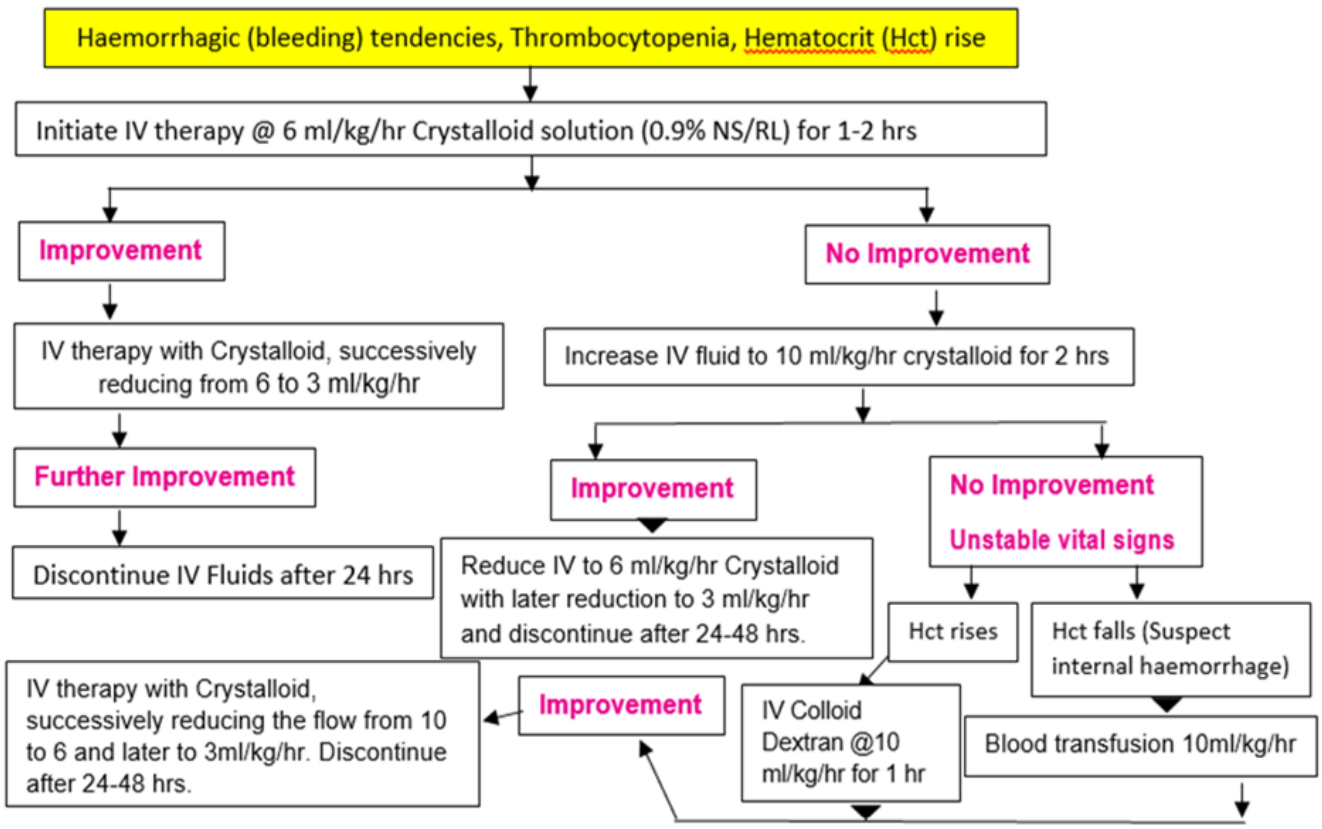


Chart 5: Management of Decompensated Shock (DHF-Grade III/IV)

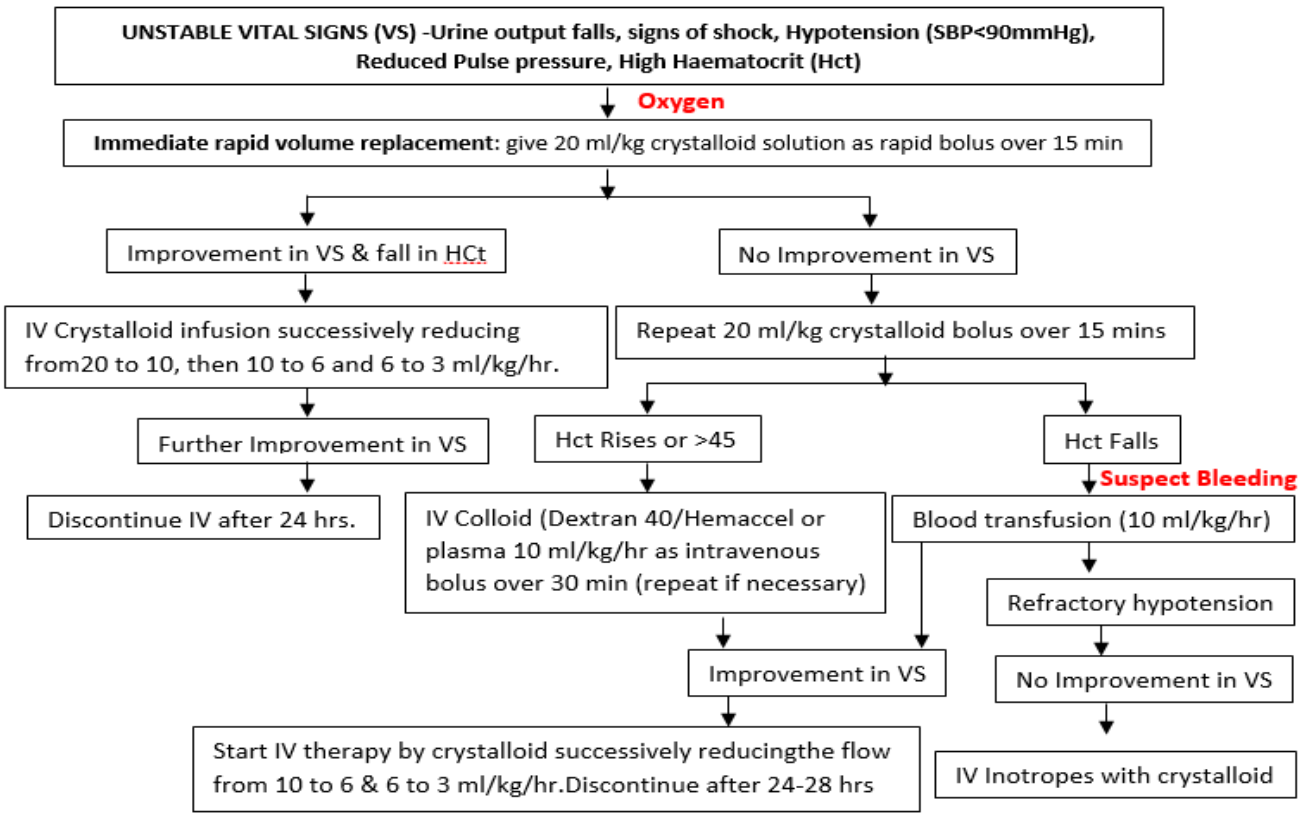


Table 12: Intravenous fluid calculation as per body weight:

	Decompensated shock: Initial IV bolus (first 1-2 hours)		Compensated shock: Initial IV bolus (first 15-30 minutes)	
Body weight (kg)	Amount of fluid	Drip rate (approximate)	Amount of fluid	Drip rate
40-49	250-300 ml/hr	65-70 drops / min	1.5-2 bottles	In jet
50-59	350-300 ml/hr	75-90 drops / min	2-2.5 bottles	
60-69	350-400 ml/hr	90-100 drops / min	2.5-3bottles	In jet, if necessary, in two channels at a time
70-79	400-500 ml/hr	100-120 drops / min	3 bottles	
80-89	500-550 ml/hr	120-140 drops / min	3-3.5 bottles	

Dengue in Paediatric Age Group

Key points:

- Full spectrum of disease can occur – asymptomatic, undifferentiated fever to dengue with warningsigns and severe dengue.
- Severe dengue is common
- Clinical presentation is overlapping, more when organ failure is present.
- Most susceptible: Babies between 4 to 9months
- Dengue in infants can be severe (DHF/ DSS/ other complications) in primary infection (the vertically transmitted residual anti-dengue antibody can cause immune/ Antibody dependent enhancement reaction with the primary infection by heterotypic dengue virus infection)
- Mortality in this age group is high.

Clinical features:

Common presentation is with "Flu" like features:

- high fever
- running nose
- cough,conjunctival congestion
- vomiting, nausea anorexia
- Irritability / excessive cry.

Laboratory diagnosis: Same as that in adults.

- Dengue fever is an important cause of febrile convulsion in infants of 5 – 12 months of age.
- Measly look and a blanchable erythematous flush /skin rash with epidemiological relevance are pointers toclinical suspicion.
- Positive tourniquet test (33% Sensitive and 76% Specific)
- Bleeding gum, nose, easy bruisability are common.
- Dengue in paediatric age group sometimes present with Diarrhea.
- Involvement of liver with raised ALT, AST is found more commonly in infants compared to older children andadults

Dengue in neonates

It is rare. However, it needs special mention.

How does it occur?

1. Vertical transmission of dengue virus: trans-placentally in late third trimester of pregnancy (Virus has been detected in cord blood). For clinical suspicion, always consider **the dengue incubation period of 4 – 10days.**
2. Vector transmission: can also occur rarely.

Features: If a pregnant mother in the peripartum period develops dengue, the possibility of dengue should always be considered in the newborn. Observe newborn for at least two weeks after birth in case of dengue positive mother at term. Severe neonatal dengue illness and even death may occur when there is insufficient time for the production of protective maternal antibody.

Full spectrum of disease can occur:

- Some neonates may be asymptomatic.
- Some may develop mild symptoms with fever, skin rash and hepatomegaly. Skin rash arouses suspicion.
- In more severe forms, bleeding manifestations, pleural effusion and hepatic & multi organ failure are common.
- Capillary leakage and circulatory collapse or shock may occur. Multi-organ failure can follow.
- Bleeding manifestation -purpura, nose bleeding, pulmonary hemorrhage, GI bleeding, intracranial bleeding is common.

Laboratory features: Anaemia, leukopenia, thrombocytopenia is frequent and early. Liver function tests show deranged function.

Close differential diagnoses are neonatal sepsis, birth trauma or other severe neonatal illnesses. Severe dengue with shock is confused with septic shock.

Diagnosis: Careful maternal history (mother developing dengue in late third trimester) and epidemiology are important diagnostic clues. Standard laboratory tests for confirmation of dengue should be done.

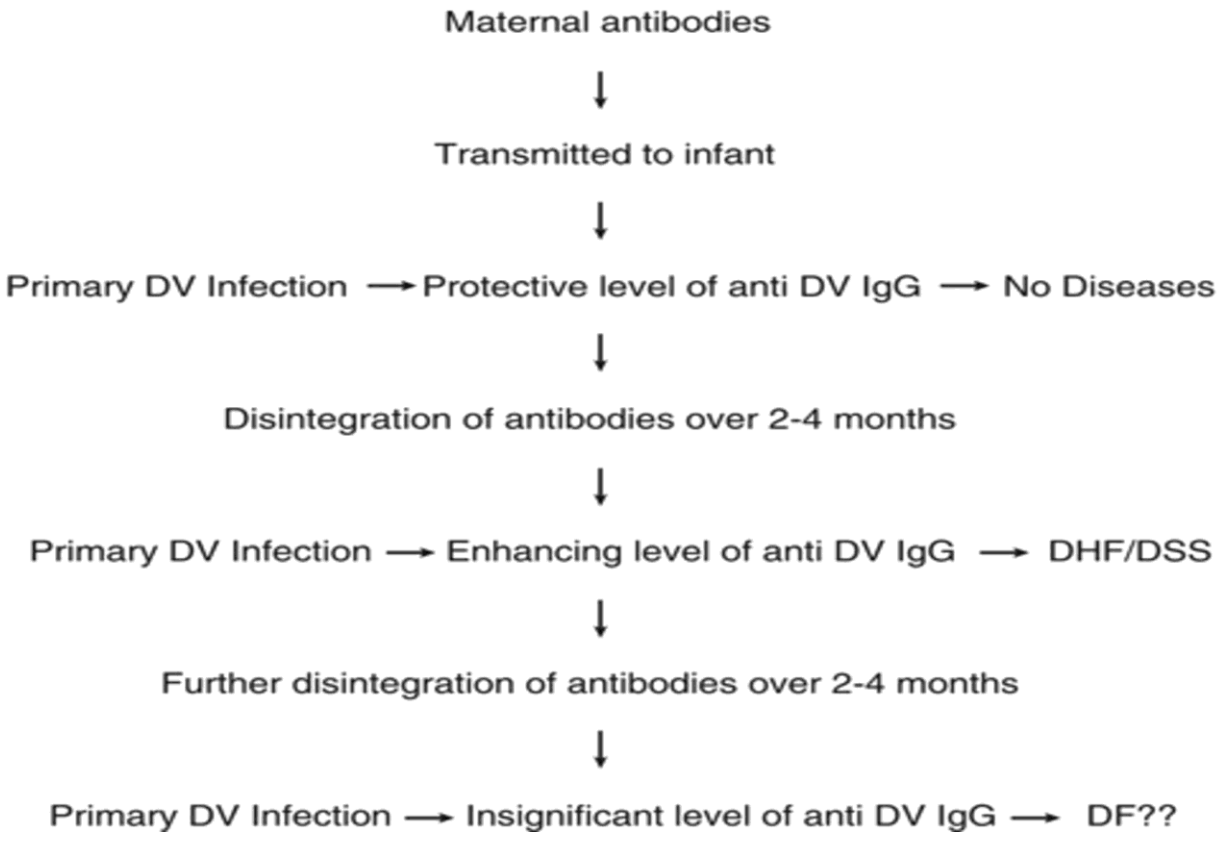
Management: Symptomatic and supportive treatment under close observation is the mainstay of management.

Dengue in infants

- Dengue in Infants is common (may be up to 2 yrs) comparing to neonatal dengue.
- Most susceptible are babies of 4-9 month (as maternal antibody is gradually decreasing over the months after birth).
- Severe dengue is more common. Shock, Plasma leakage and platelet count <50,000 is more common in infant dengue compared to older age groups. Convulsion and hepatic dysfunction are more common.
- Mortality is 4 times higher in case of dengue infection in infancy.
- NS1Ag may be missed before six months of age due to presence of maternal antibody, hence can cause confusion.
- Primary infection in infant dengue can be of severe type.
- Fluid overload complication is more common in infants.

Humoral immunopathogenesis of DHF/DSS in primary DV infection among infants.

Chart 6: Pathogenesis of Severe Dengue infection in Infant



FEMS Immunol Med Microbiol, Volume 59, Issue 2, July 2010, Pages 119–130, https://doi.org/10.1111/j.1574-695X.2010.00670.x

[Copying from original slide is acknowledged].

Dengue in toddlers and older children

Presentation of dengue in toddlers and older children are more likely adults. Common clinical manifestations are-

- Abrupt onset high fever
- Headache
- Pain in orbits
- Extreme myalgia, arthralgia ("Break bone fever")
- Vomiting, pain abdomen
- Sore throat
- Skin rash

Minor bleeding – nose/gum/easy bruisability

Paediatric Case Study:

1. 7 years old, 25 kg, diagnosed patient of Beta thalassemia Major. Patient has fever D-4, pain abdomen, lethargy. HR – 126/min, RR- 36/min, BP – 88/68 mmHg. Dengue – Dengue Ns1 Positive

   -What will you do?

   -What are the challenges of management of severe dengue in thalassemia patients?

Challenges in Management:

- Lack of haemo-concentration does not exclude plasma leakage.
- Also, most of the time cannot take HCT as guide of fluid titration
- Monitored for other signs of plasma leakage such as pleural effusion and ascites.
- Chest radiograph and abdominal ultrasound can aid diagnosis.
- Clinicians in endemic regions should have a high index of suspicion when assessing patients with fever in known thalassemia patient.
- Severe dengue, especially severe liver involvement, may occur.

Key Facts in Dengue Management:

- Only one out of 20 thalassemic patients had hemoconcentration where most of the patients had anemia
- Severe anemia can cause hemodynamic compromised and lead to hypoxemia, hypotension and shock. Prolonged shock further results in organ damage and poor outcome
- Appropriate blood component should be prepared in advance and the packed red cell should be promptly transfused in patients with anemic symptoms

2. 5 years, 30 kg, relapse Nephrotic Syndrome. Generalized edema, urine Protein – 3 +, urine output 400 ml in last 24 hours. Fever for 5 days.

From today morning cold periphery, HR – 140/min, RR- 40/min, BP – 74/58mmHg.

Dengue IgM positive

- What are the challenges?
- What should be the resuscitation fluid of choice?
- How will you Monitor?
- What will you do with steroid?

Challenges:

- Capillary leak vs decreased oncotic pressure
- How to assess capillary leak in a patient who already have edema?
- Urine output is not reliable marker

How will you Monitor?

- BP – trend is important
- HCT %
- IVC Collapsibility
- USG Lung for Pleural effusion and abdomen for Ascites
- Blood lactate

What should be the resuscitation fluid of choice?

- After 1st bolus of Crystalloid –
- Early Colloid – 5% Albumin bolus @ 10 ml/kg (5% albumin to be prepared by adding 3 times volume normal saline to 20% albumin solution)
- If severe hypoalbuminemia < 2gm/Dl – 20% Albumin @ 1gm/kg

What will you do with steroid?

Duration and dose od steroid

- Start stress dose steroid
  - Minor stress (fever >38ºC, flu, strep): use usual pills or parenteral hydrocortisone
    - 2–3× replacement: 30–50 mg/m²/d ÷ TID–QID **PO/IM/IV**
    - Some patients are taught to follow with Depo-Medrol® 10 mg/m²/d **IM** q 24 hours.
  - Major stress (surgery, MVA, meningitis): use parenteral hydrocortisone
    - Loading dose (age-based): **IM/IV**

<3 years: 25 mg/dose
3–9 years: 50 mg/dose
≥10 years: 100 mg/dose

    - Follow with 5–6× replacement: 100 mg/m²/d ÷ TID–QID **IM/IV** or continuous drip **IV**
  - **IF IN DOUBT, GIVE STRESS DOSES!**

Chronic Glucocorticoid therapy
1.Daily glucocorticoid therapy for ≥ 2 weeks of:
1. **Hydrocortisone:** > 10 mg/m²/day
2. **Prednisone/prednisolone/methylprednisolone:** any dose
3. **Dexamethasone:** any dose

2.History of chronic or repeated oral/IV steroid exposure within the past 12 months without recent HPA axis evaluation, or those with evidence of Cushingoid features on physical examination.

Dengue fever and surgical perspective

Dengue, the second most important mosquito-borne disease affecting humans continues to remain as menace till date. In true sense the Dengue Fever (DF) particularly the Dengue Hemorrhagic Fever (DHS) and Dengue Shock Syndrome (DSS) are primarily medical problems. This disease is considered a domain of physicians and surgeons have some role to play when asked for.

There are some issues related to Dengue fever and surgery namely

Complications of Dengue mimicking surgical conditions:

Abdominal pain developing in dengue patient mimics many of surgical emergencies like cholecystitis, pancreatitis and appendicitis. The pathophysiology for the abdominal inflammatory signs is due to leakage of plasma into the tissues, lymphadenitis or lymphatic follicular hyperplasia.

- In cholecystitis gall bladder is thick walled, oedematous usually without any calculus.
- In pancreatitis the pancreas is bulky, oedematous and ascitic fluid may be present.
- Right lower quadrant pain in Dengue fever mimicking appendicitis may be due to lymphadenitis and inflammation of appendicular lymphatic follicles.

All the patients with abdominal pain and tenderness should have ultrasonography of abdomen and pelvis; Plain X-ray erect view is requested when hollow viscus injury is suspected. CT scan abdomen and pelvis is asked for in specific situations. **Conservative non-operative treatment and supportive care is primarily opted in most of the situations with continuous monitoring**. Hastily taken decisions with operative management for such patients may lead to serious consequences.

Management of Dengue fever with co-morbidities

DF in Hypertension:

- Hypotension is a late sign of shock. However, a BP reading that is considered normal for age may, in reality, be low for patients with uncontrolled hypertension. Similarly, what is considered as "mild" hypotension may in fact be profound.
- Clinical signs of shock are better to guide clinical diagnosis of DSS than the BP.
- ß-blockers, a common anti-hypertensive medication, cause bradycardia and may block the tachycardic response in shock. **The heart rate should not be used as an assessment of perfusion in patients on ß- blockers.**
- Calcium channel blockers may cause tachycardia. So, tachycardia in these patients may not indicate hypovolemia. Knowing the baseline heart rate before the dengue illness is helpful in the haemodynamic assessment.

Recommendation: -

- Dose of antihypertensive drugs should be titrated according to blood pressure. **Target MAP (mean arterial pressure) should be ≥ 65 mm of Hg.**
- Diuretics should be avoided in Critical phase or during Hemoconcentration.
- Beta blockers should be withdrawn in presence of shock or heart failure.

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.

- The blood sugar may become uncontrolled sometimes requiring insulin therapy for better management.
- Hypoglycaemia may occur in those patients taking oral hypoglycemic agents (OHA) e.g. long-acting Sulphonylureas, but who has poor oral intake. **Hypoglycaemia may be aggravated by dengue hepatitis**.
- Gastrointestinal absorption of OHAs is unreliable because of vomiting and diarrhoea.
- Metformin may aggravate lactic acidosis, particularly in dengue shock syndrome (DSS).
- Hyperglycaemia results in osmotic diuresis and worsens intravascular hypovolaemia.
- A validated protocol for insulin dose adjustments to a target glucose level of < 150 mg/dl (8.3 mmol/L) should be used.
- A source of glucose may be maintained once the target is achieved whilereceiving intravenous insulin.
- Blood glucose should be monitored every 1–2hours until glucose values and insulin rates are stable and then every 4 hours thereafter.
- Not correcting the hyperglycaemic state exacerbates the shock state

- Hyperglycaemia also puts patients at risk of bacterial infection.
- Diabetic ketoacidosis and hyperosmolar hyperglycaemia: Clinical manifestations of diabetic ketoacidosis and hyperosmolar hyperglycaemia (nausea, vomiting and abdominal pain) are similar to the warning signs of severe dengue. It is not uncommon for dengue shock to be misdiagnosed as diabetic ketoacidosis.

Key points:

- If patient is on insulin, dose adjustment may be necessary according to patient's CBG
- Hold OHA in Critical period& initiate regular insulin during critical period with regular CBG Monitoring.

DF in patients on Anti-Coagulants:

- Keep Clopidogrel and Aspirin in those patients already taking these agents.
- Interrupt warfarin use and replace it with heparin as soon as the INR level is below the therapeutic range. Reintroduce warfarin after one week. Perform serial platelet monitoring and coagulogram during one week. Interrupt use of medications if platelet count is equal to or less than 50,000/mm3, and if there is bleeding or shock.
- Clopidogrel and Aspirin interruption may be considered depending on the intensity of progressive reduction in the number of platelets.
- Patients with dengue and at low short-term risk of thrombosis:
    1. Patients with stable coronary artery disease.
    2. Patients who have undergone coronary angioplasty with stent implantation more than six months before.
    3. Patients with Chronic AF and no risk factors for thrombosis (or only one risk factor).
    4. Patients with biological valvular prostheses.

  Recommendation: Interrupt the use of aspirin. Consider interrupting clopidogrel and warfarin for one week.
- **Patients with dengue hemorrhagic fever:** Interrupt immediately the use of all antithrombotic agents.

Recommended Antiplatelet management in post PCI patient with Dengue infection

	Dengue + high thrombotic risk	Dengue + low thrombotic risk	Dengue + clinically significant bleeding + high thrombotic risk	Dengue + clinically significant bleeding + low thrombotic risk
When to stop anti-platelet therapy? **When to restart anti-platelet therapy?**	Stop both anti-platelets when plt<50k* Load both anti-platelets when platelets upward trend and >50k.	Stop both anti-platelets when plt<70k* Restart both anti-platelets when platelets upward trend and >50k.	Stop both anti-platelets when plt<100k* Load both anti-platelets when platelets upward trend and >70–80k and no further bleeding.	Stop both anti-platelets when plt<100k* Restart both anti-platelets sequentially when platelets upward trend and >70–80k and no further bleeding.

*Option of stopping one anti-platelet first may also be considered.

DF with Renal Involvement:

It has been seen that End Stage Renal Disease (ESRD) on dialysis patients developed severe dengue, much higher than that of the general population. The reason for this higher incidence could possibly be attributed to the complicated pathophysiology associated with ESRD.

- Among the cytokines, TNF-α and IL-6 are reported to be increased in patients with CRF and increase vascular permeability markedly and put patients at a higher risk for developing DHF/DSS.
- Cytokine cascade can cause endothelial cell dysfunction by decreasing the attachment of endothelial cells and reducing thrombogenecity, which might also contribute to the pathogenesis of DHF/DSS in patients with renal failure.

In treating patients with DF, there are certain signs that may raise physicians' suspicion of the development of DHF/DSS:-

- Extensive petechie/echymosis, overt bleeding, marked thrombocytopenia
- Elevated liver enzymes, proteinuria, hypoalbuminaemia

Furthermore, the **low baseline hematocrit in patients with RF and low baseline platelet count in dialysis patients because of uremia and the use of heparin in dialysis could be other obstacles to early recognition of hemoconcentration and thrombocytopenia in dengue viral infection.** These may lead to ignorance of clinical symptoms/signs and misinterpretation of the laboratory data and thereby increase the risk for delayed diagnosis of DHF/DSS in patients with renal failure and dengue viral infection.

For treatment of DHF/DSS, the three most important issues are:

- Fluid supply,
- Electrolyte balance,
- Bleeding control.

Key Points in management:

- WHO recommended fluid amount may lead to hypervolemia and pulmonary oedema due to anuria.
- Urine output cannot be an indicator for monitoring of fluid status in CRF
- Diuretics may have limited effect in hypervolemia with CRF
- Dialysis may be required but intra-dialytic hypotension should be avoided by careful monitoring
- Cautious use of Ringer lactate solution otherwise it may cause hyperkalemia leading to tissue acidosis
- Safety of starch solution is not well established in CRF
- As haemodialysis is difficult in shock stage, continuous renal replacement therapy (CRRT) may be considered
- Qualitative platelet dysfunction is common cause bleeding diathesis in CRF. Desmopressin may be used for temporary correction of bleeding time.

  Desmopressin can shorten the prolonged bleeding time, release endothelial haemostatic factors, and promote the adhesion of platelets to the vascular sub-endothelium; therefore, it is used to improve platelet function in von Willebrand's disease and cause haemostasis in uremic patients. Furthermore, because desmopressin also has the effect of water retention, it seems reasonable to restore body volume in DHF/DSS.

Complications of Dengue fever – other than DHF or DSS

It is reiterated that plasma leakage and resulting hypovolemia are the main & commonest pathology of dengue. Accordingly, close monitoring and timely & proper fluid replacement are the mainstay of treatment of dengue fever. However, in last few years, a significant number of cases have been reported where vital organs were affected without any demonstrated hemorrhage/hypovolemia. Or, some vital organs had started malfunctioning before DHF/DSS set in.

Considering the large number of dengue infections, such instances cannot be said to be frequent. So, these should not be over-emphasized in compromise of the basic management modalities. Yet, in the current perspective, such complications of dengue fever like myocarditis, HLH, coagulopathy, AKI etc. need some special attention since the main aim of dengue case management is to reduce case fatality to as minimum as possible.

In this section, a few of such complications (which are relatively common) are discussed in brief along with an indicative line of management.

1. Metabolic acidosis

Compensated metabolic acidosis is an early sign of hypovolemia and shock.

Lactic acidosis due to tissue hypoxia and hypoperfusion is the most common cause of metabolic acidosis in dengue shock. Correction of shock and adequate fluid replacement will correct the metabolic acidosis.

If metabolic acidosis remains uncorrected by this strategy, one should suspect severe bleeding and check the hematocrit. Transfuse fresh whole blood or fresh packed red cells urgently.

Sodium bicarbonate for metabolic acidosis caused by tissue hypoxia is not recommended for pH $\geq$ 7.10.

Bicarbonate therapy is associated with sodium and fluid overload, an increase in lactate and pCO2 and a decrease in serum ionized calcium. A left shift in the oxy– haemoglobin dissociation curve may aggravate the tissue hypoxia.

Hyperchloremia, caused by the administration of large volumes of 0.9% sodium chloride solution (chloride concentration of 154 mmol/L), may cause metabolic acidosis with normal lactate levels.

If serum chloride levels increase, use Hartmann's solution or Ringer's lactate as crystalloid. These do not increase the lactic acidosis

2. Acute kidney injury

Dengue associated acute kidney injury

High risk group: male gender, DHF, MODS, and diabetes mellitus

Renal manifestations of dengue

- Electrolyte imbalance, tubular injury
- Glomerulonephritis
- Podocytopathy

Key points to remember during Management

- Careful assessment of warning signs and blood volume
- Judicious fluid management initially with crystalloid solutions
- Frequent serum CK levels estimation for early detection of rhabdomyolysis
- Avoidance of nephrotoxic drug
- Timely and adequate supportive treatment
- Renal replacement therapy

Currently, there are no specific recommendations for either conservative treatment or dialysis for patients with dengue, and the effects of AKI on the quality of life.

3. Dengue associated myocarditis

Dengue-associated myocarditis is a rare but potentially serious complication of dengue fever. The pathophysiology of dengue-associated myocarditis is not well understood, but it is believed to be related to the immune response to the virus. Dengue virus is known to infect and replicate within myocardial cells, leading to an inflammatory response that can result in tissue damage. In addition, the immune response to the virus can also cause damage to the heart muscle.

In 2016, a study from India showed that, out of 238 patients with severe dengue, 5% had evidence of myocarditis. In terms of mortality, a study conducted in 2017 in a tertiary care hospital in India found that out of 49 patients with dengue-associated myocarditis, 10 patients (20.4%) died. However, it is important to note that this study was conducted in a single centre and may not be representative of the overall mortality rate for dengue-associated myocarditis in India.

The clinical presentation of dengue-associated myocarditis varies, but it can include symptoms such as chest pain, shortness of breath, palpitations, and fatigue. Diagnosis is typically made based on a combination of clinical presentation, electrocardiographic abnormalities, and elevated cardiac biomarkers.

Overall, while the overall incidence of dengue-associated myocarditis in India is relatively low, it is important for clinicians to be aware of this potential complication in patients with severe dengue fever. Early recognition and management of dengue-associated myocarditis can improve outcomes and reduce mortality rates.

Chart 7: Diagnosis & Management of Myocarditis in Dengue infection

Clinical criteria: (around 5 – 7 days of symptom onset or later)

1. **Chest pain**
2. **new onset dyspnea**
3. **palpitation**
4. **syncope**
5. **refractory hypotension even after adequate fluid resuscitation (in absence of known cardiac illness)**

SUSPECT DENGUE MYOCARDITIS

Investigate further*:

1. ECG: Non-specific ST-T changes, sinus bradycardia or tachycardia, bundle branch block, low voltage
2. Echocardiography: may have reduced ejection fraction, global dyskinesia, pericardial effusion
3. IVC monitoring: decreased collapsibility (<50%)
4. Raised cardiac markers: CPK-MB, Troponin I, Troponin T, NT-ProBNP

Other tests: Chest X-ray

Diagnosis: Clinically suspected myocarditis if ≥1 clinical presentation and ≥1 diagnostic criteria OR if the patient is asymptomatic with ≥2 diagnostic criteria

Management:

1. Judicious use of fluids.
2. Decrease volume of IV fluids and encourage oral fluids with monitoring of daily intake and output.
3. Use of inotropes to maintain blood pressure, if needed.
4. Judicious use of diuretics can be done for fluid overload
5. There is no strong evidence to support the use of steroids or IV immunoglobulins in myocarditis due to Dengue except in a few case reports or retrospective studies.

* European Society of Cardiology position statement on Myocarditis (2013):

- Diagnostic criteria: https://academic.oup.com/view-large/89310717
- Full paper: https://academic.oup.com/eurheartj/article/34/33/2636/408735

4. Dengue associated coagulopathy

Dengue infection is characterized by increased vascular permeability and abnormal hemostasis, with abnormal platelet function also being observed. Coagulopathy is a multifactorial condition that may be caused by low platelet counts/ poor platelet function, deranged PT and APTT, and liver damage. Damage to liver cells can reduce the synthesis of coagulation factors, leading to prolongation in the PT and APTT. Disseminated intravascular coagulation may consume the coagulation factors and also lead to the same problem.

The non-structural protein 1 (NS1) of the dengue virus has the ability to bind to both thrombin and prothrombin. This can explain the early changes in APTT that occur before antibodies are formed. Reductions in the levels of specific coagulation factors, such as II, V, VII, VIII, IX, X, antithrombin, and alpha-2 antiplasmin, have been reported in patients with dengue hemorrhagic fever. Additionally, interleukin-6 (IL-6) plays a role in down-regulating the synthesis of factor XII, the first factor to initiate the intrinsic pathway of coagulation.

Dengue-associated coagulopathy is a significant complication of severe dengue infection and is associated with increased morbidity and mortality rates. Early recognition and management of dengue-associated coagulopathy are essential to reduce the risk of adverse outcomes in patients with severe dengue.

Management of thrombocytopenia

It should be remembered that not the low platelet count, but platelet dysfunction is usually a more important factor for bleeding in dengue. So, indiscriminate platelet transfusion should be avoided.

Indications for platelet transfusion

- **Prophylactic platelet transfusion:**
  May be given at level of<10000/mm3 in the absence of bleeding manifestations.

- **Prophylactic transfusion in surgical cases**: See chapters on Pregnancy, and Dengue with Co- morbidities.

➢ **Therapeutic transfusion:**

Recommended in -

- Haemorrhage with or without thrombocytopenia.
- Prolonged shock with coagulopathy and abnormal coagulogram.
- In case of systemic bleeding, platelet transfusion may be needed in addition to red cell transfusion. **Whole fresh blood transfusion doesn't have any role in managing thrombocytopenia.**

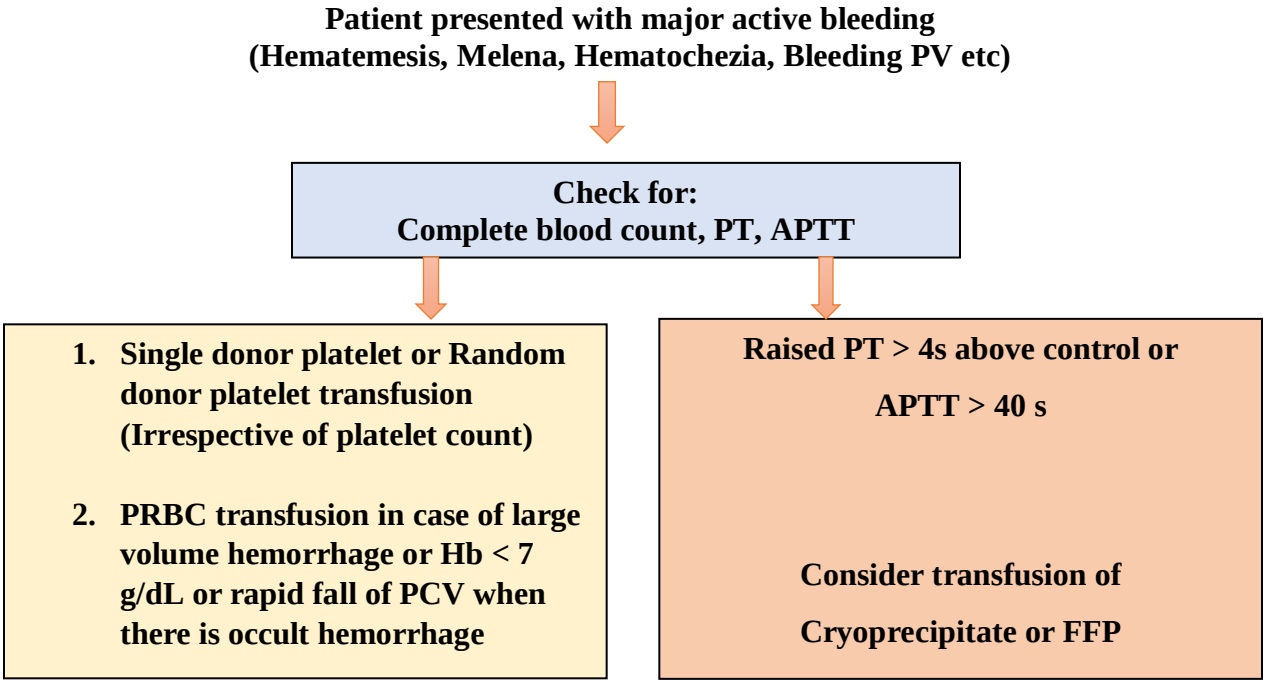
See Annexure for dose of platelet transfusion.

Management of major bleeding

In case of any major bleeding, admit the patient in the hospital and investigate to look for the cause and site of bleeding and take immediate measures to stop the bleeding.

- Patients may have severe epistaxis, haemoptysis, GI bleed or bleeding per vagina (even excessive menstrual bleeding) which may present with profound shock. Urgent blood transfusion is life-saving in this condition.
- If blood is not available, manage shock with proper IV fluid or plasma expander.
- If patient has thrombocytopenia with active bleeding, treat with blood transfusion and then if required platelet transfusion.
- Patients of severe bleeding may have liver dysfunction and, in such case, liver function test should also be performed. Rarely, intracranial bleed or pulmonary hemorrhage may also occur in patients who have severe thrombocytopenia and abnormality in coagulation profile.

Chart 8: Management of Active Bleeding



Indications for blood transfusion

- 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 transfusion is to be given @ 5ml/kg bodyweight

Surgery in presence of Dengue fever always bears a high risk. Any elective surgical procedure should be deferred. If ***surgery is unavoidable****, it can be undertaken* ***after correction of coagulation defect with platelet count at least above 1,00,000/ml***

Transfusion of platelet concentrates should be initiated (if platelet Count<50000/cumm) during or at delivery but not too far ahead of delivery

5. CNS involvement in DF:

Unlike other arboviral infections, Dengue virus doesn't usually cause neurological manifestations. However, in recent years, neurological manifestations of dengue have been documented. The serotypes most commonly associated with CNS manifestations are DEN2 and DEN3.

Clinical features:

1) Those due to neurotropic effect of virus Encephalitis, Meningitis, Myelitis, Myositis
2) Those due to systemic complications Encephalopathy, Stroke, Hypokalemic paralysis
3) Post infectious complications Encephalomyelitis, Optic neuritis, GB Syndrome

How to diagnose?

The following criteria needs to be satisfied-

1. Fever
2. Acute signs of cerebral involvement
3. Presence of IgM DENGUE Antibody (ELISA) or dengue genomic material in the serum and/or CSF
4. Exclusion of other causes of viral encephalitis

Management:

1. Dengue with CNS manifestations is considered as severe dengue and should be admitted in hospital preferably in ICU.
2. General management includes monitoring and maintenance of airway, adequate oxygenation, hydration and nutrition.
3. Standard fluid therapy guidelines for severe dengue should be followed.
4. Seizures can be controlled by standard anti-epileptics.
5. Raised ICT to be lowered by head up nursing, mannitol (cautiously) and steroids.
6. If bacterial infections remain a possibility, then empirical antibiotics to be given, followed by according to culture reports.
7. No specific antiviral therapy is effective for dengue.
8. Research into the pathogenesis of dengue may yield new treatments. Current studies have shown inhibition of dengue replication by many promising agents like ribavirin, morpholine oligomers, geneticin.
9. Given the known immune-pathogenesis, there may be also role for immune-suppressio

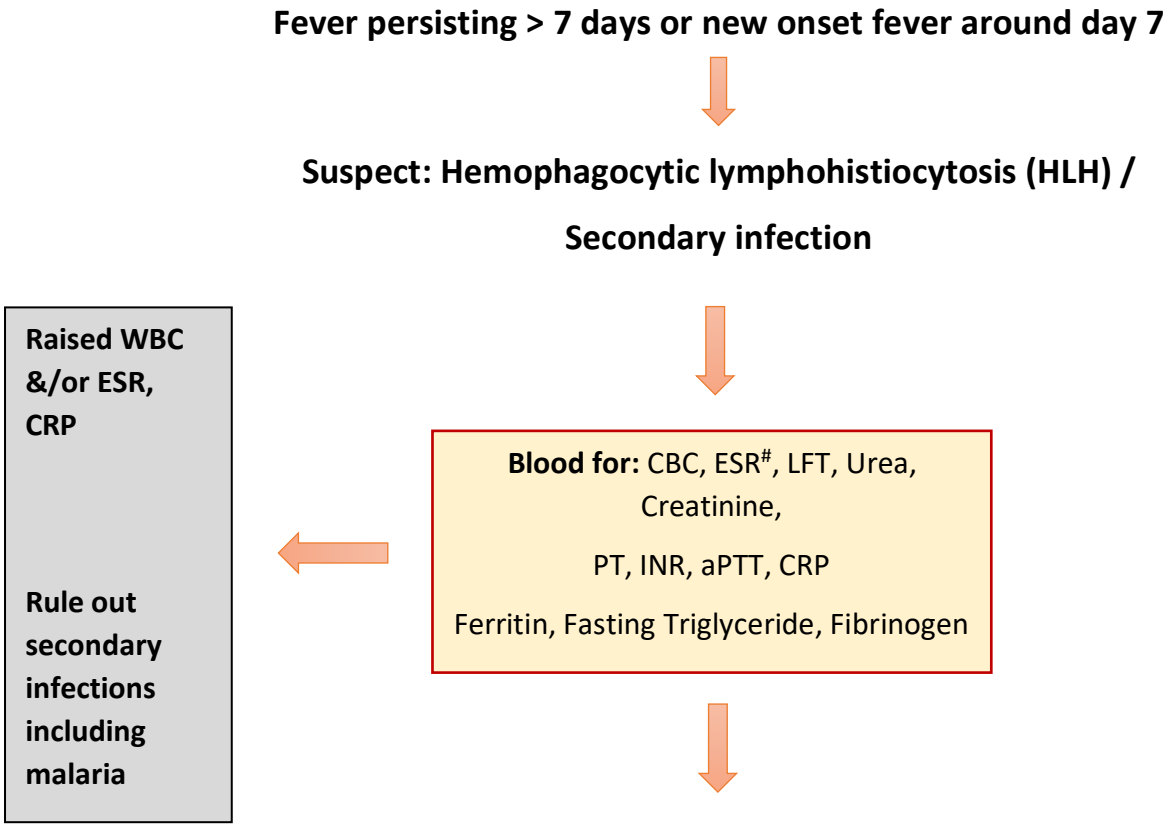
6. Dengue associated Hemophagocytic Lymphohistiocytosis

Dengue-associated hemophagocytic lymphohistiocytosis (HLH) is a rare but potentially life-threatening complication of dengue fever. The incidence of HLH in dengue patients is estimated to be between 0.3% to 1.1% (depending on the region) and is more common in adults than in children. Mortality rates of dengue-associated HLH vary, with some studies reporting rates as high as 80% in untreated patients.

HLH is characterized by the overactivation of T lymphocytes and macrophages, resulting in the excessive production of cytokines and chemokines. This leads to a cytokine storm, which can cause damage to multiple organs, leading to organ failure and, in some cases, death.

The diagnosis of dengue-associated HLH is challenging, and it requires a high index of suspicion, given that the symptoms can be nonspecific and similar to other dengue complications. Patients with HLH typically present with fever (persisting > 7 days or new onset fever around day 7 of illness) with hepatosplenomegaly. Investigations show cytopenias, hepatitis, high levels of ferritin, triglycerides, and soluble interleukin-2 receptor (sIL-2R) (where available).

Modified HLH 2009 criteria is used for diagnosis and treatment of HLH as illustrated in the algorithm below.



At least 3 out of 4 of the following:

- Fever
- Splenomegaly
- Worsening cytopenias (atleast 2 cell lines)
  - Hb < 9 g/dL
  - Absolute neutrophil count (ANC) <1000/mm^3 (or WBC < 2000/mm3)
  - Platelets < 1 lakh/mm^3
- Hepatitis

↓

Essential:

Ferritin > 10,000 ng/mL

(< 10,000 ng/mL → check serially to document rising trend)

Supportive features:

Fasting Triglycerides > 265 mg/dL

Fibrinogen < 150 mg/dL

Hyponatremia

↓

Check Modified HLH 2009 Criteria [1]
OR
H-score > 168 [2]

↓

Consider diagnosis of Dengue associated HLH

↓

Start IV Dexamethasone 10 mg/m^2 or 0.3 mg/kg/day in 3 divided doses for 5 days (after excluding other secondary infections including malaria) [3]

1. Modified HLH 2009 criteria: https://doi.org/10.1182/asheducation-2009.1.127
2. H-score calculator: https://www.mdcalc.com/calc/10089/hscore-reactive-hemophagocytic-syndrome
3. Body surface area calculator: https://www.mdcalc.com/calc/29/body-mass-index-bmi-body-surface-area-bsa

[#] Paradoxically low ESR is noted in HLH

Table 13: Managing Dengue with co-infections

Co-infection	Special consideration	Remarks
Tuberculosis	- Risk of massive haemoptysis - Risk of moderate to massive pleural effusion and ARDS	- Monitor closely for pulmonary complications - Check LFT at regular interval; consider for dose adjustment if hepatitis develops
HIV	- Higher risk of DHF, DSS, significant bleeding and organ involvement - Dengue outcome often poor in HIV positives who have opportunistic infection & very low CD4count	- Monitor vitals, check for signs of plasma leakage or shock - Check LFT, RFT and electrolytes & CD4 at frequent interval
Malaria	- Malaria should be excluded in the beginning without loss of much time as it has its specific management.	- For all dengue positive cases, routinely send blood for MP and MPDA - Start anti-malarial as soon as possible if malaria found
Chikungunya	- Acute complications of DF are sometimes severe in presence of Chikungunya	- If joint involvement is predominant in DF, chikungunya should also be investigated
Enteric Fever	- Seasonality of Dengue & Enteric Fever overlap with each other - DF may be more complicated with Typhoid if antibiotic is started late	- In highly suspected cases of enteric fever, advise blood culture or IgM test (Widal test not < 2 weeks of fever) - Consider for IV antibiotics

Oxygen therapy in severe dengue infection

Patients with Severe Dengue, Dengue shock syndrome, Dengue hemorrhagic fever and Expanded Dengue syndrome usually require Intensive care unit admission and management.

A. General supportive measures will consist of Oxygenation therapy, Maintenance of circulation by judicious fluid management, Airway management and Mechanical ventilation if needed

B. Specific supportive therapy consists of hematological and coagulation abnormalities correction, Renal support, Hepatic, Cardiac and Neurological support along with prevention and treatment of super- infection.

Oxygen therapy: Hypoxia and increased work of breathing is a common manifestation of severe Dengue.

Scenario 1. You are asked to see a patient admitted in ICU with Dengue who is short of breath and have an oxygen saturation of 85%. What steps would you take to increase the oxygenation?

Positioning of patient (comfortable and best oxygenating)

Propped up for volume overload, Ascites

Lateral position with healthy side up for unilateral pneumonia/ pleural effusion

↓

If SPO2 <90% in Room Air

↓

Start oxygen supplementation with a target SPO2 around 95% (Dengue shock state peripheral → perfusion compromised → ABG preferred)

Clinical examination and relevant investigations to determine cause of hypoxia

↓

Important causes of hypoxia in Dengue may be:

- large pleural effusion
- acute pulmonary edema due to volume overload
- alveolar hemorrhage
- acute respiratory distress syndrome
- associated bacterial pneumonia
- severe anaemia

Nasal cannula (Fig 7): the oxygen flow titrated to 1-6 L/min (Higher flow can cause irritation.
Assure humidified oxygen delivery

If oxygen requirement is more or

Flow requirement is more than 6 L/min or patient is mouth breather

Nasal cannula usually delivers 24-40% of oxygen)

Face mask (Fig. 8)

Fig 9. Nasal Cannula

Fig 10. Simple oxygen face mask

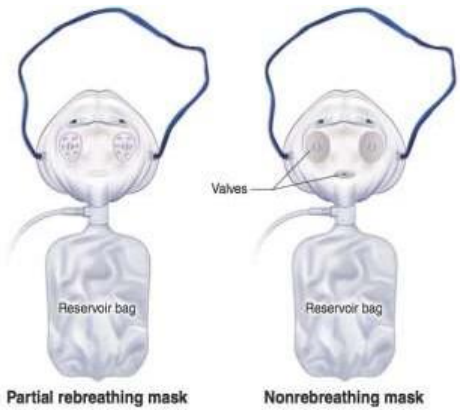
(This can increase delivered oxygen to 35-50 % at a flow rate of 5-10 L/min)

Scenario 2. This patient was started on a Simple Oxygen face mask with a flow of 8 L/min, but his oxygen saturation remains 85%, what are the next options?

Identify and treat the cause of hypoxemia (Drain pleural effusion with precaution considering the platelet count, cautious diuresis in volume overload)

partial rebreathing or non-rebreathing face mask oxygen

(provide up to 60% and 80% oxygen respectively at an oxygen flow of 10-15 L/min)



(In order to deliver the oxygen properly through these masks one has to ensure that the oxygen flow from the flowmeter is high enough that the bag remains fully expanded during respiration and only partially collapses during inspiration)

(Fig 11)

Scenario 3. The patient's work of breathing still remains high and the saturation remains below 90%, as he is becoming restless. What should be done now?

As invasive mechanical ventilation has its complications, two non-invasive devices may be tried to improve oxygen before reverting to invasive ventilation.

High Flow Nasal Cannula (HFNC)

- Can deliver controlled humidified **oxygen up to 100%**
- Uses a heated humidified circuit
- The flow can be increased **up to 60 L/min** in order to match the patients flow demand
- Particularly helpful in patients with high work of breathing
- Can provide a **positive pressure** of around 5cm H2O in order to keep the atelectatic regions of the lung open and improve oxygenation
- More comfortable than non-invasive ventilation and better tolerated by the patient
- Patients can speak and talk while on HFNC

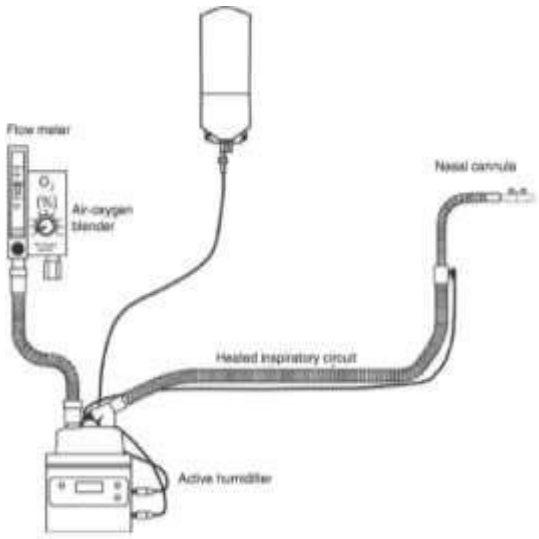


Fig12. High Flow Nasal Cannula.

If not managed then, escalate for ventilation. If NIV failed to improve patient's status, intubate by most experienced member of the team, preferably an anesthesiologist (entirely be based on clinical judgement and not on any blood gas value).

NB: AVOID emergency cricothyrotomy or tracheostomy.

Dengue controversies
Steroids: Basis of DHF pathogenesis is hypothesized to be immunologic that is tempting for immunomodulatory drugs for therapy most common of which is steroid. Currently there is no specific recommendation of steroids for patients with denguesyndrome. But steroid has been used in Dengue Encephalopathy and Hemophagocytic Syndrome empirically with anecdotal benefits. However, clinical opinions favour the benefit of steroids in dengue myocarditis There has been used of different formulation of steroids in severe dengue with refractory shock case in different regions of globe, but there is lack of sufficient conclusive evidence.
Antibiotics: No role in Dengue. Doxycycline has been reported to decrease cytokine release. In protracted disease course, secondary bacterial infections to be treated with appropriate antibiotics. If patients present in shock, antibiotics may be empirically started till aetiology of shock is clear.
Frusemide: In complicated fluid overload from plasma leakage or excessive crystalloid resuscitation, frusemide with or without 20% albumin may be administered. Benefit of frusemide in paediatric dengue with ARDS or polyserositis is well studied.
Tranexamic acid: No controlled trials to advocate or refute use of tranexamic acid in dengue. Have been used in heavy menstrual or GI bleed from dengue.
Calcium Gluconate: Hypocalcemia is seen in critical phase of dengue and is a marker of severity. Iv calcium gluconate is not well studied in adults but its role in hypocalcemic tetany for children with dengue is reported. Routine use for mild hypocalcemia to be avoided. Severe hypocalcemic symptoms like carpopedal spasm warrant iv calcium.
Glucose control: Hypoglycemia should be promptly investigated in all drowsy patients and treated with 20g iv dextrose bolus. Rechecked in 30 mins. and monitored frequently along with LFT. In critical patients a CBG of 150-180g/dl should be maintained for best outcome.

Electrolytes/ metabolic acidosis: Electrolyte and acidosis are common in critical phase or ICU patients of dengue. Acidotic breathing should prompt an ABG or venous bicarbonate. Empirical bicarbonate infusion is not indicated. Lactic acidosis may worsen with bicarbonate. Non-invasive ventilation may help in early acidosis. If CO2 level rises or pH drops below 7.25; early intubation is lifesaving.
ARDS/ ventilation: Use NIV if paO2/FiO2 ratio is more than 150. Restrictive fluids and frusemide +/- albumin may help. If paO2/FiO2 ratio is less than 150, early intubation and ARDS ventilator strategy to be followed. Indications of ventilation: **Severe hypoxia, Severe acidosis, Encephalopathy, Refractory shock, Profuse GI bleed, Large bilateral effusion with coagulopathy.**
Pleural effusion: Early detection by USG helps early identification of plasma leakage and critical phase of Dengue. Effusion should not be aspirated due to risk of haemorrhage. Large bilateral effusions are almost always transudative and best managed with diuretics +/- albumin or positive pressure ventilation.
Volume overload/ Plasma leakage: Careful volume resuscitation should be the goal once plasma leakage starts as rapid accumulation of effusion and ascites can jeopardize ventilation. Presence of shock along with plasma leakage makes a case for colloids (4 to 5% albumin) and Norepinephrine.
Vasopressors and ionotropes: If fluid resuscitation according to Dengue protocol fails to correct shock, patient should be shifted to ICU. Norepinephrine is the drug of choice if Mean Blood Pressure is less than 60mmHg or drop in Systolic BP less than 90 with decreasing urine output. In resource constrained settings Adrenaline may be used although it increases lactic acidosis. Dopamine is usually contraindicated (except children) because of usual tachycardia in Dengue. Vasopressin may be added to Norepinephrine in refractory shock. In myocarditis and low cardiac output state, dobutamine with Norepinephrine may be considered.

Dengue case management : Operational points

Laboratory Facility for dengue patient:

- Please ensure that PCV (Haematocrit) and Platelet Count are checked at least twice a day i.e. morning & evening - for all dengue cases and suspected dengue cases who are admitted.
- Please arrange fast tracking of the samples of the dengue patients. Make some local arrangements so that the reports come to the IPD early once the tests are done. [Some hospitals are using Whatsapp group for sharing of reports/patient information among the care providers].

Laboratory screening of dengue suspects:

- Hospitals not having dengue testing facility will send daily samples (serum) to identified labs by messenger.
- An Excel line list of samples to be sent to the lab online.
- Lab will perform tests and report back to the sample referring hospital as early as possible. Results to be entered in line list and reported back electronically.
- Lab to upload details of positive cases in the State portal – DKPI for govt. labs and CE Portal for the private labs.
- Municipality & Ward/ Block & GP are now mandatory fields in the portal.

  Please mention these information in the requisition.

Other Operational Issues:

- Sensitization is needed at intervals – not only for the Doctors but also for all Staff concerned with service to the dengue patients.
- Ramp up the lab facility, if not already done, for the additional baseline tests. Ensure **equipment upkeep and logistic availability.**

Notes

Acute Encephalitis Syndrome/ Japanese Encephalitis

Case Management Guidance of Acute Encephalitis Syndrome/ Japanese Encephalitis in West Bengal

Introduction

Japanese encephalitis (JE) is a common mosquito borne flaviviral encephalitis. It is one of the leading forms of viral encephalitis worldwide, mostly prevalent in eastern and southern Asia, covering a region with a population of over three billion. Most infections of JE are asymptomatic, but if clinical illness develops, it causes significant morbidity and mortality. JE is a disease of public health importance because of its epidemic potential and high fatality rate. The disease affects the Central Nervous System and can cause severe complications, seizures and even death. Those who survive may suffer from various degrees of neurological sequelae. (An estimated 25% of the affected children die, and among those who survive, about 30-40% suffers from physical & mental impairment).

Acute Encephalitis Syndrome (AES) including Japanese Encephalitis (JE) is a group of clinically similar neurologic manifestation caused by several different viruses, bacteria, fungus, parasites, spirochetes, chemical/ toxins etc. There is seasonal and geographical variation in the causative organism. The outbreak of JE usually coincides with the monsoon and post monsoon period when the density of mosquitoes increases while encephalitis due to other viruses specially entero-viruses occurs throughout the year as it is a water borne disease.

For surveillance purposes, all the cases of Acute Encephalitis Cases should be reported and the reporting would be under the heading of “AES” or “AES/JE”. Laboratory confirmation of JE should be done out of the AES cases by utilizing the sample referral system that is in place.

Clinical Manifestations

- Following an incubation period of 5-15 days after an infective mosquito bite a prodrome of fever, headache, nausea, diarrhea, vomiting, and myalgia occurs lasting for few days followed by irritability, altered behavior, neck stiffness, convulsions and coma.
- The progression of disease is rapid. Signs of raised intra cranial tension are commonly present in acute stage of illness.
- The patient may develop difficulty of speech and other neurological deficits like ocular palsies, hemiplegia, quadriplegia and extrapyramidal signs in the form of dystonia, choreoathetosis and coarse tremors.

Danger Sign

Fever with any one of the following:

- Lethargy
- Unconsciousness
- Convulsions
- May be associated with other significant findings e.g. paralysis, rash, hepatosplenomegaly etc.

Case Definition of Suspected Case of AES/JE :

- Acute onset of fever, not more than 5-7 days duration.
- Change in mental status with/ without
  - New onset of seizures (excluding febrile seizures)
  - (Other early clinical findings – may include irritability, somnolence or abnormal behavior greater than that seen with usual febrile illness).

Important

- **In an epidemic situation fever with altered sensorium persisting for more than two hours with a focal seizure or paralysis of any part of body, is encephalitis.**
- **Presence of rash on body excludes Japanese Encephalitis.**
- **AES with symmetrical signs and fever is likely to be cerebral Malaria.**

Laboratory-Confirmed Case of JE :

A suspected case with any one of the following markers:

- Presence of lgM antibody in serum and/ or CSF to a specific virus including JE/Entero Virus or others
- Four fold difference in lgG antibody titre in paired sera
- Virus isolation from brain tissue
- Antigen detection by immunofluroscence
- Nucleic acid detection by PCR.

In the sentinel surveillance network, JE will be diagnosed by lgM Capture ELISA, and virus isolation is done in National Reference Laboratory.

Probable Case of JE :

Suspected case in close geographic and temporal relationship to a laboratory-confirmed case of AES/JE in an outbreak

Non-JE Acute Encephalitis Syndrome :

A suspected case of AES in which diagnostic testing is performed and an etiological agent other than JE is identified.

Clinical features of Japanese Encephalitis

Depending upon the disease process vis-a-vis involvement of Central Nervous System, the encephalitis can be categorised into 3 stages.

Prodromal Stage

- Lasts 2–3 days. (Preceding the signs of CNS involvement).
- Onset of the disease may be
    - 1. Acute (less than 24 hours),
    - 2. Sub-acute (1–3 days),
    - 3. Gradual (More than 3 days).
- The essential features of this stage are generalised malaise, headache and fever with chills & rigors in 90% of cases.
- The duration of this stage is between 1 – 6 days.
- It is observed that with rapid onset of disease, the case fatality will be higher.
- Hence, shifting the case to an appropriate medical care unit is vital at this stage.

Acute Encephalitis Stage

- Lasts 3–4 days (is marked by CNS manifestastions).
- The predominant features of this stage are continuous fever, neck rigidity, motor deficits, convulsions and altered sensorium progressing in many cases to coma.
- Fever continues from prodromal stage, usually high and varies from 100.0 to 107.0 F.
- The patient sometimes presents with sudden behavioural changes like confusion, delirium, restlessness, disorientation, irrelevant speech, grasping etc.
- Speech disturbance like motor aphasia, dysphasia, monotonous speech may be observed.
- Abnormal spontaneous eye movement with absent corneal reflex and absent pupillary light reflex are also noted.
- In acute stage, patient can exhibit signs of Raised Intracranial Pressure which can be identified by irregular breathing, headache, vomiting and asymmetric paralysis. Sometimes it may lead to convulsions & Coma.

Convalescent Stage (Recovery Stage)

- Lasts 4–7 weeks.
- Marked by gradual recovery and sequelae.
- After a period varying from few days to few weeks of acute stage, either steady improvement occurs or neurological deficits get established.
- This stage begins when active inflammation is subsiding, suggested by temperature and ESR coming to normal and neurological signs becoming stationary or tending to improve.
- Patients who recover from acute episode may have neurological sequelae with variable frequency. This depends on the age and severity of the illness.

Differentiation of Japanese Encephalitis and Non JE/ AES

	Japanese Encephalitis	Epidemic Brain Attack (EBA)
Relation to onset of Rains	About 6 weeks after onset of rains	Starts within 3 days after the onset of rains
Pain in abdomen	No	in 50%
Diarrhea	No	in 50%
CSF	lymphocytic pleocytosis	normal except for increased tension
CT scan	Thalami hypodense	Infarct in Middle cerebral artery territory
MRI scan	Thalami hyperintense	Infarct in Middle cerebral artery territory.

Clinical Differentiation of JE from other Viral/Bacterial/ Parasitic Infections

JE primarily involves the gray matter of many parts of the Central Nervous System. Differentiation of Encephalitis and Encephalopathy and making a probable etiological diagnosis of Japanese Encephalitis and Epidemic Brain Attack in rural areas, (where facilities are minimum but expectations are maximum), on clinical grounds is extremely important to manage the encephalitis case not only as an individual but also for the community since the management of JE and EBA call for immediate reporting to the Health Authorities for a wider coordinated intervention by many different departments to contain the epidemic. Epidemics of Viral Encephalitis demand a clinical diagnosis about the causative Virus for controlling the epidemic at the earliest and for asking for the specific test.

Simple clinical observations help in assessing the depth of coma, planning emergency measures necessary to save the child, limit disability, prognosticate and to initiate epidemic control measures. This must be followed by neurological examination for any localizing signs and to plan for the urgent investigations for a final diagnosis.

Exclusion of treatable conditions like Cerebral malaria, Epidemic Brain Attack, Meningoencephalits, Herpes simplex virus encephalitis, Varicella / Zoster encephalitis, Metabolic causes of encephalopathy, Tuberculous Meningitis is extremely important since they require prompt additional specific treatment.

The therapy for JE/Epidemic Brain Attack is primarily conservative and supportive since there is no specific treatment for both Japanese Encephalitis and Epidemic Brain Attack, and both have a high case fatality rate, if prompt medical and nursing care is not provided.

Analysis of fatal cases of JE/Epidemic Brain Attack revealed that ignorance is killing more children than the pathogen per se. Only 1 death out of every 35 deaths is directly due to JEV and all others are preventable with prompt and early management bringing down the USUALLY REPORTED case fatality rate of JE from 35-50% to less than 1%. Similar degree of lowering of morbidity is also possible. Same is the case with Epidemic Brain Attack also.

The prognosis of JE depends on the extent of involvement at primary presentation, timely management and autoimmune mechanisms of this disease.

Important points to note:

For all the AES cases attended at the health facility, the following **diagnostic tests should be done at the least:**

- Tests to exclude **Malaria** – Microscopy/ RDT
- Serology with CSF and serum for **JE** – IgM ELISA
- Serology for **Scrub Typhus** – IgM ELISA, or PCR (if available)
- Serology for **Dengue** – NS-1 ELISA or IgM ELISA depending on duration of disease.

Empirical therapy for Scrub Typhus (suspected)

It is to be borne in mind that, without waiting for laboratory confirmation of the Rickettsial infection (Scrub Typhus), antibiotic therapy should be instituted when a Rickettsial disease is suspected. Further, if the patient requires referral to a higher facility due to complications, treatment with doxycyline/azithromycin should be initiated before referring the patient. (Please see Annexure 2).

Litchi associated encephalopathy

In West Bengal, occasional AES outbreaks in a few districts have been linked to children eating unripe litchi fruit on empty stomachs. Unripe litchi contain the toxins hypoglycin A and methylene cyclopropyl glycine (MCPG). Hypoglycin A is a naturally occurring amino acid that causes severe vomiting if ingested in large quantities, while MCPG is a poisonous compound found in litchi seeds that causes a sudden drop in blood sugar, vomiting, altered mental states leading to lethargy, unconsciousness, coma and death. These toxins cause sudden unconsciousness and seizures serious enough to require hospitalization in young children, especially the malnourished ones. Stoppage of going to bed without a meal, prevention of consumption of litchi in empty stomach, and in case of sick children the detection of hypoglycaemia and immediate correction with IV glucose injection are effective solutions of the problem.

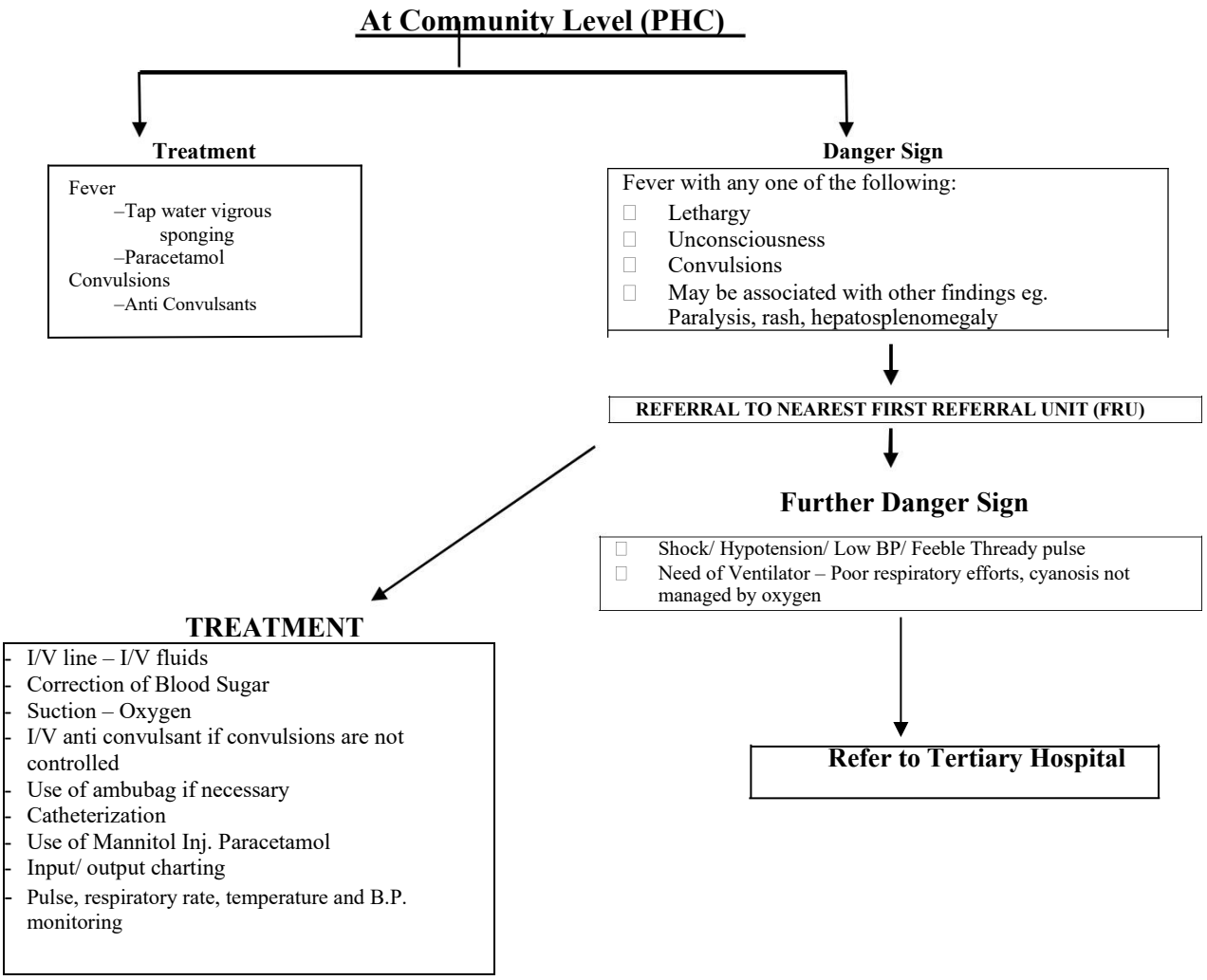
Management of Acute Encephalitis Syndrome (AES) including Japanese Encephalitis

Case Management

One of the major components of the Programme Strategy is the case Management of the patients, most of whom are admitted in Health Institutions in a serious condition.

Management of Acute Encephalitis Syndrome including Japanese Encephalitis is essentially symptomatic. To reduce severe morbidity and mortality, it is important to identify early warning signs and refer patients to health facility

Chart : Management of AES including Japanese Encephalitis at aglance



Management Plan

Background:

Treatment at the health facility, it is important to exclude other causes of CNS affliction like meningitis or cerebral malaria which require specific treatment. Treatment will depend on the condition in which patient is received in the health facility. Since patients are likely to arrive with high grade fever and change in mental status or convulsions proceed with the assessment of patency of airway.

Point to consider:

- The treatment at PHC/ CHC District level or at tertiary care hospitals remains the same.
- Depending upon the needs of care and availability of facilities available at the centre/ hospital the patients to be transferred to the nearest higher centre for further management.
- It should be ensured before transferring the case, all the available treatment is provided to the patient.
- Only needy patients where such facilities are not available, to be transported.
- The time consumed in transportation itself is a major cause of high mortality rate.

The treatment of the patients may require, as follow:-

1.) Management of Airways and Breathing.

2.) Management of Circulation.

3.) Control of Convulsion and Intracranial pressure

4.) Control of Temperature

5.) Fluid and Electrolytes and Calories/ Nutrition

6.) General management

7.) Specific treatment of any for treatable cause

8.) Investigations, Samples Collection & Transportation

9.) Reporting of a case

10.) Rehabilitation

Management of Airway and Breathing

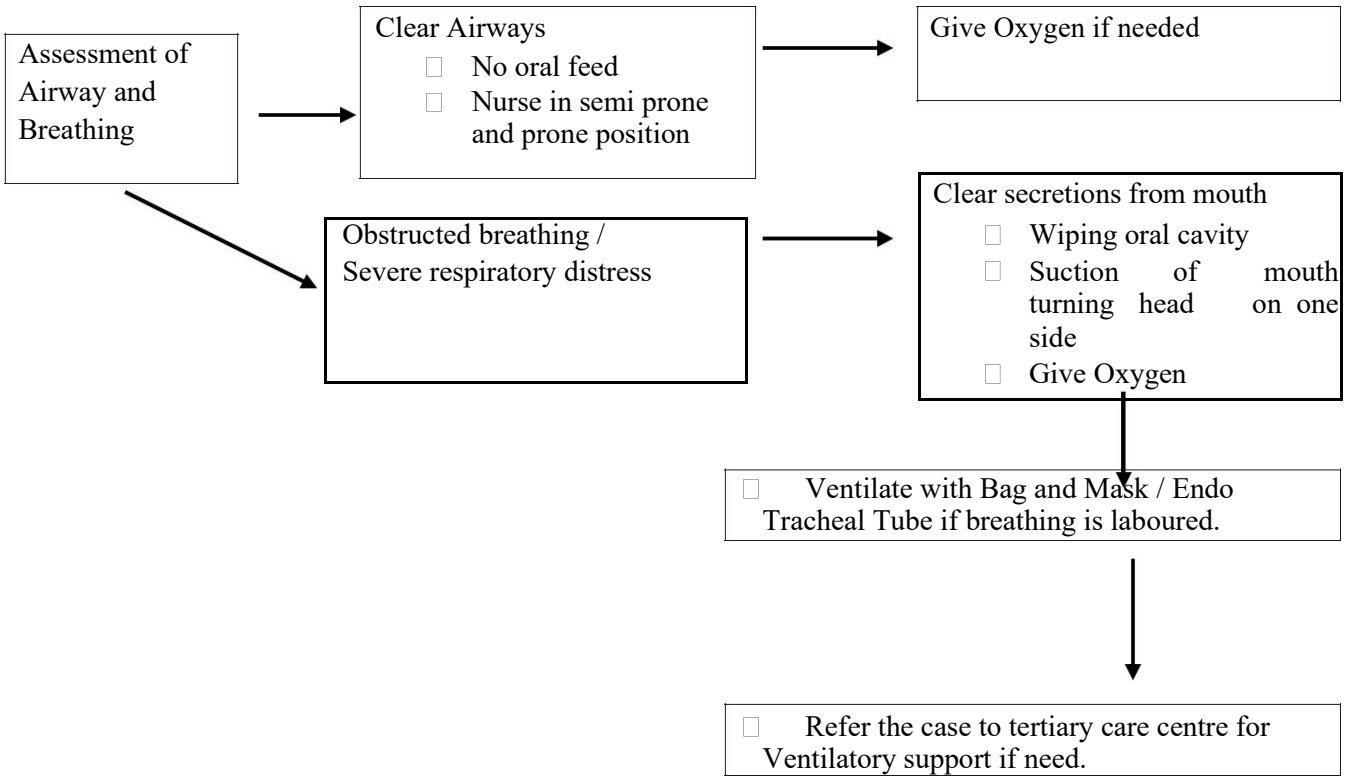
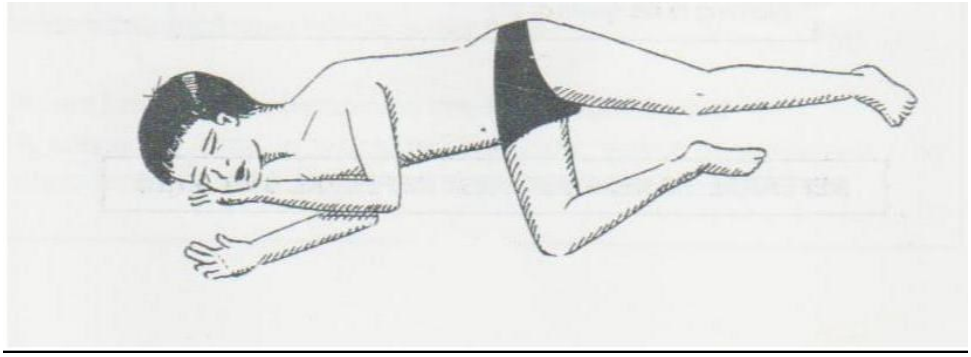


Fig 1. Position of the Patient

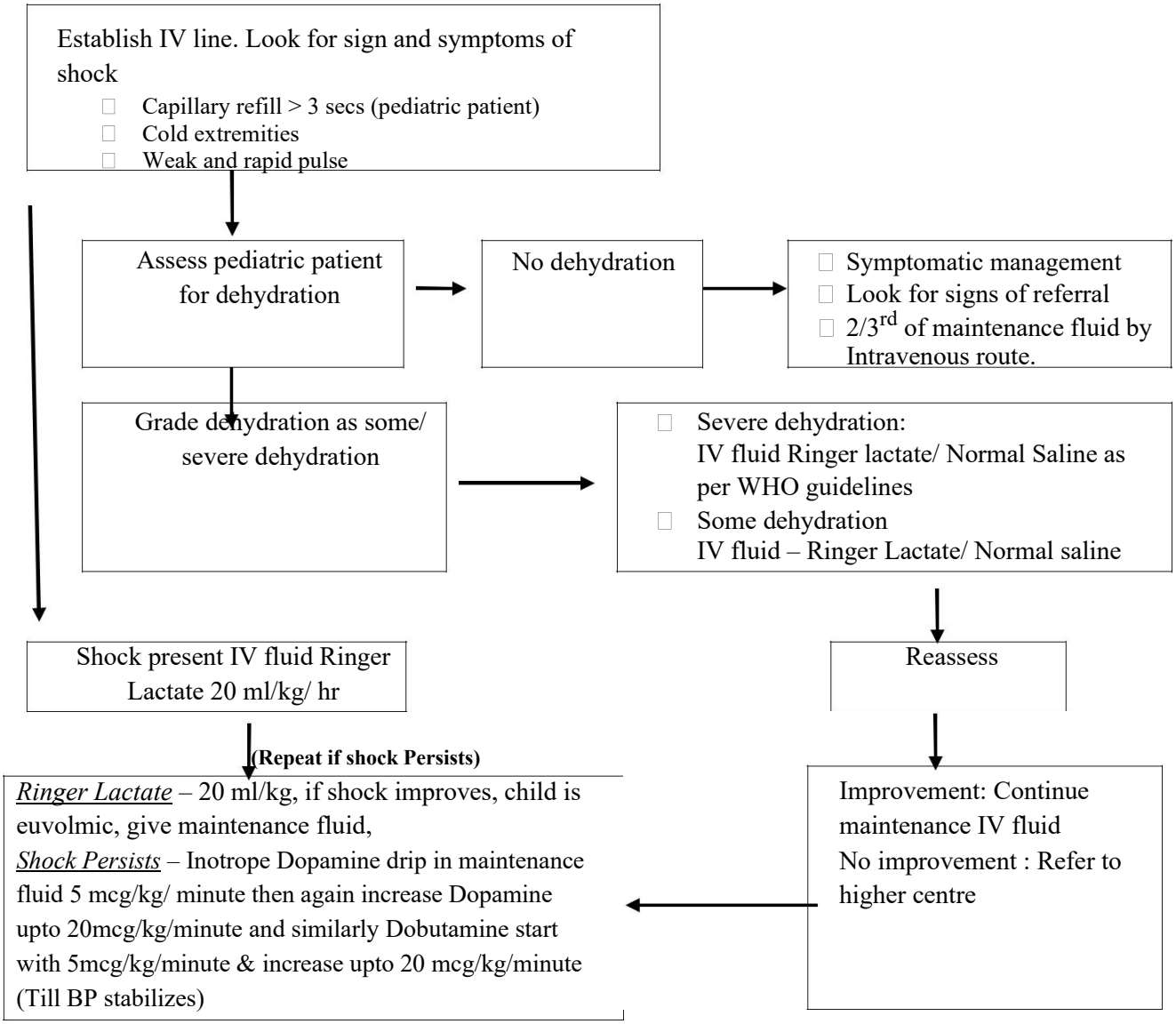
- Turn the patient on the prone side to reduce risk of aspiration.
- Keep the neck slightly extended and stabilize by placing cheek on one hand.
- Bend one leg to stabilize the body position.



Indications of Ventilatory Support

1. Deteriorating General Condition
2. Very Shallow Respiration/ Severe Respiratory Distress/ Heart Sound are Feeble
3. Capillary Refilling time/ colour of Patient Not Improved
4. Dusky Colour of body/ Cyanosis
5. Needs continuous Bag and Mask (Ambu) respiration
6. ABG Parameters

MANAGEMENT OF CIRCULATION



NB : These are broad guidelines; ultimate decision regarding management will depend upon the attending physician.

Management of Convulsions & I.C.T.

Give anti convulsants if there was a history of convulsions and not given earlier, or convulsions are present. Number one to three are first drug of choice, if convulsions are not controlled.

Anti Convulsants

Sl. No.	Name of Drugs	Closes	Available as	Route of Administration	Indication	Limitation/ Side Effects
1.	Phenobarbitone (Gardinal/Luminal)	20-40mg/kg As loading dose	200mg per ml. ampule	I/V Slowly after dilution in normal Saline	Convulsion in infants can be used in all age Groups	Good drug controlling seizure & long term use.
2.	Phenytoin (Eptoin/Dilantin)	15-20mg/kg	100mg/ 2ml amp.	I/V Slowly after dilution in normal Saline	Convulsion in all age all Groups	Good drug for control of seizure & as maintenance
3.	Sod. Valporate	20-40 mg/kg	I/V Oral Syrup	Syrup can be given as per rectal	All age group	-do-
4.	Diazepam	0.1-0.3mg/kg	I/V or P/R	I/V slowly Syrup Suppository P\R	Uncontrolled Convulsions	May cause respiratory arrest in newborns & infants. Short acting
5.	Lorazepam	0.05-0.1mg/kg oral,	I\V	I/V Slowly	Uncontrolled Convulsion Safe in infants	Tachy cardea, depression Confusion blurred vision
6.	Midazolam	0.2mg/kg	1mg/5kg	S/C, intra nasal safe in Injections	Uncontrolled convulsion in Infants	Short acting
7.	Inj. Paraldehyde 11%	0.1-0.2mcg/kg deep gluteal can be replaced after ½-hrs.				

Maintenance Dose

- Phenobarbitone 3-8mg/kg/day I/V or oral
- Phenytoin 5-8 mg/kg/day I/V or oral
- Sodium Valproate 40-60mg/kg/day Oral

Management of Increased Intracranial Pressure (Only after correction of Dehydration)

i. Mannitol 20% I/V – 5 ml/kg in ½ hrs as 1st dose than 2.5 ml/kg at 6 hrs. intervals upto 48 hours (8 doses).
ii. Injection Lasix I/V – 1 mg /kg upto 40 mg can be given.
iii. Glycerol solution:- Oral – 0.5 ml/kg mix with fruit juice can be given by nasogastric tube – 3 times a day
iv. Steroids – are not indicated in viral encephalitis including JE.

Control of Temperature

a) If No Rigors:-

i. Tap Water Sponging: Not only on forehead, palms or soles, whole body to be wet with water and fan(ceiling/table/manual) is on. Cold sponging is harmful.
ii. If temperature is too high – Cold Sponges may be kept on head, axilla and groins.
iii. Injection Paracetamol: 5mg/kg, deep intra muscular at either lateral side of thigh or upper outer Quadrant of hip. If injection is not available give Paracetamol 10-15mg/kg maximum upto 600 mg by Nasogastric tube. Paracetamol Suppository are also available which may be used. Other antipyretic medicines e.g. nemusulide/ brufen/ meftal/ aspirin etc are not advisable, specially in children.

b) If chills or Rigors present : _

i. Don't cover patients
ii. Don't do water sponging
iii. Use Paracetamol injection, syrup, through nasogastric tube or Paracetamol suppository as advised above.

Management of Fluid Electrolytes And Calories/Nutrition

(A) Assessment of Dehydration

Dehydration is classified into No/ some/ Severe Dehydration. Since it is difficult to assess dehydration in a patient of encephalitis as the patient is lethargic and unable to drink, therefore, skin turgor takes precedence over other signs. An objective way of classification would be as follows:

(i) Some Dehydration:

- Irritability
- Thirsty
- Sunken Eyes
- Less Tears
- Dry Mouth
- Skin Turgor Delay

(ii) Severe Dehydration:

- Floppiness
- Drowsiness/ Lethargy
- Unconscious
- Inability to Drink

(iii) Signs of shock

- Oliguria/ anuria
- Rapid and thready pulse
- Capillary filling time > 3secs
- Low Blood Pressure

(B) Management of Dehydration:

(a) **Some Dehydration:**

- IV fluid Ringer lactate/ N saline 100m/kg to be given over 8 hrs.
- Where the facility for IV fluids is not available administer ORS 75m/kg in 4 hrs through nasogasrtic tube
- Reassess: if there is improvement continue with maintenance IV fluid/if no improvement is detected, switch to plan for severe dehydration

(b) Severe Dehydration

- IV fluid Ringer lactate 100ml/kg is given as per the table below Table 1:

Rate of Fluid (Ringer Lactate)	30ml/kg	70ml/kg
< 1yr	2 hrs	4 hrs
>1yr	1 hrs	5 hrs

- Reassess: If there is improvement switch to maintenance/ if no improvement is detected or deterioration is observed infuse IV fluid more rapidly.

(b) Maintenance

Maintenance fluid is administered at the following rate Table 2:

Weight	Fluid Volume
1 – 10	10 ml / kg
11 – 20	1000 ml + 50cc/kg over & above 10 kg
21 – 40	1500 ml+20cc/kg over & above 10 kg

(C) <u>Calories/ Nutrition</u>

During CNS infections and convulsion and hyperpyrexia state, calories specially glucose required is increased and it should be given in form of 10% Dextrose or even 25% Dextrose may be given on arrival of the patient. A total dose of 200 mg/kg may be

given. All I/V fluids with Dextrose should be continued till patient is stabilized, convulsions are controlled, no vomiting and distention of abdomen, at this time, intra gastric feeding may added and slowly I/V fluids are replaced by total nasogastric feeding.

GENERAL MANAGEMENT

i. ***Suction :*** Frequent suction either by mucous sucker, or suction machine to be done on an unconscious patient, so secretion may not collect in mouth to avoid aspiration and maintenance the patency of airways.

ii. ***Nasogastric Aspiration :*** Nil orally, place a Nasogastric/ Ryles tube into stomach and do a frequent suction to avoid any vomiting and aspiration. It will also help in decompensation of stomach and decrease intra-abdominal pressure. It will help in respiration.

iii. ***Care of Eye, Bowel Bladder & Back :***

- Eyes to be covered by wet gauge
- An antibiotic Eye ointment may be applied twice a day or liquid paraffin may be put in eyes to avoid drying of Cornea.
- If child does not pass stool, put a glycerine enema.
- Bed should be well maintained, don't allow to form any bed sore. Spirit & powder may be applied on back and on all pressure points.
- Frequent changing of patient's position.
- Catheterize the patient to avoid soiling of beds.
- Physiotherapy once patient is stabilized
- Other General Nursing Care
- Treat Secondary infections – by appropriate antibiotics
- Treat underlying other pathology – e .g. anemia, malnutrition, etc.

TREATMENT OF SPECIFIC CAUSE IF ANY

i. **Herpes -** Acyclovir – 10 mg/kg/dose, slowly over a period of one hour – 8 hourly X 21 days.

ii. **Zoster Varicella -** Acyclovir – 10mg/kg/dose, 1/2hrs slowly, over a period of 1 hour – 8 hourly X 2-3 weeks.

iii. **Malaria -** I/V Quinine – 20 mg/kg in 5% Dextrose slowly over a period of 1hr then 10mg/kg 8 hourly. Monitor Blood Sugar and Blood Pressure.

iv. **Meningitis (Pyogenic) -**

Start with inj. Ampicillin 400 mg kg 6 hourly upto 12gm/day+

Inj. Ceftrioxone 100-150mg/kg as stat dose than in two dived doses 12 hourly+ Steroid Change antibiotics according to C/S report and response.

v. **TBM -**Anti Tubercular Drugs (1NH, PZA, Rifampicin + Ethambutol + Steroids)

vi. **Toxoplasmosis -** Pyrimethamine 2mg/kg/24 hours in two divided doses X 2 days than 1mg/kg/ on alternate day.

vii. **Amoebiasis -**Metronidazole – 10mg/kg I/V slowly 8 hourly X 10-14 days.

viii. **Fungal Infection -** Inj. Amphotericin – B 5mg/kg/24 hours or Fluconazole – oral 200-400mg/kg for 3-6 months.

ix. **Neurocysticercosis -** Albendazole oral 10/mg/kg(upto 400 mg)/day X 2 weeks.

x. **Scrub Typhus -** Doxycycline 200 mg/ day in two divided doses for individuals above 45 kg for duration of 7 days. OR Azithromycin 500 mg in a single oral dose for 5 days. In children, Azithromycin in the single dose of 10 mg'/kg body weight for 5 days.

REHABILITATION

- Physiotherapy/ PMR
- Advice of Pediatric Neurologist
- Correction to fix deformity – by Orthopaedic Surgeon
- Various prosthesis
- Artificial appliances

Management in Tertiary Level Hospitals

i. Hypoxia is alleviated by intubation, positive pressure ventilation, and ensuring an arterial Pao_2 of 65 mm Hg or better.

ii. Hypotension is treated in a stepwise fashion by first volume infusion with isotonic fluids to normovolemia, next vasopressors and finally treatment is directed at reducing ICP in an effort to maintain CPP greater than 50.

iii. Brainstem involvement may necessitate intubation & mechanical ventilation.

iv. Cardiac arrest requires resuscitation measures.

v. SIADH (Syndrome of Inappropriate Anti Diuretic Hormone) is treated with Hypertonic saline.

Role of Immunoglobulins in Case Management of AES cases:

The experts are of the opinion that IV immunoglobulin cannot be recommended for routine use in AES cases including JE in view of the current scientific evidence.

Investigations, Sample Collection & Transportation

A. Investigations

i. Complete blood counts

ii. Peripheral blood smear-Malarial parasite

iii. Blood glucose, Electrolytes

iv. CSF and Blood for serology by lgM ELISA/ virus isolation, CSF is preferred since by the time patient presents with CNS manifestations the level of viremia in blood has decreased and there is reaction with other flaviviruses.cross

v. Other test if necessary : LFT/KFT/Blood Culture/X-ray/Ultrasound/ CT/MRI/ECHO/ any specific test . Enzyme/ECG/EEG/Suspected Etiology

Virus isolation should be done only in Apex Reference Laboratories and only for selected cases by investigating team.

B. Specimen Collection

Blood (serum) and CSF specimen are to be collected. Blood specimen should be collected within 4 days after onset of illness for isolation of virus and at least 5 days after onset of illness for detection if IgM antibodies. A second convalescent sample should be collected 10-14 days after the first sample.

1) **Blood/Serum**

i) Equipment required

- 5ml vacutainer tube(non-heparinized) with 23g needle/5ml syringe with needle
- 5ml blood collection tube if syringe and needle are used for blood collection
- Disposable gloves and face mask
- Tourniquet
- Sterlized swabs
- Sterile serum storage vial
- Specimen labels, marker pen
- Band aid
- Zip lock plastic bags
- Lab request form
- Cold box(vaccine carrier) with ice pack
- First- aid kit

ii) Collection procedure

 Collect 5ml blood in a sterile tube labelled with patient identification and date of collection.

 Keep at room temperature till clot retracts from serum.

 Blood can be stored at 4-8° Celsius for 24hrs before serum is separated, do not freeze whole blood.

 Transport whole clotted blood specimen to laboratory on ice if it can reach lab in 24 hrs/centrifuge at 1000rpm for 10mins to separate the serum or if centrifuge is not available carefully remove serum with a pipette and transfer serum to a sterile vial and store at 4-8°C.

2) **CSF -** All attempts should be made to collect CSF specimens for confirmation of diagnosis.

i) Collection

 Usually 2-3 ml of fluid is collected in a sterile screw capped bottle.

 Divide it into three parts – 1) For cell count and biochemistry 2) For serology (JE, Scrub, Dengue etc.) 3) For culture and sensitivity. If culture is not done, then two parts will be enough.

 Transport to the laboratory as soon as possible.

C. Transportation

Blood :

 Specimen should be transported to laboratory as soon as possible, do not wait for collection of additional specimens.

 Put specimen in zip pouch/plastic bag with absorbent material(cotton/tissue).

 Use vaccine carrier/thermos flask for transport. In vaccine carrier use frozen.

packs along the sides and place specimen in the centre. Transport as in reverse cold chain.

 Place lab request form in a plastic bag and tape to inside of carrier.

 Inform the lab about the time and manner of transportation.

 Transport the serum on wet ice within 48hrs or it can be stored at 4-8°C for 7 days.

 If a delay is anticipated sera should be frozen at -20°C and transported on frozen ice packs. Repeated freezing and thawing should be avoided as it affects the stability of IgM.

CSF :

 Store at 4°C as soon as possible after collection and dispatch at the earliest on wet ice in vaccine carrier/thermos flask.

Sample part meant for culture and sensitivity is to be kept in room temperature (Not in Refrigerator / vaccine carrier).

 Hands carry the specimen to laboratory preferably due to urgency.

 For PCR transport specimen on dry ice.

 A designated person should be responsible for storage, packing and transportation as per national guidelines.

List of JE Sentinel Labs and tagging with Districts

Sl No.	**District/Health District**	**JE Sentinel Labs**
1	Coochbehar	MJN District Hospital
2	Alipurduar	
3	Jalpaiguri	Jalpaiguri Distrct Hospital
4	Darjeeling	North Bengal Medical College Hospital
5	Kalimpong	
6	Uttar Dinajpur	Raigang District Hospital
7	Dakshin Dinajpur	Balurghat District Hospital
8	Malda	Malda Medical College Hospital
9	Murshidabad	Murshidabad Medical College Hospital
10	Howrah	SSKM Hospital
11	South 24 Parganas	
12	Diamond Harbour HD	
13	Purba Bardhaman	Burdwan Medical College Hospital
14	Paschim Bardhaman	
15	Birbhum	Suri District Hospital
16	Rampurhat HD	
17	Bankura	Bankura Sammilani Medical College Hospital
18	Bishnupur HD	
19	Purulia	
20	Paschim Medinipur	Midnapur Medical College Hospital
21	Jhargram	
22	Kolkata	School of Tropical Medicine, Kolkata
23	Midnapur East	
24	Nandigram HD	
25	Hooghly	
26	Nadia	
27	North 24 Parganas	
28	Basirhat HD	

Laboratory Request Form : IgM ELISA test for Japanese Encephalitis

Name of the patient (IN CAPITAL LETTER) :

Name of guardian/husband : Age : Sex : M / F

Address (in detail, including name of the Block/Municipality with Ward No.) :

Contact phone no. of the patient:

Name of the institution where admitted:

Full address, phone no. & e-mail of the facility (if a private facility):

Hospital IPD Regn. No.- Date & time of admission :

Ward : Bed no. :

Name of the treating physician:

Date of onset of present illness:

Relevant signs & symptoms : [Tick in the blank cells where applicable]

Fever		Convulsion		Comatose/ unconscious	
Meningeal sign		Change in mental status : Y / N; mention what change-			
Any other sign/symptom (specify) :					

Whether a case of AES: Yes ☐ No ☐. Whether vaccinated against JE : ☐ (Y/ N/ Unknown)

Type of sample(s) : (Tick) **CSF / Serum** [Both may preferably be collected]

Date & time of collection of sample (serum): Sample no. :

Date & time of collection of sample (CSF): Sample no. :

Date on which sample sent to the laboratory :

Full name of the Doctor/ Superintendent sending the sample(s) :

Date of despatch of sample by Dy.CMOH-II,
if routed through his office : Signature & Seal
Signature :

NB : 1. Please fill up the form properly before sending samples to the laboratory. Lab. may refuse asample if not accompanied by a completely filled up laboratory request form.

2. Test for JE is not to be requested if it is not a case of Acute Encephalitis Syndrome (AES), unless specially suggested from state level for surveillance purpose.

3. Sample for JE-IgM ELISA is not to be collected before 4 days of disease onset.

4. Serum & CSF samples for JE-serology are to be stored & transported maintaining cold chain (2-8˚C).

Clinical case definition of AES :A person of any age, at any time of the year with acute onset of fever and a change in mental status (including symptoms such as confusion, disorientation, coma, or inability to talk) AND/OR new onset of seizures (excluding simple febrile seizures).

Government of West Bengal
Directorate of Health Services (Public Health Branch)

Swasthya Bhawan, 1st Floor,

GN-29, Sector-V, Salt Lake, Kolkata-700091

Memo. No. HPH/10"P-2/2019/226 Date: 03.12.19

ORDER

After due consideration, following protocol for management of scrub typhus has been decided.

I. For acute febrile illness of any duration with any one of the following:
1. Mark of mite Bite i.e. eschar.
2. Encephalitis or Meningo-encephalitis.
3. Sign of vital organ involvement.
4. Haemorrhagic manifestation.

Immediate empirical antibiotic treatment for Scrub Typhus is to be started.

II. Acute febrile illness for 5 days or more, which have been already tested for malaria and dengue and found to be negative but with any two of the following criteria:
1. Maculo popular Rash.
2. Lymphadenopathy.
3. Definite myalgia.
4. Dry cough.
5. Hepatomegaly/ Hepatitis with Jaundice.

Immediate antibiotic treatment for scrub typhus to be started.

The treatment required for Scrub Typhus:

Adults:

- Doxycycline 200mg/day in 2 divided doses for 7 days (Contraindicated in Pregnant women) OR
- Azithromycine 500 mg in a single oral dose for 5 days (in Pregnant women)

Children:

- Doxycycline 4.5mg/kg bw/day in 2 divided doses for 7 days (below 45 kg) OR
- Azithromycine 10mg/kg bw/day in a single oral dose for 5 days

Complicated cases:

- IV Doxycycline 100mg twice daily in 100ml NS over 30 mins followed by Oral Therapy for 7-15 days OR
- IV Azithromycine 500mg in 250ml NS over 60 mins OD for 1-2 days followed by Oral Therapy for 5 days OR
- IV Chloramphenicol 50-100mg/kg/day in 6 hrly doses over 1 hr initially followed by Oral Therapy for 7-15 days

Testing: IgM ELISA for Scrub Typhus is to be performed for confirmation of diagnosis, after 7 days of onset. Serum sample is to be sent to laboratory in cold chain (2-8°C).

3/12/19
Director of Health Services
Government of West Bengal

03/12/19
Director of Medical Education
Government of West Bengal

Notes

MALARIA

Introduction

- Malaria is a potentially life-threatening parasitic disease caused by parasites known as *Plasmodium vivax (P. vivax), Plasmodium falciparum (P. falciparum), Plasmodium malariae (P. malariae), Plasmodium ovale (P. ovale)* and *Plasmodium knowlesi* (*P. knowlesi)*
- It is transmitted by the infective bite of female *Anopheles* mosquito
- Man develops disease after 10 to 14 days of being bitten by an infective mosquito
- There are two types of parasites of human malaria, *Plasmodium vivax & P. falciparum*, which are commonly reported from India.
- The parasite completes life cycle in liver cells (pre-erythrocytic schizogony) and red blood cells (erythrocytic schizogony).

Clinical features

Fever is the cardinal symptom of malaria. It can be intermittent with or without periodicity or continuous.

Many cases have chills and rigors.

The fever is often accompanied by:

- Headache
- Myalgia
- Arthralgia
- Anorexia
- Nausea and vomiting

The symptoms of malaria can be non-specific and mimic other diseases like viral infections, enteric fever etc. Malaria should be suspected in patients presenting with above features. Malaria is known to mimic the signs and symptoms of many common infectious diseases. The other causes of fever should also be suspected and investigated in the presence of manifestations like running nose, cough and other signs of respiratory infection, diarrhoea/dysentery, burning micturition and/or lower abdominal pain, skin rash/infections, abscess, painful swelling of joints, ear discharge, lymphadenopathy, etc.

All clinically suspected malaria cases should be investigated immediately by microscopy and/or Rapid Diagnostic Test (RDT).

Diagnosis

Microscopy: Microscopy of stained thick and thin blood smears remains the gold standard for confirmation ofdiagnosis of malaria. The advantages of microscopy are:

- The sensitivity is high. It is possible to detect malaria parasites at low densities. It also helps to quantify theparasite load.
- It is possible to distinguish different species of malaria parasites and their different stages.

Rapid Diagnostic Test:

Rapid Diagnostic Tests are based on the detection of circulating parasite antigens. Severaltypes of RDTs are available (http:// www.wpro.who.int/sites/rdt). The NVBDCP has rolled out bivalent RDTs (for detecting *P. falciparum* and *P. vivax*) for use in the public health sector.

RDTs are produced by different manufacturers, so there may be differences in the contents and in the manner in which the test is done. The user manual should always be read properly and instructions followed meticulously. The results should be read at the specified time. It is the responsibility of the health care personnel doing a rapid test for malaria to ensure that the kit is within its expiry date and has been transported and stored under recommended conditions. Ensure that correct buffer is always used and not done with buffer for other kits or with normal saline/ distilled water. Failure to observe these criteria can lead to incorrect results. It should be noted that Pf HRP-2 based kit may show positive result up to three weeks after successful treatment and parasite clearance. In these cases, results should be correlated with microscopic diagnosis.

Diagnosis of severe malaria cases negative on microscopy

Microscopic evidence may be negative for asexual parasites in patients with severe infections due to sequestration and partial treatment. Efforts should be made to confirm these cases by RDT or repeat microscopy. However, if clinical presentation indicates severe malaria and there is no alternative explanation, these patients should be treated accordingly.

Severe malaria due to *P. vivax*

In recent years, increased attention has been drawn to severe malaria caused by *P. vivax*. Some cases have beenreported in India along with deaths, and there is reason to fear that this problem may become more common in the coming years. Severe malaria caused by *P. vivax* should be treated like severe *P. falciparum* malaria, however, primaquine should be given for 14 days for preventing relapse as per guidelines after the patient recovers from acute illness and can tolerate primaquine.

Severe malaria: Clinical features

Clinical features of severe manifestations can develop in *P. falciparum* infection over a span of time as short as12–24 hours and may lead to death, if not treated promptly and adequately. Severe malaria is characterized byone or more of the following features:

- **Impaired consciousness/coma** [A Glasgow coma score < 11 in adults or a Blantyre coma score < 3 in children. The coma should persist for at least 1 hour after a generalized convulsion]
- **Repeated generalized convulsions** [> 2 episodes within 24 hours]
- **Prostration**: Generalized weakness so that the person is unable to sit, stand or walk without assistance
- **Renal failure** (Serum Creatinine > 3 mg/dl.)
- **Jaundice** (Serum Bilirubin > 3 mg/dl)
- **Severe anaemia** (Hb < 5 g/dl or a haematocrit of ≤ 15% in children < 12 years of age (< 7 g/Dl and < 20%, respectively, in adults) with a parasite count > 10 000/μL)
- **Pulmonary edema/acute respiratory distress** syndrome [Radiologically confirmed or oxygen saturation
    - < 92 % in room air with a respiratory rate >30/min, often with chest in-drawing and crepitations on auscultation.]
- **Hypoglycaemia** [Plasma Glucose < 40 mg/dl]
- **Metabolic acidosis** [A base deficit of > 8 mEq/L or, if not available, a plasma bicarbonate level of < 15 mmol/L or venous plasma lactate of ≥ 5 mmol/L. Severe acidosis - respiratory distress (rapid, deep, labored breathing)]
- **Circulatory collapse/shock** [Systolic BP < 80 mm Hg in adults, < 50 mm Hg in children aged 1–5 years with evidence of impaired perfusion (cold peripheries or prolonged capillary refill ≥ 3 sec)]
- **Abnormal bleeding and Disseminated Intravascular Coagulation (DIC) [Significant bleeding including recurrent or prolonged bleeding from the nose, gums or venipuncture sites; hematemesis or melena]**
- **Haemoglobinuria**
- **Hyperpyrexia** (Temperature > 106.7 °F or > 41.5 °C)
- **Hyperparasitaemia** (*P. falciparum* parasitaemia > 10%).
    - Foetal and maternal complications are more common in pregnancy with severe malaria; therefore, those need prompt attention.

EXCERPTS FROM GUIDELINES FOR DIAGNOSIS & TREATMENT OF MALARIA IN INDIA (Based on National Drug Policy on Malaria, 2013)

Treatment of Vivax Malaria:

AGE	Day1		Day2		Day3		Day 4 to 14
	CQ (150 mg)	PQ (2.5mg)	CQ (150mg)	PQ (2.5mg)	CQ (150mg)	PQ (2.5mg)	PQ (2.5mg)
Less than 1year	½	0	½	0	¼	0	0
1-4 years	1	1	1	1	½	1	1
5-8 years	2	2	2	2	1	2	2
9-14 years	3	4	3	4	1½	4	4
15 years or more	4	6	4	6	2	6	6
Pregnancy	4	0	4	0	2	0	0

Treatment of Falciparum Malaria:

It is imperative to start the treatment for falciparum malaria immediately on diagnosis.

A. Treatment of uncomplicated *P. falciparum* cases:

All tablets for a particular day should be taken together, swallowed with water.

Age Group (Years)	1st day		2nd day		3rd day
	AS	SP	AS	PQ	AS
0-1*	(25mg)	(250+12.5 mg)	(25mg)	Nil	(25mg)
1-4	(50 mg)	(500+25 mg)	(50mg)	1 (7.5 mg)	(50mg)
5-8	(100mg)	(750+37.5 mg)	(100mg)	2 (7.5mg)	(100mg)
9-14	(150mg)	2 (500+25 mg each)	(150mg)	4 (7.5mg)	(150mg)
15 & above	(200mg)	2 (750+37.5 mg each)	(200mg)	6 (7.5mg)	(200mg)

AS = artesunate, SP = sulphadoxine-pyrimethamine, PQ = primaquine; prevents transmission of Pf malaria to others by killing the gametocytes. *SP is not to be prescribed for children < 5 months of age, who should be treated with alternate ACT.

B. Treatment of uncomplicated *P. falciparum* cases in pregnancy:

- **1st trimester**: Quinine salt 10mg/kg 3 times daily for 7days.

Quinine may induce hypoglycemia. Pregnant women should not start taking quinine on an empty stomach andshould eat regularly, while on quinine treatment.

In severe malaria in first trimester of pregnancy, parenteral quinine is the drug of choice. However, if quinineis not available, artemisinin derivatives may be given to save the life of mother.

- **2nd and 3rd trimester**: ACT-SP.

  [Primaquine is contraindicated in pregnancy].

In severe malaria during second or third trimester, parenteral artemisinin derivatives are preferred.

C. Treatment of mixed infections (*P. vivax* + *P. falciparum)* cases:

Mixed infections should be treated with full course of ACT (like falciparum malaria) and Primaquine 0.25mg per kgbody weight daily for 14 days (like vivax malaria).

D. Anti-malarial for severe malaria cases:

CHOOSE ONE of following four options	Follow-up treatment, when patient can take oral medication following parenteral Rx
Artesunate: 2.4 mg/kg i.v. or i.m. given on admission (time=0), then at 12 hr and 24 hr,then once a day **(most preferred among artemisinin derivatives).Or Artemether:** 3.2mg/kg bw i.m. given on admission, then1.6mg/kg per day. **Or Arteether:** 150mg daily i.m. for 3 days in adults only (not recommended for children).	Full oral course of Area-specific ACT is to be givenafter parenteral therapy. Treat with ACT-SP for 3 days+ PQ single dose (asmentioned above).
Quinine: 20mg quinine salt/kg body weight on admission (IV infusion or divided IM inj.) followedby maintenance dose of 10mg/kg 8 hourly; infusion rate should not exceed 5mg/kg per hour. Loading dose of 20mg/kgshould not be given, if patient has already received quinine.	**Quinine:** -10mg/kg orally three times a day with doxycycline100mg once a day or clindamycin (doxycycline is contraindicated in pregnant & lactatingwomen and children< 8 years of age) - Complete 7 days of treatment.

Rapid intravenous administration of quinine is dangerous.

Each dose of parenteral quinine must be administered as a slow, rate-controlled infusion (usually diluted in 5% dextrose and infused over 4 hours). The infusion rate should not exceed 5 mg salt/ kg bw per hour. It may cause hypotension if administered rapidly.
If intramuscular quinine is to be given, give it to anterior thigh; and should not be given in buttock in order to avoidsciatic nerve injury. The first dose should be split, with 10mg/ kg bw into each thigh.

The parenteral treatment in severe malaria cases should be given for minimum of 24 hourd once started irrespective of patient's ability to take oral medication earlier than 24 hours. [In parenteral treatment with quinine it should beminimum 48 hours].

After parenteral artemisinin therapy, start within 8-12 hours a full course of area-specific oral ACT for 3 days. After parenteral Quinine therapy a patient should receive oral Quinine10 mg/kg bw three times a day for 7 days(including the days when parenteral dose was given) plus Doxycycline 3mg/kg bw once a day or Clindamycin 10mg/kg bw 12-hourly for 7 days or ACT as described. [Contraindication of Doxycycline: see table above].

Revised dose recommendation for parenteral artesunate in young children [Annex 1]

Children weighing < 2 0 kg should receive a higher dose of artesunate (3 mg/ kg bw per dose) than largerchildren and adults (2.4 mg/ kg bw per dose) to ensure equivalent exposure to the drug.

Management of severe *P. falciparum* malaria

Severe malaria is an emergency. In an unconscious or **comatose (cerebral malaria)** patient A, B, C i.e. Airway, Breathing and Circulation should be assessed first and maintained.

1. The patient should preferably be kept in a bed with railed cot on his or her side. Every two hourly change of posture is done. Air mattress is preferred to protect pressure points.

2. Airway is maintained by chin lift or neck extension. Oropharyngeal airway tube or endotracheal tube is placed to suck the secretions in oropharynx and to prevent the falling back of the tongue.

3. Adequate breathing should be ensured. If necessary, mouth to mouth ventilation can be given. If SpO2 is decreasing, O2 should be given either by nasal cannula (with a flow rate of 1-5 L/min) or face mask (flow rate of 5-10 L/min) or non-rebreathing face mask (flow rate of 10-15 L/min). Sometimes patient may require intubation and mechanical ventilation.

4. Then adequate circulation should be maintained by intravenous fluid. If carotid or femoral pulses are palpable, ventilation with O2 is continued.

5. After resuscitation by basic life support, a Ryle's tube is inserted and to measure urine output a condom catheter is preferable in male patients as indwelling catheters are common source of UTI.

6. A rapid clinical assessment of the degree of dehydration and the intravascular volume should be made. Vital signs (pulse, BP, respiration, temperature, oxygen saturation) and capillary refill time

should be recorded. The assessment of fluid balance is critical in severe malaria. In children judicious fluid management should be done. Children who are severely dehydrated on admission need rehydration but rapid fluid loading is harmful. Also, in case of adults, overhydration may precipitate pulmonary oedema and underhydration may cause shock or precipitate or worsen renal impairment and acidosis. Frequent and careful evaluations of the jugular venous pressure, peripheral perfusion, skin turgor and urine output should be done.

7. Respiratory pattern should be observed to identify any signs of respiratory distress (deep laboured breathing, flaring of the ala nasae, intercostal or substernal retraction).

8. Other treatable causes of coma (e.g. hypoglycaemia, continuous seizure activity, bacterial meningitis) should be excluded. Immediate measurements of blood glucose (rapid stick test), urea, creatinine, parasitaemia (parasite count, stage of development of parasite and proportion of neutrophils containing malaria pigment) should be done. Blood glucose should be checked every 4 hours until recovery of consciousness. But these glucose stick tests may overestimate the frequency of hypoglycaemia so laboratory confirmation may be necessary.

9. Blood should be taken for cross-matching, complete blood count (specially haemoglobin, haematocrit, platelet count), clotting studies, LFT, KFT, electrolytes and blood culture.

10. The degree of acidosis is an important determinant of severity. Arterial blood gas (ABG) analysis and if possible venous lactate should be measured in unconscious patients who are hyperventilating or in shock.

11. Weight based parenteral antimalarial treatment should be started as soon as possible. Artesunate should be given by intravenous or intramuscular injection and artemether by intramuscular injection only. If quinine dihydrochloride is used a full loading dose (20 mg salt/kg) should be given to all patients if no clear history of adequate pretreatment. Quinine is given in dextrose solution. It should *never* be given by bolus intravenous injection.

12. In children with severe malaria, usually sepsis cannot be reliably excluded. So after sending blood culture empirical broad-spectrum antibiotics should be given until a bacterial infection can be excluded.

13. Urgent blood transfusion is required for severely anaemic (haematocrit <15%) children who has acidotic breathing or respiratory distress which indicate hypovolemia.

14. Adjuvant treatments e.g. corticosteroids, mannitol, heparin and adrenaline should be avoided.

14. After these immediate measures, a more detailed clinical examination should be done, with particular emphasis on the level of consciousness and recording of the coma score. The Glasgow Coma Scale (GCS) is used for adults and the Blantyre Coma Scale (BCS) is used in children.

15. Subsequent clinical observations should be frequent notice of vital signs, assessment of respiratory rate and pattern, assessment of the coma score and urine output.

16. Important indicators of recovery are time to recover consciousness (GCS 15 or BCS 5), time to drink and time to sit unaided and walk.

Convulsions: Airway should be maintained. Intravenous or in case children rectal/ intraosseous lorazepam (0.1 mg/kg) should be started promptly (or if unavailable, other options are diazepam 0.4 mg/kg slow iv or intramuscular paraldehyde 2 mg/kg or midazolam). If seizures are not controlled by above medications, then phenytoin (18 mg/kg diluted in 100 mL normal saline, infused over 20 minutes) or phenobarbitone (phenobarbital 15-20 mg/kg, slow IV push) may be used. The role of prophylactic anticonvulsants is controversial and should not be used.

Hyperpyrexia: Tepid sponging, ice bag on head, fanning, cooling blanket and antipyretic drugs like iv or oral paracetamol are used.

Acute pulmonary oedema Patient should be propped up at an angle of 45°. Oxygen and diuretics are given. Intravenous fluids are stopped. Intubation and positive end-expiratory pressure/continuous positive airway pressure ventilation should be started if the patient is hypoxic.

Acute kidney injury: After excluding pre-renal causes and checking fluid balance and urinary sodium, if patient is in established renal failure with multiple organ dysfunction, haemofiltration or haemodialysis should be started early or if not available, then peritoneal dialysis is started. Haemofiltration or haemodialysis are preferable to peritoneal dialysis as it is associated with more rapid resolution of biochemical abnormalities and lower mortality than peritoneal dialysis. In acute renal failure, the benefits of loop diuretics or dopamine are not proven. In the acute phase of the disease, renal impairment is hypercatabolic and indications for dialysis are uraemic complications, metabolic acidosis, volume overload or less commonly hyperkalaemia. An ECG should be performed in suspected acute renal failure but measurement of serum potassium is immediately not available. If there are signs of hyperkalaemia (peaked T waves, widening of the QRS complex) then intravenous calcium and glucose plus insulin, should be given immediately.

The dose of quinine should be reduced by between one-third and one-half on the 3rd day of treatment. Tetracycline is contraindicated, but doxycycline can still be given. There is no need of dose adjustment for Artesunate.

Hypoglycaemia: (blood glucose concentration of <2.2 mmol/L): Although hypoglycaemia is defined as glucose < 40mg/dL, the threshold for intervention for < 5 years of children is < 54mg/dL and for older children and adults is <40mg/dL. Blood glucose should be checked every 4 hourly. Hypoglycaemia should be treated by slow intravenous injection of 0.5–1 mL/kg of 25% dextrose and prevented by administering a 10% dextrose infusion at 1–2 mg/kg per hour.

Metabolic acidosis: Hypovolaemia, hypoglycaemia and septicaemia should be excluded or treated. In case of severe acidosis, haemofiltration or haemodialysis is started. Inj. sodium bicarbonate (7.5%) 1 meq/kg, lV may be given only in very severe acidosis (e.g. pH <7.15).

Severe anaemia (haemoglobin <5 g/100 mL or packed cell volume <15%): Fresh whole blood is transfused.

Spontaneous bleeding and coagulopathy: Patients with cerebral malaria may have haematemesis or a bloody nasogastric aspirate because of acute gastric erosions which is due to high-dose corticosteroids. In severe malaria < 5% of patients develop clinically significant DIC. Fresh whole

blood (cryoprecipitate, fresh frozen plasma and platelets if available) and vitamin K injection should be given to these patients.

Shock: Bacterial infection or septicaemia should be suspected if there are hypotension, cool extremities, delayed capillary refill and hyperlactatemia. Blood cultures should be sent before starting empirical antibiotic therapy with activity against gram- negative organism. Severe anaemia has been implicated as a primary risk factor for invasive bacterial infection most commonly nontyphoidal Salmonella. Haemodynamic disturbances are corrected. Supervening bacterial infections particularly pneumonia and catheter-related urinary tract infections are common. Aspiration pneumonia commonly follows generalized seizures and occurs if enteral feeding is started in unintubated comatose patients. Empirical treatment for pneumonia is third-generation cephalosporin and for aspiration pneumonia penicillin or clindamycin. Though continued fever after parasite clearance is common but sustained high fever in the acute phase of severe malaria is a poor prognostic sign. Antibiotic is only indicated if there is a definite focus of infection or the patient is severely ill.

1. Treatment of patients co-infected with HIV:

In people who have HIV/ AIDS and uncomplicated *P. falciparum* malaria, avoid artesunate + SP if they are being treated with co-trimoxazole, and avoid artesunate + amodiaquine if they are being treated with efavirenz or zidovudine.

2. Additional consideration for clinical management:

I. **Use of Antipyretics**: Antipyretics should be used if the core temperature is > 38.5 ^{0}C. Paracetamol at a dose of 15 mg/kg bw every 4 hr. Aspirin & other NSAIDs is no longer recommended because of the risk of gastrointestinal bleeding, renal impairment and Reye's syndrome.

II. **Use of anti-emetics**: Anti-emetics like domperidone or 5 HT3 antagonists like ondansetron be used.

III. **Management of seizures**: If the seizure continues, the airways should be maintained and anticonvulsants given (inj. valproate @20 mg/kg loading followed by maintenance @ 10 mg/kg 12 hrly). There is no evidence that prophylactic anticonvulsants are beneficial.

IV. **Fluid therapy**: Fluid requirements should be assessed individually. Adults with severe malaria are very vulnerable to fluid overload, while children are more likely to be dehydrated. The fluid regimen must also be adapted to the infusion of antimalarial drugs. Rapid bolus infusion of colloid or crystalloids is contraindicated.

Points to Note –

- **Pre-referral treatment options**

Where complete treatment of severe malaria is not possible but injections are available, give adults and childrena single dose of artesunate injection and then refer to an appropriate facility for further care.

Every 24 × 7 govt. health facility must have at least 2 doses of injection artesunate as a reserve stock as per a govt.circular.

- **Initiation of treatment and advice to the patient/caretaker**

Once a suspected case is diagnosed positive by RDT or microscopy, treatment is started. The first dose is alwaystaken in the presence of the health volunteer/worker. The blister pack with remaining tablets is given to the patient/caretaker to take home with clear instructions.

- That if the treatment is not completed as prescribed, the disease may manifest again with moreserious features and may be more difficult to treat.
- To come back immediately, if there is no improvement after 24 hours, if the situation gets worse orthe fever comes back.

- That regular use of a mosquito net (preferably insecticide treated net) is the best way to preventmalaria

Caution: If the patient isa child under 5 years or pregnant, ask the patient to wait for 15 minutes after taking the first dose. If it is vomited within this period, let the patient rest for 15 minutes, and then give the first dose again i.e. open a new blister-pack and discard what remains of the old. If the patient vomits the first dose again, it is considered a case of severe malaria, refer the patient immediately to the nearest Block PHC/ RH/Hospital.

General recommendations for the management of uncomplicated malaria

- Avoid starting treatment on an empty stomach. The first dose should be given under observation.
- Dose should be repeated if vomiting occurs within half an hour of antimalarial intake after anti-emetics.
- The patient should be asked to report back, if there is no improvement after 48 hours or if the situationdeteriorates.
- The patient should also be examined and investigated for concomitant illnesses.

Primaquine therapy: Caution

Caution should be exercised before administering primaquine in areas known to have high prevalence of G6PD deficiency. Patient should be advised to stop primaquine immediately if he/she develops any of the following symptoms and should report to the doctor immediately: (i) dark coloured urine (ii) yellow conjunctiva (iii) bluish discoloration of lips (iv)abdominal pain (v) nausea (vi) vomiting (vii) breathlessness, etc.

Considering the varying relapse rates, G6PD deficiency and facilities for G6PD testing, individual clinicians should weigh risks versus benefits while prescribing primaquine.

Clinical observation of admitted cases

- **Vitals signs with temperature recording**
- **Urine output**
- **Coma score**
- **Blood glucose in comatose/ unconscious patient every 4 hourly**

Other points

- If a suspected malaria patient has a negative RDT, it can be assumed that the patient does not have malaria and another cause of the symptoms should be sought for. If no other cause can be found and the clinical suspicion is high for Malaria (e.g. intermittent fever with rigors and sweats), the test should be repeated after about 24 hours and special efforts should be made to obtain the microscopy result rapidly.
- If the tests for malaria (both RDT & microscopy) are negative, but history & examination findings clearly point to Malaria (uncomplicated/severe) and there is no alternative explanation, such a case should only be treated accordingly (full course of chloroquine/ inj. antimalarial respectively). Also, tests for malaria should be repeated. **It is to be re-emphasized that there is no presumptive treatment of Malaria under current Guideline**

Don’ts in severe malaria:

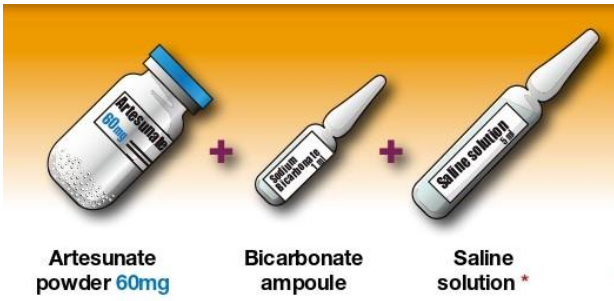
- **Do not use**
  - adrenaline
  - corticosteroids
  - intravenous mannitol
  - heparin (as anticoagulant)
- **Do not overhydrate the patient.**

- **MONOTHERAPY OF ORAL ARTEMISININ DERIVATIVES IS BANNED IN INDIA**
- **Injectable artemisinin derivatives should be used only in severe malaria, followed by oralcombination therapy.**
- **The presently recommended ACT for the North-Eastern States is fixed dose combination of Artemether- Lumefantrine (AL). Adult dose: 4 tablets twice daily for 3 days (80 mg/ 480 mg per dose). It may be required in case of malaria imported from the NE States. For age-wise schedule of AL please go through National Drug Policy on Malaria, 2013.**
- In a case of uncomplicated falciparum malaria, resistance should be suspected if in spite of full treatment with no history of vomiting or diarrhoea, patient does not respond within 72 hours, clinically and parasitologically; or if danger signs of severe malaria develops even after one day of therapy. Such cases not responding to ACT, should be treated with oral quinine with Tetracycline / Doxycycline, or in the line of severe Malaria if signs of severe Malaria have appeared. These instances should be reported to the concerned Dy.CMOH-II / DDHS (Malaria).

For any query about this module, you may contact:

- Dr. T. Ray, SPO (NVBDCP), Contact No. 9434115672
- Dr. P. Roy, State Coordinator (NTD), WHO, Contact. No. 9831846130
- Dr. D. Maji, JTDHS (PH), Contact. No. 9836046212

Annexure: Guideline for administration of Injectable Artesunate for Severe Malaria



Artesunate powder 60mg | Bicarbonate ampoule | Saline solution *

PRODUCT DESCRIPTION [1]

Dose: For children < 20 kg: 3.0 mg/kg
For children > 20 kg and adults: 2.4 mg/kg

Can be given by intravenous route (IV) or intramuscular route (IM).
IV is the preferred route of administration.
Please refer to the patient information leaflet for more information.

*** Water for injection is not an appropriate dilutant**

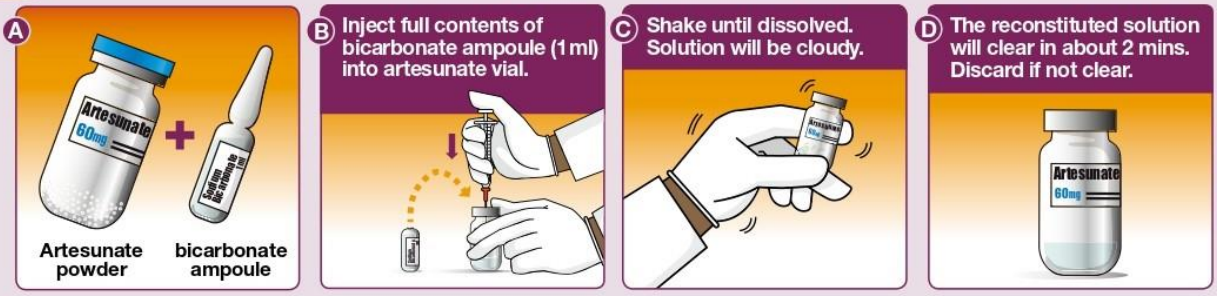
1 WEIGH THE PATIENT

2 DETERMINE THE NUMBER OF VIALS NEEDED

Weight	less than 25 kg	26-50 kg	51-75 kg	76-100 kg
60 mg vial	1	2	3	4

3 RECONSTITUTE

- Activate the drug: artesunate powder + bicarbonate ampoule (immediately before use)



4 DILUTE

- Reconstituted artesunate + saline solution (or dextrose 5%)
- Volume for dilution

	IV	IM
Bicarbonate solution volume	1 ml	1 ml
Saline solution volume	5 ml	2 ml
Total volume	**6 ml**	**3 ml**
Artesunate 60 mg solution concentration	10 mg/ml	20 mg/ml

IMPORTANT

Water for injection is not an appropriate dilutant

1. World Health Organization (WHO) List of Prequalified Medicinal Products (http://apps.who.int/prequal/query/ProductRegistry.aspx?list=ma): artesunate injectable, reference N° MA051, prequalified on 05-Nov-2010.
2. World Health Organization, Management of Severe Malaria - A practical handbook - Third edition - April 2013 - (http://www.who.int/malaria/publications/atoz/9789241548526/en/index.html)

5 CALCULATE THE DOSE

■ Calculate and withdraw the required dose **in ml** according to route of administration:

Less than 20 kg

For intravenous route (IV)

Concentration: 10 mg/ml

3.0 mg x body weight (kg)

IV artesunate solution concentration **10 mg/ml**

Round up to the next whole number

Example:

Dose needed (ml) for 8 kg child:

$$\frac{3.0 \times 8}{10} = 2.4 \text{ ml}$$

2.4 ml rounded up to **3 ml**

Weight kg	Dose mg	Dose ml
6 - 7	20	2
8 - 10	30	3
11 - 13	40	4
14 - 16	50	5
17 - 20	60	6

For intramuscular route (IM)

Concentration: 20 mg/ml

3.0 mg x body weight (kg)

IM artesunate solution concentration **20 mg/ml**

Round up to the next whole number

Example:

Dose needed (ml) for 8 kg child:

$$\frac{3.0 \times 8}{20} = 1.2 \text{ ml}$$

1.2 ml rounded up to **2 ml**

Weight kg	Dose mg	Dose ml
6 - 7	20	1
8 - 10	30	2
11 - 13	40	2
14 - 16	50	3
17 - 20	60	3

More than 20 kg

Concentration: 10 mg/ml

2.4 mg x body weight (kg)

IV artesunate solution concentration **10 mg/ml**

Round up to the next whole number

Example:

Dose needed (ml) for 26 kg child:

$$\frac{2.4 \times 26}{10} = 6.24 \text{ ml}$$

6.24 ml rounded up to **7 ml**

Weight kg	Dose mg	Dose ml
20 - 25	60	6
26 - 29	70	7
30 - 33	80	8
34 - 37	90	9
38 - 41	100	10
42 - 45	110	11
46 - 50	120	12
51 - 54	130	13
55 - 58	140	14
59 - 62	150	15
63 - 66	160	16
67 - 70	170	17
71 - 75	180	18
76 - 79	190	19
80 - 83	200	20
84 - 87	210	21
88 - 91	220	22
92 - 95	230	23
96 - 100	240	24

Concentration: 20 mg/ml

2.4 mg x body weight (kg)

IM artesunate solution concentration **20 mg/ml**

Round up to the next whole number

Example:

Dose needed (ml) for 26 kg child:

$$\frac{2.4 \times 26}{20} = 3.12 \text{ ml}$$

3.12 ml rounded up to **4 ml**

Weight kg	Dose mg	Dose ml
20 - 25	60	3
26 - 29	70	4
30 - 33	80	4
34 - 37	90	5
38 - 41	100	5
42 - 45	110	6
46 - 50	120	6
51 - 54	130	7
55 - 58	140	7
59 - 62	150	8
63 - 66	160	8
67 - 70	170	9
71 - 75	180	9
76 - 79	190	10
80 - 83	200	10
84 - 87	210	11
88 - 91	220	11
92 - 95	230	12
96 - 100	240	12

Remark: the upper limit for each weight band is 0.9 kg e.g. 14 - 16 kg covers 14 - 16.9 kg.

6 ADMINISTER

IV: slow bolus 3-4 ml per minute.

IM: Inject slowly. Spread the doses of more than 2 ml over different sites for babies and 5 ml for adults.

7 DOSING SCHEDULE

1. Give **3 parenteral doses** over 24 hours as indicated in the opposite table

2. Give **parenteral doses** for a minimum of 24 hours once started irrespective of the patients ability to tolerate oral treatment earlier.

- **Day 1** **Dose 1: on admission (0 Hours)**
  Dose 2: 12 hours later
- **Day 2** **Dose 3: 24 hours after first dose**

- When the patient can take oral medication, prescribe a full 3-day course of recommended first line oral Artemisinin Combination Therapy (ACT). The first dose of ACT should be taken **between 8 and 12 hours** after the last injection of artesunate.
- Until the patient is able to take oral medication, continue parenteral treatment (one dose a day) **for a maximum of 7 days.**
- A course of injectable artesunate should always be followed by a 3-day course of ACT.

- Evaluate the patient's progress regularly.

IMPORTANT

- **Prepare a fresh solution for each administration.**
- **Discard any unused solution after use.**

Notes