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Dengue- A Viral Infection and Global Risk to Human Life

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HUMAN

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ABSTRACT

Dengue a viral infection is one of the most important mosquito-borne viral diseases affecting humans worldwide. Dengue is a serious viral illness caused by RNA virus belonging to the family '*Flaviviridae*' genus '*Flavivirus*' and spread through '*Aedes Mosquitoes'*. It is widely spread in tropical and subtropical region. Tens of millions of cases occurs in each year resulting in approximately 20,000-25,000 deaths mainly in children. Presently it has been estimated that about more than 120 countries have been affected by the dengue virus. And, it has been seen that more than two million cases were registered as '*Dengue Fever*' and half a million as the '*Dengue Hemorrhagic Fever*' over the entire world. So, therefore people living in dengue endemic area are prone to dengue infections in their lifetime. About 40-80% of dengue infections are asymptomatic. The dengue virus has basically five types of serotypes, out of which one usually gives the immunity against the infection. Symptoms are usually seen in 2-14 days after the infection and average of about 4-7 days. It usually starts with high fever, headache, muscle pain, joint pain, myalgia and arthralgia. Prevention can be done by the protection against mosquito bites. Dengue Hemorrhagic Fever and Dengue Shock Syndrome are the two complications which occur in people who live in an area affected by dengue. The clinical manifestation and management to control the dengue is divided into three phases- febrile, critical and recovery. Primary and secondary care is being taken to evaluate the clinical outcome of dengue. Therefore, although the full global burden of the disease is uncertain, this observed growth only brings us closer to a more accurate estimate of the full extent of the burden. This article provides a detail overview on dengue virus infection in mosquito and in humans, also its symptoms, treatment, complication, diagnosis, prevention and control, epidemiology, clinical manifestation and management.

INTRODUCTION

Dengue an epidemic-prone viral disease-causing severe flu-like illness and causing a potentially lethal complication called severe Dengue. Severe dengue earlier known as hemorrhagic fever and was first found in the 1950s in the Philippines and Thailand during dengue epidemics. Today it affects all over the world and majorly affects the Asian and Latin American countries and it is the foremost cause for hospitalization and death among children and adults. [3]

Dengue fever is caused by the virus which plays the role of mosquito as a man transmitter or vector and humans are the victim and source of infection. [2]

Dengue is caused by Dengue Virus (DENV), a mosquito borne *Flavivirus*. Dengue virus is a single-stranded RNA positive-strand virus belonging to the family *Flavivirus,* and it is a life-threatening syndrome called Dengue Hemorrhagic Fever (DHF) or Dengue shock Syndrome (DSS).[2]

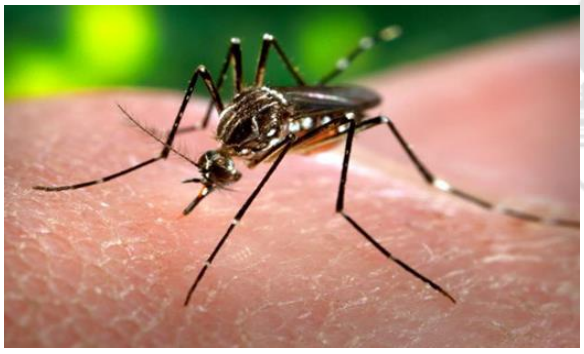

Figure No. 1: Aedes aegypti mosquito.

Figure No. 2*:* Aedes albopictus mosquito.

Dengue virus is classified into four types of Serotypes (DEN-1, DENV-2, DENV-3, and DENV-4). [1,2]

Annually, 100 million cases of dengue fever and 50 million cases of DHF occur extensively. Children, less than 15 years of age has 90% of DHF cases. At present, dengue is endemic in about 112 countries in the world. [17]

The number of dengue cases reported to WHO increased over 15-fold over the last two decades, from 505,430 cases in 2000 to over 2,400,138 in 2010 and 3,312,040 in 2015. Deaths from 2000 to 2015 increased from 960 to more than 4032. Therefore, although the full

global risk of the disease is uncertain, this observed growth only brings us closer to a more accurate estimate of the full extent of the burden. [1]

HISTORY

It is derived from the Swahili phrase '*Ka-dinga pepo*', meaning 'cramp-like seizure caused by an evil spirit'. The Swahili word '*dinga*' may have its origin in the Spanish word '*Dengue*' meaning particular or careful, which would describe a person suffering from bone pain of dengue fever. Slaves in the West Indies who caught dengue were said to have the posture and gait of a dandy, and the disease was known as '*Dandy Fever*'.[2]

The initial record of a case of Dengue fever is in a Chinese medical encyclopedia from the Jin Dynasty (265–420 AD) which belonged to a "water poison" associated with flying insects. The first recognized Dengue epidemics occurred almost concurrently in Asia, Africa, and North America in the 1780s, shortly after the identification and description of the disease in 1779. The first confirmed case report dates from 1789 and is by Benjamin Rush, who coined the term "Break-bone fever" because of the symptoms of myalgia and arthralgia. [13]

The viral etiology and the transmission by mosquitoes were only explained in the 20th century. The socioeconomic impact of World War II resulted in increased spread of the virus globally. [2]

In another report, Benjamin Rush observed the first detailed symptoms of dengue shock syndrome (now severe dengue) in 1780 during an outbreak in Philadelphia near Delaware River. Similar disease symptoms were observed in North America along the Atlantic coast during the 18th and 19th centuries, on the Caribbean Islands and the Mississippi basin. Bancroft reported that the *Aedes aegypti* mosquito is vector of the dengue virus. However, advanced research about the dengue virus was not started until 1943–1944. [13]

Nowadays, about 2.5 billion people, or 40% of the world's population, live in areas where there is a danger of dengue transmission. Dengue spread to more than 120 countries in Asia, the Pacific, the Americas, Africa, and the Caribbean.

Possible factors for dengue fever spread include: [2]

1. Unplanned urban overpopulation of areas leading to poor housing and public health systems (water, sewerage and waste management).

2. Poor vector control, e.g., filthy pools of water for mosquito breeding.

3. Climate change and viral development.

4. Increased international travel (recreational, business or military) to endemic areas.

All these factors must be discussed to control the spread of dengue. Unplanned urbanization is believed to have had the largest impression on disease amplification in individual countries, whereas travel is believed to have the largest impact on global spread. [2]

DENGUE VIRUS

Dengue is caused by the mosquito-borne *Flavivirus* also called as dengue virus (DENV). DENV is a single-stranded RNA positive-strand virus belonging to the family '*Flaviviridae'*, genus *'Flavivirus'*. [2]

Sometimes the genus also includes West Nile virus, tick-borne encephalitis virus, yellow fever virus and several other viruses which cause encephalitis.[2]

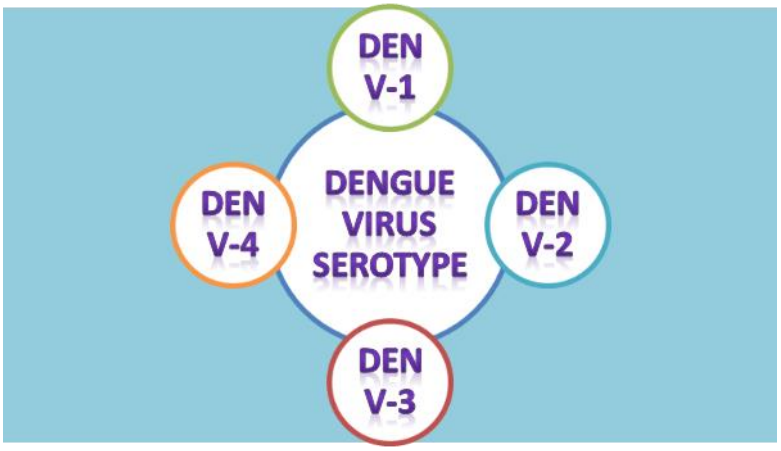

Figure No. 3: Types of Serotypes.

Dengue is mainly affected by humans hence dengue fever is a life-threatening syndrome called dengue hemorrhagic fever (DHF) or dengue shock syndrome (DSS). Antigenically

they are different type of serotypes of virus (see figure no. 3), although from one of the reports in 2013, 5th serotype has also been found. [2]

The transmission cycle of dengue virus by the mosquito *Aedes aegypti* begins with dengue-infected person. This person will have virus circulating in the blood—a viremia that lasts for about five days. [5, 6]

THE MOSQUITO

The main vector that transmits the virus that causes dengue is *'Aedes aegypti'*. The virus transmits to human when a female infective *Aedes mosquito* bites which mainly acquires the virus period while finding the blood of an infected person life cycle of the virus starts within the mosquito, the virus infects the mosquito's midgut and spread to the salivary glands which occurs over a period of 8-12 days of incubation period. Once the incubation is completed the virus can be transmitted to humans by probing or feeding. [3]

Life Stages of *Aedes Mosquitoes*

Eggs:

- Adult, female mosquitoes lay their eggs on the inner, wet walls of containers with water, above the waterline.

- Mosquitoes generally lay 100 eggs at a time.

- Eggs are very hardy; they stick to the walls of a container like glue and can sustain drying out for up to 8 months— even over the winter in the southern United States.

- It only takes a very small amount of water to attract a female mosquito. Bowls, cups, fountains, tires, barrels, vases and any other container storing water makes for a high "nursery". [2,7]

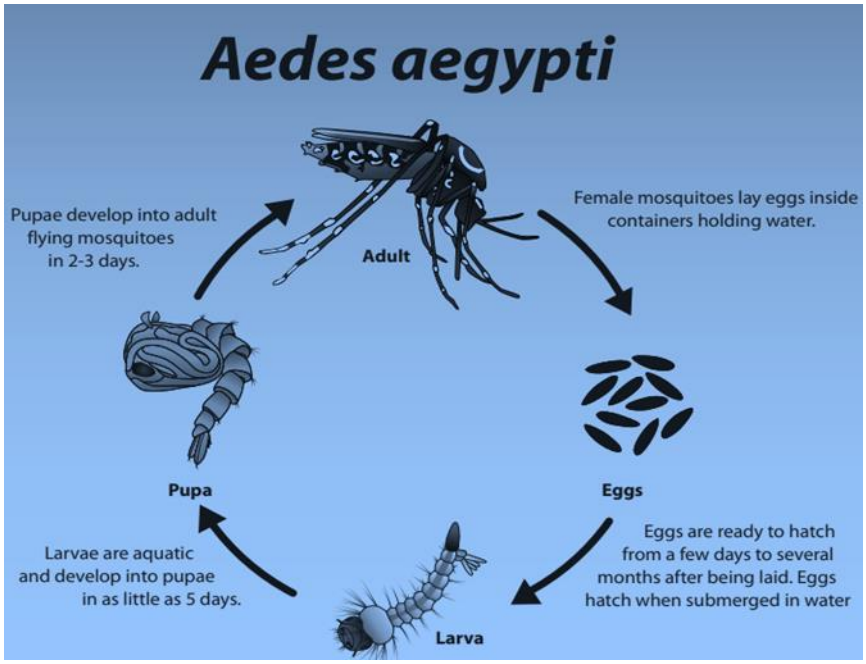

Figure No. 4: Life cycle of Aedes Mosquito

Larva:

- Larvae emerge from mosquito eggs, but only after the water level raises to cover the eggs. This means that rainwater or humans adding water to containers with eggs will trigger the larvae to appear.

- Larvae feed on microorganisms in the water. After losing three times, the larva becomes a pupa. [2,7]

Pupa:

- Pupae will develop until the body of the newly formed adult flying mosquito emerges from the pupa skin and leaves the water. [2,7]

Adult:

- After adult mosquitoes emerge, male mosquitoes feed on nectar from flowers and female mosquitoes feed on individuals and animals for blood to hatch eggs.

- After feeding, female mosquitoes will look for water sources to lay more eggs.

- Aedes aegypti only flies a few bars during its life.

- Unlike other mosquito species, Aedes aegypti mosquitoes prefer to bite people.

- Aedes aegypti mosquitoes prefer to live near people. They can be found inside homes, buildings, and businesses where window and door screens are not in use, or doors are left propped open. [2,7]

Their stages are found in water-filled habitats, mostly and closely associated with human homes. The female *Aedes aegypti* spend their lifetime in and around the houses where they grow as adults which means the mosquitoes rapidly leave the virus in and around the community and places. [3]

Dengue infective rate are higher in outdoors during the daytime because these mosquito bites usually. The indoor environment is less active in climate variations and increases the mosquito's survival. The other species of dengue virus is '*Aedes albopictus'*, *'Aedes polynesiensis'* and several species of the '*Aedes Scutellaris'* each of the species has its ecology adaptation and geographical distribution. [3]

THE HUMANS

Once, infected humans become the main carriers and multipliers of the virus, which serves as a source for viruses for uninfected mosquitoes. The virus circulates the blood of an infected person for 2-4 days at the same time the person catches a fever. Patients who are already infected with the virus can transmit the infection through *Aedes mosquito* after the first symptoms occur for 4-5 days. [3]

In human's recovery from one dengue virus infection provides permanent immunity against that particular virus serotype. Meanwhile, the immunity gives only partial and transient protection against consequent infection by the other three serotypes of this virus. [3]

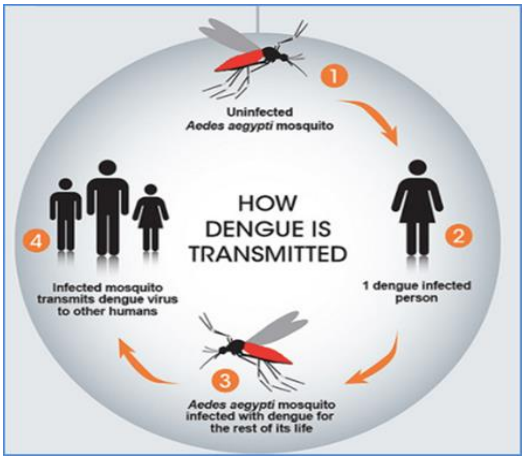

Figure No. 5: Transmission of dengue

PATHOPHYSIOLOGY:

Dengue virus is a mosquito borne disease caused by distinct serotypes of dengue viruses which is related to 1 or 4 closely related antigen. Individual can infect by any of 4 types of serotypes. Several serotypes can be found in circulation during the epidemic period. [4,5,6,7]

Transmission of Dengue Virus:

➢ The transmission cycle of dengue virus by the mosquito *Aedes aegypti* begins with a dengue- infected person. This person will have virus circulating in the blood—a viremia that lasts for about five days.

➢ During the viremic period, an uninfected female *Aedes aegypti* mosquito bites the person and ingests blood that contains dengue virus. Then, within the mosquito, the virus replicates during an extrinsic incubation period of eight to twelve days. [4,5,6,7]

➢ The mosquito then bites a susceptible person and transmits the virus. The virus then replicates in the second person and produces symptoms.

➢ The symptoms begin to appear an average of four to seven days after the mosquito bite—this is the intrinsic incubation period, within humans. It can range from 3 to 14 days (average 4-7 days).

➢ While, viral replication takes place in target dendritic cells. Infection of target cells, primarily those of the reticuloendothelial system, such as dendritic cells, hepatocytes, and endothelial cells. [4,5,6,7]

➢ This result in the production of immune mediators that serve to shape the quantity, type, and duration of cellular and humoral immune response.

➢ Fever typically begins on the third day of illness and persists 5-7 days, abating with the cessation of viremia. Fever may reach 41°C.

➢ Occasionally, and more frequently in children, the fever abates for a day and recurs, a pattern that is termed a saddleback fever; however, this pattern is more commonly seen in dengue hemorrhagic fever. [4,5,6,7]

➢ The significance of vertical transmission for maintenance of the virus is not well understood. Sylvatic dengue strains in some parts of Africa and Asia may also lead to human infection, causing mild illness.

➢ Several factors can influence the dynamics of virus transmission -- including environmental and climate factors, host pathogen interactions and population immunological factors.

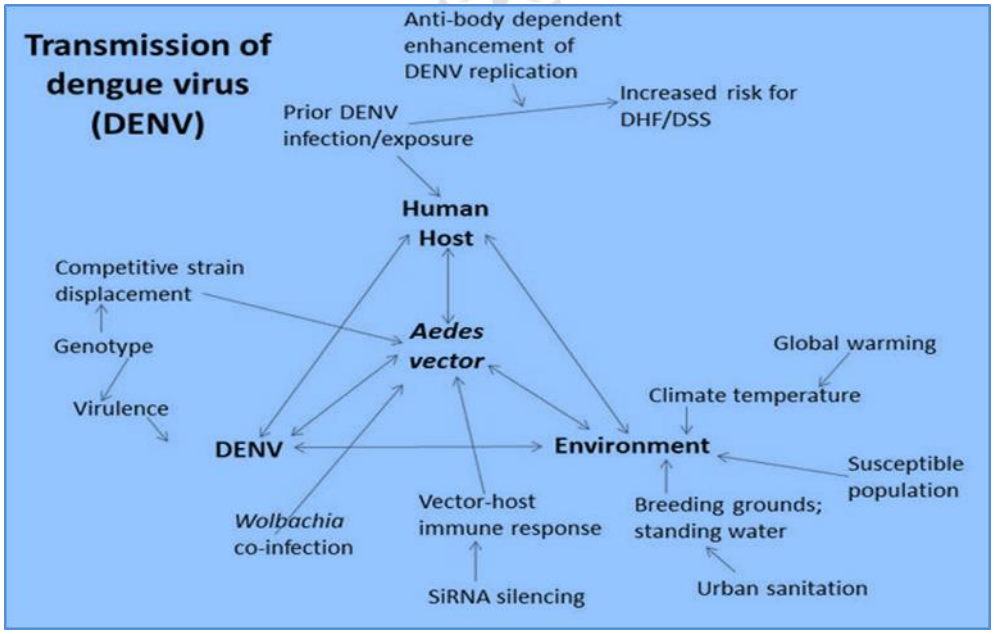

Figure No 6: Effects of pathogen vector interaction on transmission on Dengue fever.

➢ Climate directly influences the biology of the vectors and thereby their abundance and distribution; it is consequently an important determinant of vector-borne disease epidemics. [1]

CLINICAL MANAGEMENT AND DELIVERY OF CLINICAL SERVICES

Dengue infection is a systemic and dynamic disease. It has a wide clinical spectrum that includes both severe and non-severe clinical manifestations. After the incubation period, the illness begins abruptly and is followed by the three phases - febrile, critical and recovery. [1]

For a disease that is complex in its manifestations, management is relatively simple, in expensive and very effective in saving lives. The key is early recognition and understanding of the clinical problems during the different phases of the disease, leading to a rational approach to case management and a good clinical outcome. Activities at the primary and secondary care levels are critical in determining the clinical outcome of dengue. A well-managed front-line response not only reduces the number of unnecessary hospital admissions but also saves the lives of dengue patients. [1]

1. Febrile Phase:

✦ Patients typically develop high-grade fever suddenly. This acute febrile phase usually lasts 2–7 days.

✦ And is often accompanied by facial flushing, skin erythema, generalized body ache, myalgia, arthralgia and headache.

✦ Some patients may have sore throat, injected pharynx and conjunctival injection &Anorexia, nausea and vomiting are common.

✦ It can be difficult to distinguish dengue clinically from non-dengue febrile diseases in the early febrile phase.

✦ Therefore monitoring for warning signs and other clinical parameters is crucial to recognizing progression to the critical phase.

✦ Mild hemorrhagic manifestations like petechiae and mucosal membrane bleeding (e.g. nose and gums) may be seen. Massive vaginal bleeding and gastrointestinal bleeding may occur during this phase but is not common (during pregnancy).

✦ The liver is often enlarged and tender after a few days of fever. The earliest abnormality in the full blood count is a progressive decrease in total white cell count, which should alert the physician to a high probability of dengue. [1]

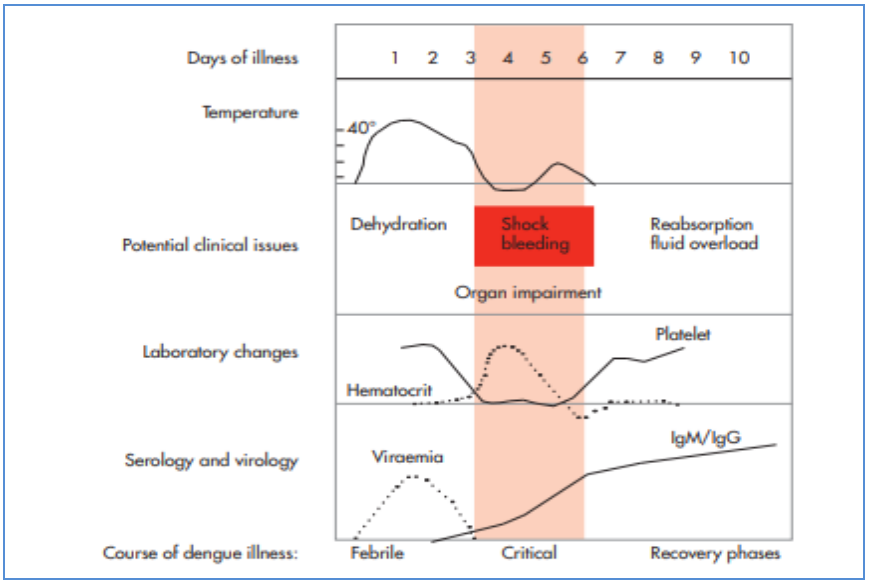

Figure No. 7: Clinical course of dengue fever

2. Critical Phase:

✦ Around the time of defervescence, when the temperature drops to 37.5–38ºC or less and remains below this level, usually on days 3–7 of illness, an increase in capillary permeability in parallel with increasing hematocrit levels may occur. This marks the beginning of the critical phase.

✦ The period of clinically significant plasma leakage usually lasts 24–48 hours.

✦ Progressive leukopenia followed by a rapid decrease in platelet count usually precedes plasma leakage. At this point patients without an increase in capillary permeability will improve, while those with increased capillary permeability may become worse as a result of lost plasma volume.

✦ Pleural effusion and ascites may be clinically detectable depending on the degree of plasma leakage and the volume of fluid therapy. Hence chest x-ray and abdominal ultrasound can be useful tools for diagnosis.

✦ It is often preceded by warning signs. The body temperature may be subnormal when shock occurs. With prolonged shock, organ hypoperfusion results in progressive organ impairment, metabolic acidosis and disseminated intravascular coagulation.

✦ Those who improve after defervescence are said to have non-severe dengue.

✦ Those who deteriorate will manifest with warning signs. This is called dengue with warning signs. Cases of dengue with warning signs will probably recover with early intravenous rehydration. Some cases will deteriorate to severe dengue. [1]

3. Recovery phase:

✦ If the patient survives the 24–48 hour critical phase, a gradual reabsorption of extravascular compartment fluid takes place in the following 48–72 hours.

✦ General well-being improves, appetite returns, gastrointestinal symptoms abate, haemodynamic status stabilizes and diuresis ensues. Some patients may have a rash of "isles of white in the sea of red".

✦ Some may experience generalized pruritus. Bradycardia and electrocardiographic changes are common during this stage.

✦ White blood cell count usually starts to rise soon after defervescence but the recovery of platelet count is typically later than that of white blood cell count.

✦ Respiratory distress from massive pleural effusion and ascites will occur at any time if excessive intravenous fluids have been administered.

✦ During the critical and/or recovery phases, excessive fluid therapy is associated with pulmonary oedema or congestive heart failure. [1]

4. Dengue During Pregnancy

✦ Data are limited on health outcomes of dengue in pregnancy and effects of maternal infection on the developing fetus.

✦ Perinatal transmission can occur, and peripartum maternal infection may increase the likelihood of symptomatic infection in the newborn.

✦ Of 41 perinatal transmission cases described in the literature, all developed thrombocytopenia, most had evidence of plasma leakage evidenced by ascites or pleural effusions, and fever was absent in only two cases. Nearly 40% had a hemorrhagic manifestation, and 1 in 4 had hypotension.

✦ Perinatally infected neonates typically become ill during the first week of life.

✦ Placental transfer of maternal IgG against dengue virus (from a previous maternal infection) may increase risk for severe dengue among infants infected at 6–12 months of age, when the protective effect of these antibodies' wanes.[7]

DENGUE VIRUS GENOME AND STRUCTURE

The dengue virus genome is a single strand of RNA. It is referred to as *positive-sense RNA* because it can be directly translated into proteins. The viral genome encodes ten genes (Figure). [8]

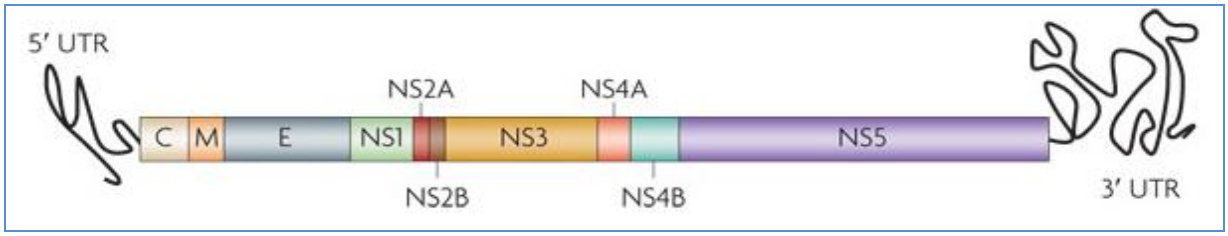

Figure No. 8: The viral genome structure encoding genes

The genome is translated as a single, long polypeptide and then cut into ten proteins. The dengue virus genome encodes, three are structural proteins: the capsid (C), envelope (E), and membrane (M) proteins. Seven are nonstructural proteins: NS1, NS2A, NS2B, NS3, NS4A, NS4B, and NS5. These nonstructural proteins play roles in viral replication and assembly. The structure of the dengue virus is roughly spherical; with a diameter of approximately 50 nm (1 nm is one millionth of 1 mm). [8, 2, 22]

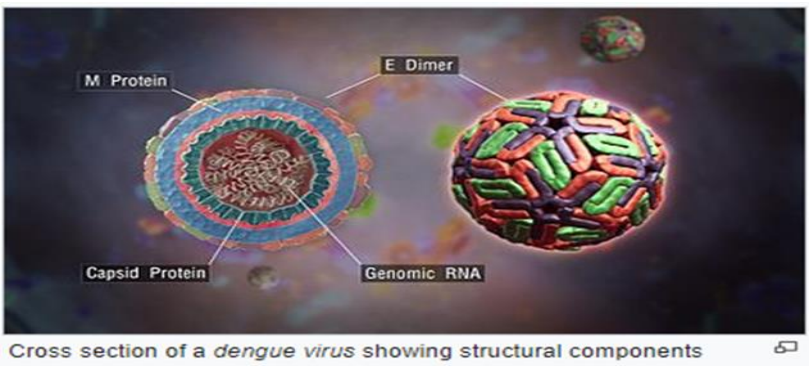

Figure No. 9: Dengue virus showing structural components.

The core of the virus is the nucleocapsid, a structure that is made of the viral genome along with C proteins. The nucleocapsid is surrounded by a membrane called the viral envelope, a lipid bilayer that is taken from the host. Embedded in the viral envelope are 180 copies of the E and M proteins that span through the lipid bilayer. These proteins form a protective outer layer that controls the entry of the virus into human cells. [8,2,22]

DENGUE VIRUS REPLICATION AND INFECTIOUS CYCLE

The dengue viral replication process begins when the virus attaches to a human skin cell. After this attachment, the skin cell's membrane folds around the virus and forms a pouch that seals around the virus particle. This pouch is called an endosome. A cell normally uses endosomes to take in large molecules and particles from outside the cell for nourishment. By hijacking this normal cell process, the dengue virus is able to enter a host cell. Once the virus has entered a host cell, the virus penetrates deeper into the cell while still inside the endosome. [8,2]

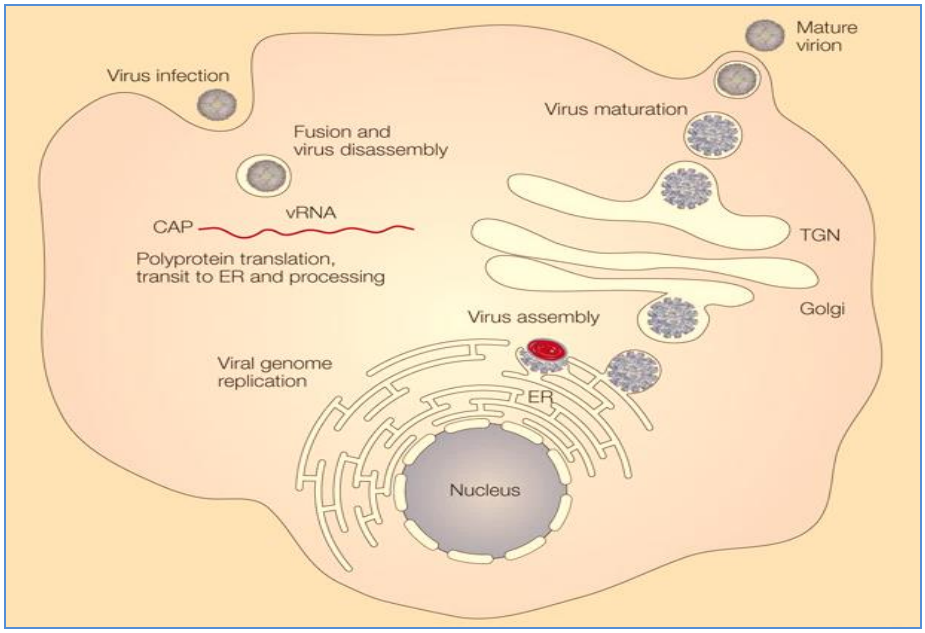

Figure No. 10: Dengue virus replication

Researchers have learned that two conditions are needed for the dengue virus to exit the endosome:

- The endosome must be deep inside the cell where the environment is acidic.
- The endosomal membrane must gain a negative charge.

These two conditions allow the virus envelope to fuse with the endosomal membrane, and that process releases the dengue nucleocapsid into the cytoplasm of the cell. [2,8]

Once it is released into the cell cytoplasm, the nucleocapsid opens to uncoat the viral genome. This process releases the viral RNA into the cytoplasm. The viral RNA then hijacks the host cell's machinery to replicate itself. The virus uses ribosomes on the host's rough endoplasmic reticulum (ER) to translate the viral RNA and produce the viral polypeptide. This polypeptide is then cut to form the ten dengue proteins.

The newly synthesized viral RNA is enclosed in the C proteins, forming a nucleocapid. The nucleocapsid enters the rough ER and is enveloped in the ER membrane and surrounded by the M and E proteins. This step adds the viral envelope and protective outer layer. The immature viruses travel through the Golgi apparatus complex, where the viruses mature and convert into their infectious form. The mature dengue viruses are then released from the cell and can go on to infect other cells. [8, 2]

DENGUE CASE CLASSIFICATION

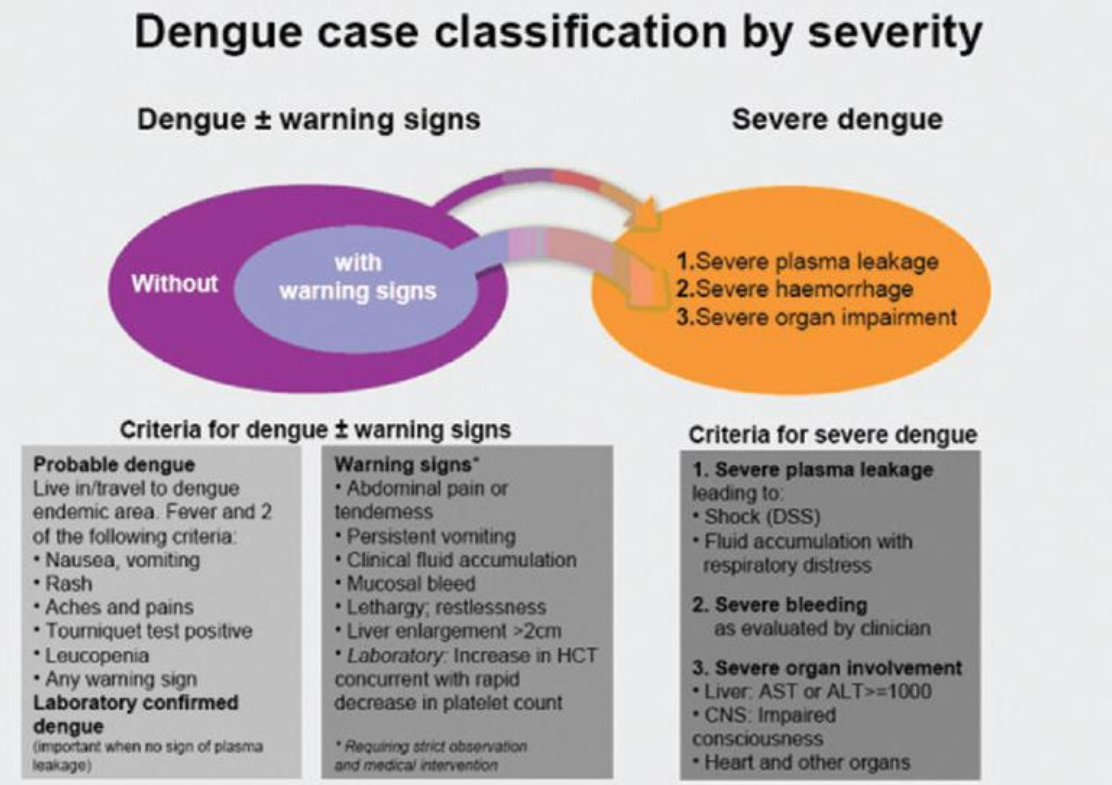

Figure No. 11: Dengue case classification

The development of the revised dengue case classification into dengue (with or without warning signs) and severe dengue was introduced in 2009. The most recent systematic review compared the 1997 classification with the revised dengue case classification. Five years after its introduction, the classification is able to detect disease severity with high sensitivity and thus assisting the clinical management and potentially contributing to reduce mortality. It is recommended that a clinical diagnosis of dengue (e.g., probable dengue based on case definition or laboratory confirmed dengue) should be made first and then the warning signs should be applied to help in triage. [21,1]

SIGNS AND SYMPTOMS

The person infected by the dengue virus develops severe flu-like symptoms. As the disease is also known as break-bone fever, therefore it mainly affects infant's children and adults similarly and could be fatal sometimes.

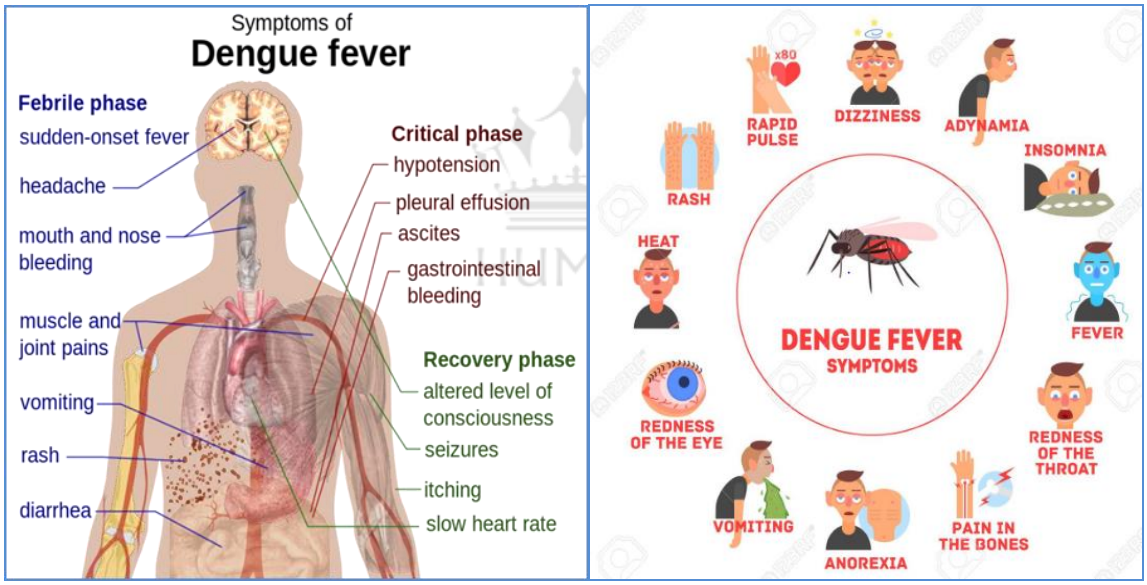

Figure No. 12: Schematic depiction of the symptoms of dengue fever

The clinical manifestation of the dengue fever alters according to the age of the patients. Individuals should suspect dengue when a high fever (40°C/104°F) is accompanied by any two of the following symptoms. [3]

- Severe Headache
- Pain behind the Eyes

- Nausea /Vomiting
- Swollen Glands
- Muscle Joint Pains
- Rash

Symptoms usually last for 2-7 days after an incubation period of 4-10 days after the bite from an infected mosquito. [3]

Severe dengue is a life-threatening complication due to plasma leaking accumulation, respiratory distress, severe bleeding or organ impairment.

The warning signs occur for about 3-7 days after the first symptoms of concomitance with a disease in temperature below (38ºC / 100ºF) which include. [3]

- Severe abdominal pain
- Persistent vomiting
- Rapid breathing
- Bleeding gums
- Blood in vomit
- Fatigue restlessness

The next 24 hours can be malignant proper medical case needed to avoid complications and risk of death. [3]

TREATMENT

There is no specific treatment for dengue fever. Patients should seek medical advice, rest and drink excess of water and fluids. Doctor may recommend that you drink plenty of fluids to avoid dehydration from vomiting and a high fever. Paracetamol can be taken to bring down fever and reduce joint pains. For severe dengue medical care by physicians and nurses

constantly saves life. While recovering from dengue fever, watch for signs and symptoms of dehydration. [3,10]

Call your doctor right away if you develop any of the following:

- Decreased urination
- Few or no tears
- Dry mouth or lips
- Lethargy or confusion
- Cold or clammy extremities

Natural Remedies for Dengue Fever:

Irrespective of the type of dengue fever you contact, there is no medical remedy and you need to re-sort to home remedies. Here are some of the popular and effective home remedies you can follow in case of dengue fever.[14]

Drink enough Water: Excessive sweating, exertion during dengue fever can lead to extreme dehydration. As a result, ensure that you take a lot of fluids and stay well hydrated. Drink water at frequent intervals to keep your body well hydrated. Staying hydrated also reduces the symptoms of headaches, as well as muscle cramps. When you have dengue fever, the toxins in your body complicate the impact of the viral pathogens. Water also helps in flushing out these excess toxins from your body to help you recover. With the availability of several RO water purifier systems. RO water is free of contaminants and reduces the chances of contacting any other diseases. [14]

Juice of Papaya Leaves: Another very effective remedy is drinking papaya leaf juice. Papaya leaves are known to be the natural cure for dengue fever. The leaves have a mix of nutrients and organic compounds which help in increasing your platelet count. Papaya leaves also have a high level of vitamin C which stimulates the immune system whereas the antioxidants help in reducing the stress and remove toxins from the body. All you need to do is crush the leaves and stain the juice from the crushed leaves. [14]

Figure No. 13: Natural remedies for dengue

Chew Basil Leaves: Basil leaves are miraculous herbs that not only help during dengue fever, but also improve your overall immunity. Chewing 5-6 basil leaves boosts your immunity Basil leaves have essential oils with natural insecticidal properties which keep mosquitoes at bay.

Neem Leaves: Neem leaves have medicinal properties, which is the reason why they are recommended for a variety of ailments. Steep neem leaves and drink the brew to increase platelet and white blood cell count. Properly brewed neem leaves also improve the immune system if suffering from dengue.

Orange Juice: Oranges are rich in antioxidants and vitamins which help in treating the secondary symptoms of dengue. Orange juice also helps in eliminating dengue virus. The miraculous drink promotes antibodies in the immune system, increases urination, thereby releasing toxins from the body. Orange juice also repairs your body cells as it has Vitamin C which is crucial in creating collagen. [14]

Apart from the remedies, Acetaminophen (Tylenol, others) can alleviate pain and reduce fever. Avoid pain relievers that can increase bleeding complications — such as aspirin, ibuprofen (Advil, Motrin IB, others) and naproxen sodium (Aleve, others).

If you have severe dengue fever, you may need:

- Supportive care in a hospital

- Intravenous (IV) fluid and electrolyte replacement
- Blood pressure monitoring
- Transfusion to replace blood loss

Sustenance of the patients circulating fluid volume is the central feature of such care. [3,10]

COMPLICATIONS

Dengue fever can result in the following complications:

1. Dengue hemorrhagic fever
2. Dengue shock syndrome

These two conditions are rare in occasional travelers to endemic areas, being more common in people who live in an area affected by Dengue and have been repeatedly exposed to the virus. [9]

1. DENGUE HAEMORRHAGIC FEVER (DHF)

Dengue hemorrhagic fever is a potentially fatal complication of dengue that can cause an enlarged liver and, in severe cases, can lead to shock (a sudden drop in blood pressure). This is called dengue shock syndrome (see below).

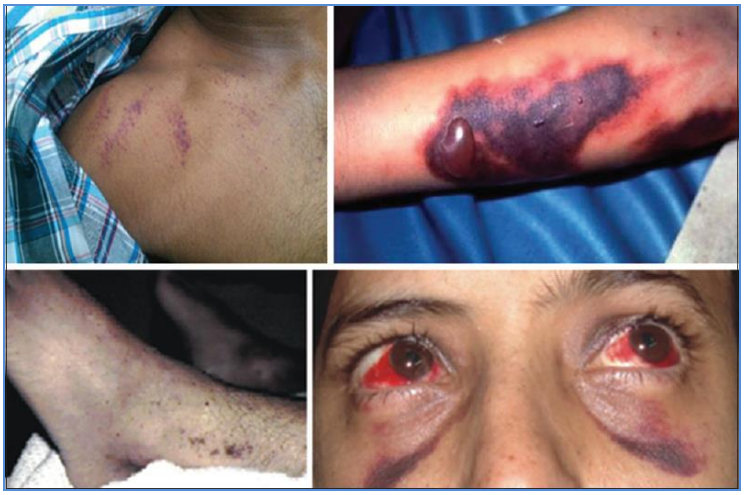

Figure No. 14: Bleeding manifestations in dengue hemorrhagic fever

Symptoms of dengue hemorrhagic fever are the same as those for dengue,

- Tiny spots of blood on the skin
- Larger patches of blood under the skin
- Bleeding from your gums and nose
- A weak pulse and clammy skin
- Sweatiness
- A tender abdomen (tummy) and body
- Discomfort (malaise)
- Loss of appetite
- Fatigue (tiredness)
- Sore throat and cough

➢ Four different strains of the dengue virus can cause this complication. If you have previously been infected with one strain of dengue and are infected again with a different strain of the virus, this can cause dengue hemorrhagic fever.

➢ Previous immunity (the body's ability to resist infection) to a different strain of dengue virus plays a role in this serious complication.

➢ You are also at an increased risk of getting dengue hemorrhagic fever if you are female and under 12 years of age.

➢ The main feature of treatment for dengue hemorrhagic fever is keeping the patient's fluids at the right level to prevent dehydration. [9]

2. DENGUE SHOCK SYNDROME (DSS)

This is a complication of dengue hemorrhagic fever in which the symptoms above can be accompanied by symptoms of shock.

Symptoms of shock include:

- A sudden drop in blood pressure
- Cold, clammy skin
- A weak rapid pulse
- Dry mouth
- Irregular breathing
- Dilated pupils
- Reduced flow of urine [9]

➢ Mortality rates can be as high as 40% if this serious complication is not treated. If it is treated, the mortality rate is 1-2%.

➢ If you have any symptoms of dengue, dengue hemorrhagic fever or dengue shock syndrome, seek immediate medical help to prevent the disease progressing. [9]

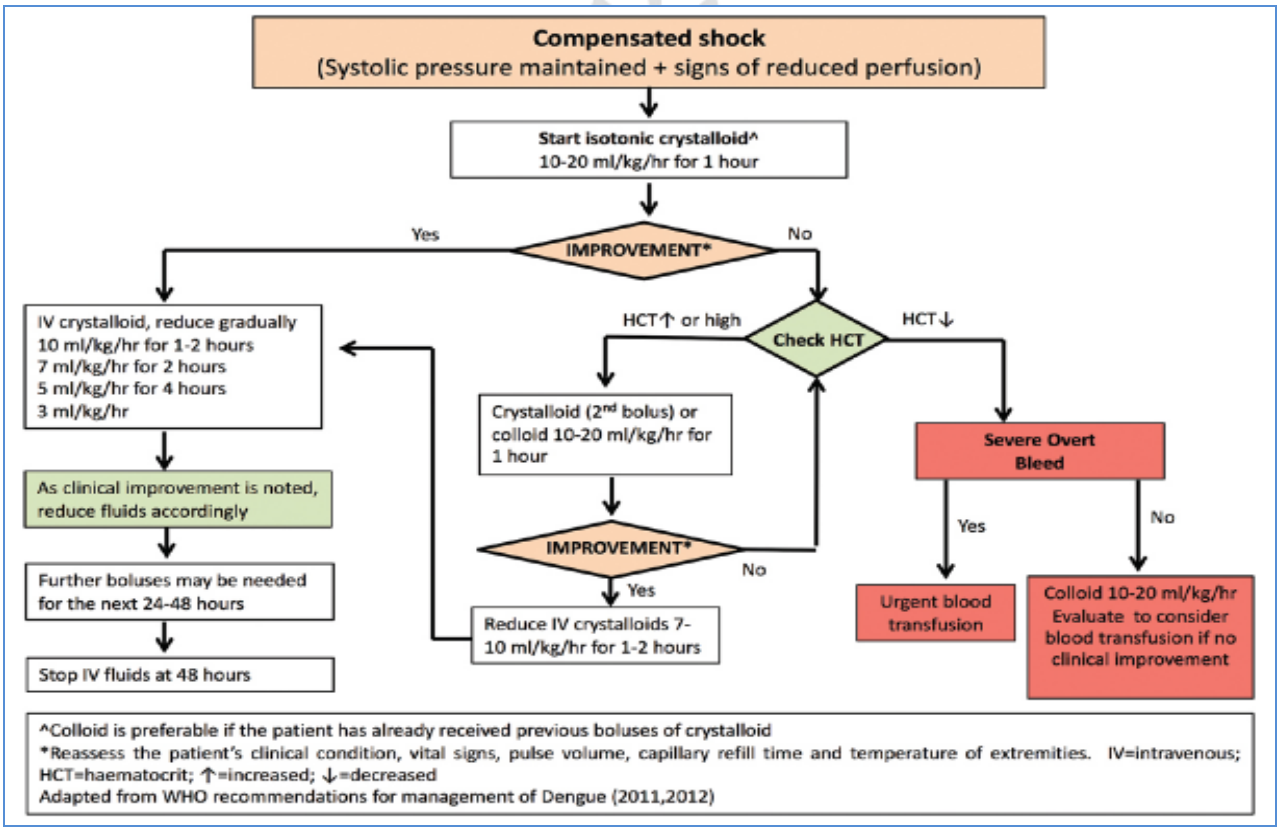

Figure No. 15: Algorithm for fluid management in hypotensive shock – infants, children, and adults

PREVENTION AND CONTROL

The only current method or preventing dengue virus delivery is adequately fought the vector mosquitoes. Vector control is implemented by integrated vector management (IVM) which is a wise decision-making process for the optimal use of resources of vector control. Proper disposal of solid waste and improved water storage practices including covering containers to prevent in by egg layering female mosquitoes are among methods that help through community-based programs. [3]

Although there is a commercially available vaccine against dengue, prevention is still the most important step to reduce the risk of dengue infection. There are several ways of prevention: [2]

1. Mosquito control by either larval control or adult mosquito control.

2. Reduce mosquito bites, especially during daylight hours.

A. Prevention by Mosquito Control

The best way to reduce mosquitoes is to eliminate the places where the mosquito lays her eggs, like artificial containers that hold water in and around the home (see figure). In urban areas, *Aedes mosquitoes* breed on water collections in artificial containers such as plastic cups, used tires, broken bottles, flower pots, etc. Periodic draining or removal of artificial containers is the most effective way of reducing the breeding grounds for mosquitoes. Larvicide treatment is another effective way to control the vector larvae but the larvicide chosen should be long-lasting and preferably. There are some very effective insect growth regulators (IGRs) available which are both safe and long-lasting (e.g. pyriproxyfen). For reducing the adult mosquito load, fogging with insecticide is somewhat effective. [2]

To eliminate standing water:

- Unclog roof gutters;
- Empty children's wading pools at least once a week;
- Change water in birdbaths at least weekly;
- Get rid of old tires in your yard, as they collect standing water;

- Empty unused containers, such as flower pots, regularly or store them upside down;
- Drain any collected water from a fire pit regularly.

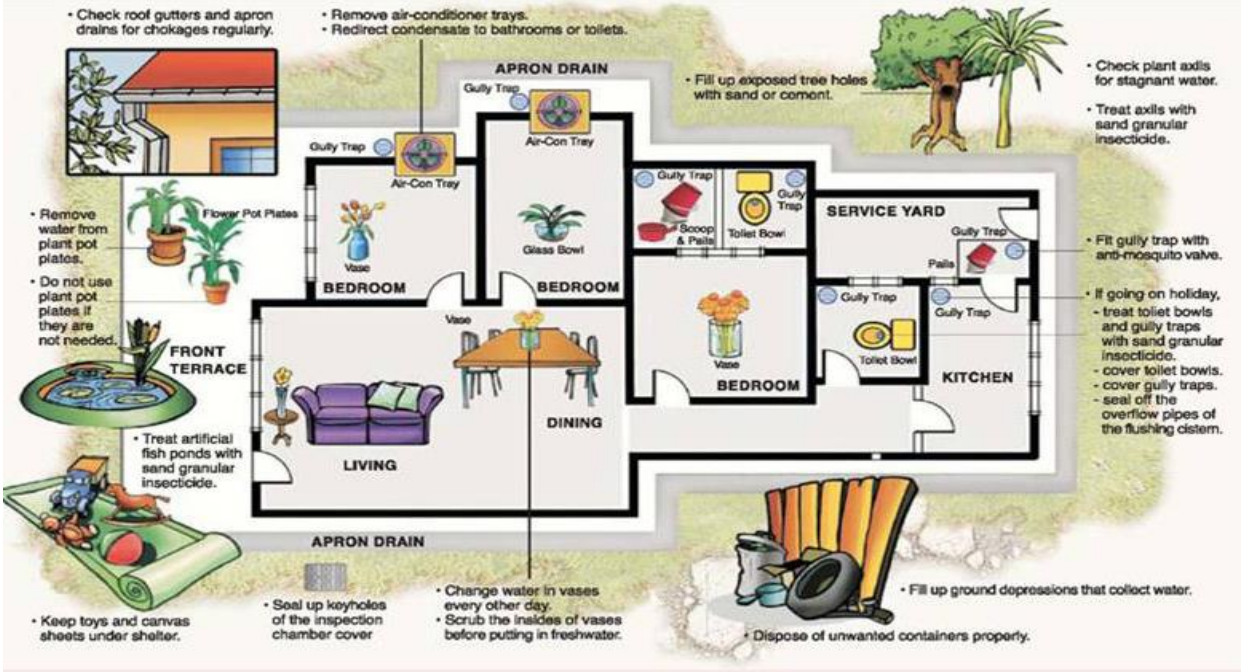

Figure No. 16: Check for Aedes mosquito breeding in your home. Source: National Environmental Agency, Singapore

B. Prevention by Reducing Mosquito Bites

Prevention of mosquito bites is another way of preventing disease. The adult mosquitoes like to bite inside as well as around homes, during the day and at night when the lights are on. To protect yourself, use insect repellent on your skin while indoors or out, mosquito traps or mosquito nets. Keep in mind that even though some of them are classified as pesticides by the Environmental Protection Agency (EPA), repellents don't kill mosquitoes. [2]

Common insect repellents include:

1. ***DEET (N, N-diethylmetatoluamide)*** blocks a mosquito's ability to find people who've applied it. Apply repellent with a 10% to 30% concentration of DEET to your skin and clothing. Choose the concentration based on the hours of protection you need — the higher the concentration of DEET, the longer you are protected. A 10% concentration protects you for about two hours. Keep in mind that chemical repellents can be toxic, and use only the

amount needed for the time you'll be outdoors. Don't use DEET on the hands of young children or on infants younger than age 2 months. [2]

2. ***Picaridin***- This repellant, also called KBR 3023, offers protection that's comparable to DEET at similar concentrations. It also blocks a mosquito's ability to find people who've applied it. Picaridin is nearly odorless, which may make it a good alternative if you're sensitive to the smells of insect repellents.

3. ***Oil of lemon eucalyptus***- this plant-based chemical may offer protection that's comparable to low concentrations of DEET. Don't use this product on children younger than 3 years. [2]

4. Others, Shorter acting repellents that may offer limited protection generally contain plant-based oils such as oil of geranium, cedar, lemongrass, soy or citronella.

When possible, wear also long sleeves and pants for additional protection. Also, make sure window and door screens are secure and without holes. [2]

Figure No. 17: Dengue prevention from mosquito control and mosquito repellants

Clothing tips to keep in mind include:

- Wear long-sleeved shirts.

- Wear socks.

- Wear long pants and consider tucking your pants into your socks.

- Wear light-colored clothing, since mosquitoes are more attracted to darker colors.

- Apply mosquito repellent to your clothing, shoes, and camping gear and bed netting.

- Wear a full-brimmed hat to protect your head and neck.

- Consider wearing a mosquito net to cover your head and face or torso. [2]

DIAGNOSIS

The diagnosis of dengue is usually made clinically. The classic picture is high fever with no localizing source of infection, a petechial rash with thrombocytopenia and relative leukopenia (low platelet and white blood cell count). Care has to be taken as diagnosis of Dengue Hemorrhagic Fever (DHF) can mask end stage liver disease and vice versa. If one has persistent fever for more than 2 days then one should go for a complete blood picture (CBP). If the platelet count and WBC count are below than their usual range one should go for Dengue Antigen test. [2]

Dengue is always a diagnosis of exclusion, and other diseases with the same initial clinical presentation must be suspected. In order to help the clinician in the detection of severe forms of dengue (DHF/DSS), even when the definitive diagnosis has not been made yet, the following three essential laboratory tests may help in the evaluation of the real clinical conditions of the patient and its early supportive management: [2]

a) ***Total White Blood Cells Count:*** In case of dengue, this test will reveal leukopenia. The presence of leukocytosis and neutrophilia excludes the possibility of dengue and bacterial infections (leptospirosis, Meningoencephalitis, Septicemia, and Pyelonephritis etc.) must be considered. [2]

b) Thrombocytopenia (less than 100.000 per mm**):** Total platelets count must be obtained in every patient with symptoms suggestive of dengue for three or more days of presentation. Leptospirosis, measles, rubella, meningococcemia and septicemia may also course with thrombocytopenia. [2]

c) Hematocrit (micro-hematocrit): According to the definition of DHF, it's necessary the presence of hemoconcentration (hematocrit elevated by more than 20%); when it's not possible to know the previous value of hematocrit, we must regard as significantly elevated the results more than 45%.[2]

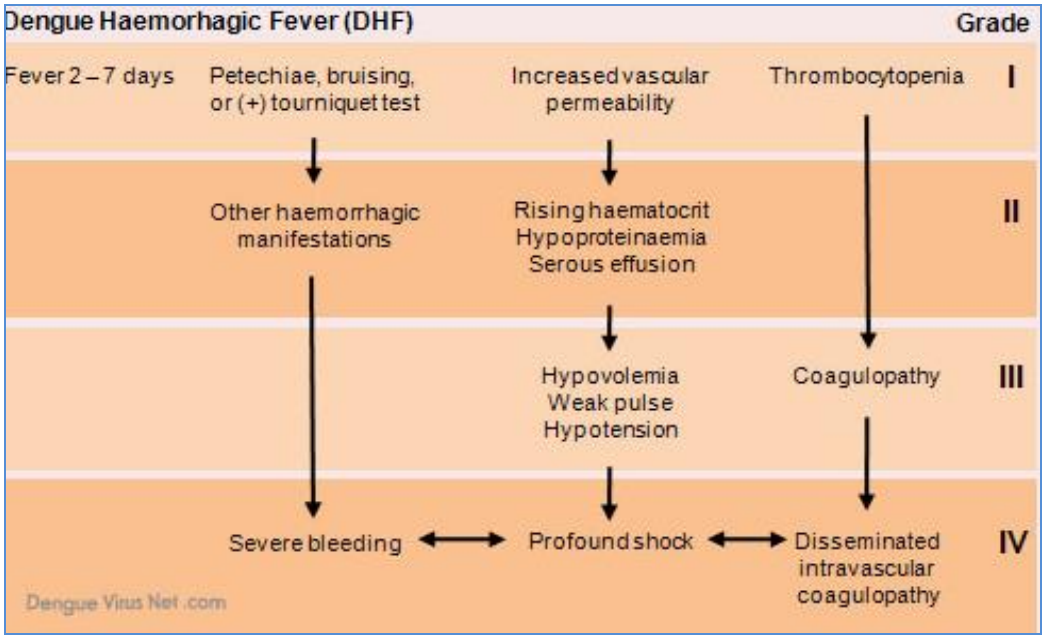

Figure No. 18: Case definition of dengue hemorrhagic fever

Diagnostic Tests for Dengue and Specimens:

Table no. 1: Diagnostic tests for dengue and its specimens

Diagnostic Test	≤7 Days After Symptom Onset	>7 Days Post Symptom Onset	Specimen Types
Molecular Tests	✓	—	Serum, plasma, whole blood, cerebrospinal fluid*
Dengue Virus Antigen Detection (NS1)	✓	—	Serum
Serologic Tests	✓	✓	Serum, cerebrospinal fluid*
Tissue Tests	✓	✓	Fixed tissue

Patients with symptoms consistent with dengue can be tested with both molecular and serologic diagnostic tests during the first 7 days of illness. After the first 7 days of illness, test only with serologic diagnostic tests. Testing cerebrospinal fluid is recommended in suspect patients with central nervous system clinical manifestations such as encephalopathy and aseptic meningitis. [7]

Acute Phase: Initial 1-7 days after symptom onset

- The initial 1-7 days after symptom onset are referred to as the acute phase of dengue.
- During this period, dengue virus is typically present in blood or blood-derived fluids such as serum or plasma.
- Dengue virus RNA can be detected with molecular tests.
- The non-structural protein NS1 is a dengue virus protein that also can be detected using some commercial tests.
- A negative result from a molecular or NS1 test is not conclusive. [7]

Convalescent Phase: >7 days post symptom onset

- The period beyond 7 days following symptom onset is referred to as the convalescent phase of dengue.
- Patients with negative NAAT or NS1 test results and negative IgM antibody tests from the first 7 days of illness should have a convalescent sample tested for IgM antibody test.
- During the convalescent phase, IgM antibodies are usually present and can be reliably detected by an IgM antibody test. IgM antibodies against dengue virus can remain detectable for 3 months or longer after infection.
- Patients who have IgM antibodies against dengue virus detected in their serum specimen with an IgM antibody test and either:

1) Have a negative NAAT or NS1 result in the acute phase specimen, or

2) Without an acute phase specimen, are classified as having a presumptive, recent dengue virus infection. [7]

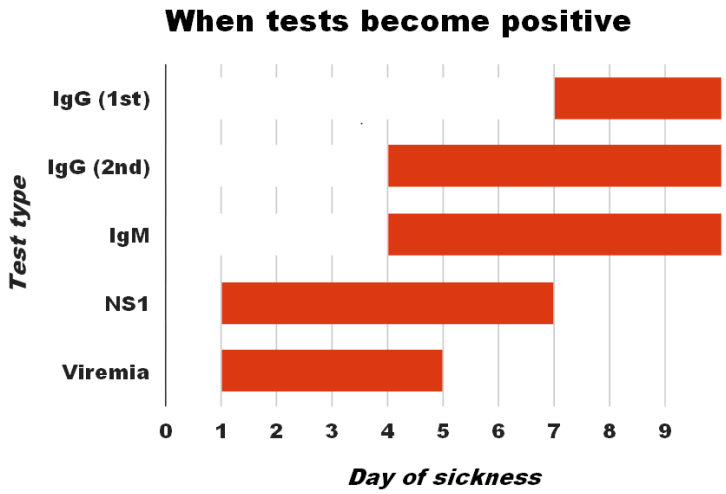

Figure No. 19: Graph of laboratory tests for dengue fever becomes positive

1. Molecular testing:

❖ **Nucleic Acid Amplification Test (NAAT):**

▪ NAAT is a generic term referring to molecular tests used to detect viral genomic material. NAAT assays are the preferred method of diagnosis because they can provide confirmed evidence of infection. Serum specimens have been the most extensively validated. The relative sensitivity of serum, plasma, and whole blood is not as well documented. Dengue virus has occasionally been detected in cerebrospinal fluid. [7]

2. Serologic Test:

❖ ***IgM Antibody Capture Enzyme-Linked Immunosorbent Assay (MAC-ELISA)***

- The dengue MAC-ELISA is used for the qualitative detection of dengue virus IgM antibodies.

- MAC-ELISA is based on capturing human IgM antibodies on a microtiter plate using anti-human-IgM antibody followed by the addition of dengue virus antigens. The antigens used for this assay are derived from the envelope proteins of the four dengue virus serotypes (DENV-1-4). [7]

3. Dengue Virus Antigen Detection

- NS1 tests detect the non-structural protein NS1 of dengue virus. This protein is secreted into the blood during dengue infection.

- NS1 tests have been developed for use in serum. Most of these tests use synthetically labeled antibodies to detect dengue NS1 protein. [7]

4. Tissue Tests

❖ **Nucleic Acid Amplification Test (NAAT)**

- A NAAT, like real-time reverse transcription polymerase chain reaction (rRT-PCR) or *in situ* hybridization, detects dengue virus RNA. Fixed liver, kidney, spleen, and lung tissue are optimal for dengue virus testing. Please note that in the setting of unexplained, potentially infectious deaths with multisystem involvement, submission of specimens from all major organs is recommended, specifically those with any significant pathologic findings. [7]

❖ **Immunohistochemical (IHC):**

- The technique uses specific antibodies, which localize to the antigens of the etiologic agent of interest.

- Because the technique uses formalin-fixed tissues, specimen transport is simplified, allowing retrospective studies and minimizing laboratory worker exposure to infectious agents. [7]

CLINICAL MANAGEMENT:

Step I— Overall Assessment

a. History

The history should include:

- Date of onset of fever/illness.

- Quantity of oral intake.

- Assessment for warning signs.
- Diarrhea.
- Change in mental state/seizure/dizziness.
- Urine output (frequency, volume and time of last voiding).
- Other important relevant histories, such as family or neighborhood dengue, travel to dengue endemic areas, co-existing conditions (e.g. Infancy, pregnancy, obesity, diabetes mellitus, hypertension), jungle trekking and swimming in waterfall (consider leptospirosis, typhus, malaria), recent unprotected sex or drug abuse (consider acute HIV seroconversion illness). [1]

b. Physical examination

The physical examination should include:

- Assessment of mental state.
- Assessment of hydration status.
- Assessment of haemodynamic status.
- Checking for tachypnoea/acidotic breathing/pleural effusion.
- Checking for abdominal tenderness/hepatomegaly/ascites.
- Examination for rash and bleeding manifestations.
- Tourniquet test (repeat if previously negative or if there is no bleeding manifestation).[1]

c. Investigation:

A full blood count should be done at the first visit. A haematocrit test in the early febrile phase establishes the patient's own baseline haematocrit. A decreasing white blood cell count makes dengue very likely. A rapid decrease in platelet count in parallel with a rising haematocrit compared to the baseline is suggestive of progress to the plasma leakage/critical phase of the disease. In the absence of the patient's baseline, age specific population haematocrit levels could be used as a surrogate during the critical phase. Laboratory tests

should be performed to confirm the diagnosis. However, it is not necessary for the acute management of patients, except in cases with unusual manifestations.

Additional tests should be considered as indicated (and if available). These should include tests of liver function, glucose, serum electrolytes, urea and creatinine, bicarbonate or lactate, cardiac enzymes, ECG and urine specific gravity. [1]

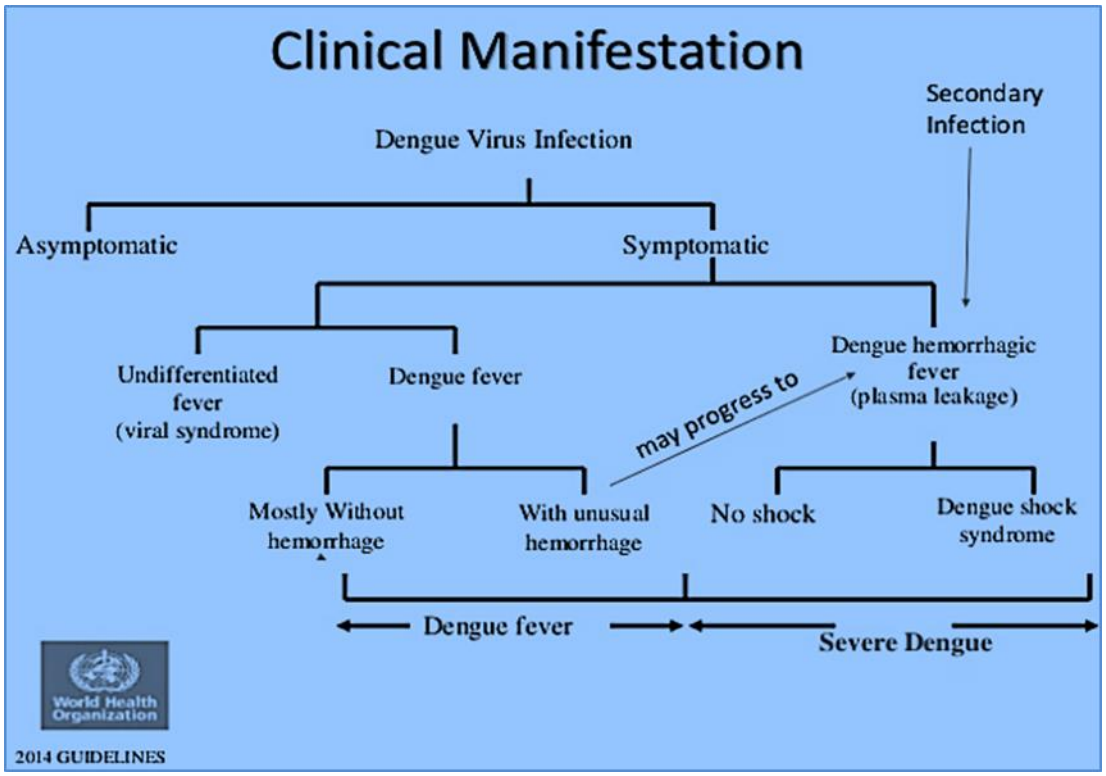

Figure No. 20: Clinical manifestation of the Dengue virus infection

Step II—Diagnosis, Assessment of Disease Phase & Severity

On the basis of evaluations of the history, physical examination and/or full blood count and haematocrit, clinicians should be able to determine whether the disease is dengue, which phase it is in (febrile, critical or recovery), whether there are warning signs, the hydration and haemodynamic status of the patient, and whether the patient requires admission. [1]

Step III—Management

A. Disease notification: In dengue-endemic countries, cases of suspected, probable and confirmed dengue should be notified as soon as possible so that appropriate public health measures can be initiated (Chapter 5). Laboratory confirmation is not necessary before notification but should be obtained. In non-endemic countries, usually only confirmed cases will be notified. Suggested criteria for early notification of suspected cases are that the patient lives in or has travelled to a dengue-endemic area, has fever for three days or more, has low or decreasing white cell counts, and/or has thrombocytopaenia ± positive tourniquet test. In dengue-endemic countries, the later the notification, the more difficult it is to prevent dengue transmission. [1]

B. Management decisions: Depending on the clinical manifestations and other circumstances, patients may be sent home (Group A), be referred for in-hospital management (Group B), or require emergency treatment and urgent referral (Group C). [1]

Table 5: Management of categories

Group A	Group B: (Needs Hospitalization)	Group C (Admission to High Dependency Unit /Paediatric ICU)
Group A1 **(Send Home with information card in local language)** 1. **Dengue fever without warning signs** and normal *Hemoglobin* and Platelets>1 Lakh (EXCEPT High risk and social reasons) *Review them in outpatient department (OPD) Q48H with Hb/platelets; earlier if there is any WS or any other concern* 2. **Dengue fever without warning signs**, with platelet count 50,000 to 1 Lakh (EXCEPT High risk & social reasons) *Review them in OPD every 24 hours with Hemoglobin, Platelets, or earlier if there are any warning signs.* **Group A2** **(Observe in 'Dengue area')** 1. High risk children without warning signs 2. Children without warning signs with low platelets (<50,000) + Stable /normal Hb 3. Children with social reasons/circumstances that preclude observation at home.	**B1** **(Admission to Wards)** All children needing IV Fluids - Volume Replacement Therapy (VRT) **B2** **(Admission inside Emergency Room – In Patient area (Short stay)** 1. All children – waiting for ward admission (on Volume Replacement Therapy -VRT) –have to be shifted within 8-12 hrs 2. Children with warning signs on oral hydration	**Severe Dengue** (Severe Plasma leakage, Severe Bleeding, Severe organ involvement) 1. Fluid assessment and management 2. Management of complications

VRT: Volume replacement therapy, OPD: Outpatient department, Hb: Hemoglobin, IV: Intravenous, ICU: Intensive Care Unit, WS: Warning signs

Figure No. 21: Management of categories

Vector management:

Aedes aegypti uses a wide range of confined larval habitats, both man-made and natural.

However, it may not be feasible or cost-effective to attempt to control the immature stages in all such habitats in a community. Some man-made container habitats produce large numbers of adult mosquitoes, whereas others are less productive. Consequently, control efforts should target the habitats that are most productive and hence epidemiologically more important rather than all types of container, especially when there are major resource constraints. Such targeted strategies require a thorough understanding of the local vector ecology and the attitudes and habits of residents pertaining to the containers. [1]

Environmental management:

Environmental management seeks to change the environment in order to prevent or minimize vector propagation and human contact with the vector-pathogen by destroying, altering, removing or recycling non-essential containers that provide larval habitats. Such actions should be the mainstay of dengue vector control. Three types of environmental management are defined: [1]

a. ***Environmental modification*** – long-lasting physical transformations to reduce vector larval habitats, such as installation of a reliable piped water supply to communities, including household connections.

b. ***Environmental manipulation*** – temporary changes to vector habitats involving the management of "essential" containers, such as frequent emptying and cleaning by scrubbing of water-storage vessels, flower vases and desert room coolers; cleaning of gutters; sheltering stored tyres from rainfall; recycling or proper disposal of discarded containers and tyres; management or removal from the vicinity of homes of plants such as ornamental or wild bromeliads that collect water in the leaf axils.

c. ***Changes to human habitation or behaviour*** – actions to reduce human–vector contact, such as installing mosquito screening on windows, doors and other entry points, and using mosquito nets while sleeping during daytime. The choice of approach should be effective, practicable and appropriate to local circumstances. Actual or potentially important container types that cannot be removed from the area should be dealt with in situ. [1]

RECENT ADVANCEMENT

Till now, there is not practically or commercially available, therapy or vaccine for the dengue virus. Various groups have then made intense efforts and made good advancements to develop a safe, affordable and active vaccine against all serotypes for global public health. Vaccines that mean being developed using various strategies such as live attenuated viruses, inactivated viruses, subunit vaccines, DNA vaccines, and chimeric viruses using yellow fever vaccine and attenuated dengue viruses as backbones (Table 2).[9]

- A vaccine to prevent dengue (Dengvaxia®) is licensed and prepared available in some countries for people ages 9-45 years old. The World Health Organization recommends that vaccines only be given to persons with confirmed earlier dengue virus infection.[7]

- The vaccine manufacturer, **'Sanofi Pasteur'**, announced in 2017 that people who accept the vaccine and have not been previously infected with a dengue virus may be at risk of developing severe dengue if people get dengue after being vaccinated.[7]

Following are some of the vaccines which are discussed and can be used in the prevention of the dengue virus:

1. Live attenuated yellow fever 17D/DENV chimeric vaccines
2. Live attenuated DENV delta-30 mutation and intertype DENV chimeric vaccines
3. Dengue-measles vaccine
4. Dengue prM-E DNA vaccine
5. Purified inactivated vaccine (PIV) [12]

Apart from vaccines, several natural and herbal home remedies such as use of Ipecacuanha, Astragalus, Echinacea, papaya, Neem, grape and orange juices etc to control the dengue virus and fever. As home remedies are easily available, inexpensive, valuable and highly effective, it is recommended to dengue patients to use these home remedies.[14]

CONCLUSION

Dengue fever is a common disease encountered as a primary care especially in the tropical and subtropical countries. The course of the disease progression and clinical problems to look out the different phases of the disease will enable primary care physicians to manage dengue fever in an appropriate and timely manner to reduce morbidity and mortality. With appropriate and timely treatment, the morbidity and mortality can be reduced. It is important for primary care doctors to adopt a practical approach to assess, classify and manage dengue fever. It is crucial to identify high-risk individual and refer them accordingly.

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