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FACULTÉ DE MÉDECINE
ET DE PHARMACIE
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Dedications

I dedicate this work to my family, my brothers, sister, uncles, cousins and to all my friends.

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Madam Mariama CHADLI

Professor of microbiology

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List of Abbreviations

Abbreviations

DF : Dengue fever

DHF : Dengue haemorrhagic fever

DNA : Deoxyribonucleic acid

DSS : Dengue shock syndrome

ELISA : Enzyme-linked immunosorbent assay

HI : Haemagglutination-inhibition

ICU : Intensive care unit

IgA : Immunoglobulin A

IgG : Immunoglobulin G

IgM : Immunoglobulin M

IV : Intravenous

LAV : Live attenuated vaccine

MAC-ELISA : IgM antibody-capture enzyme-linked immunosorbent assay

NAAT : Nucleic acid amplification test

NASBA : Nucleic acid sequence based amplification

NS : Non-structural protein

NSAID : Non-steroidal anti-inflammatory drugs

ORS : Oral rehydration solution

PCR : Polymerase chain reaction

PRNT : plaque reduction and neutralization test

RNA : RIBONUCLEIC acid

RT-PCR : Reverse transcriptase-polymerase chain reaction

TNF alfa : Tumor necrosis factor alfa

WBC : White blood cells

WHO : World Health Organizaion

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Introduction

1-Introduction:

Dengue is a mosquito borne viral disease caused by infection from any of the four serotypes of dengue virus (DENV-1-4). DENV are enveloped RNA viruses belonging to the family Flaviviridae in the genus Flavivirus.

Dengue is endemic in tropical and subtropical parts of the world. It is transmitted by the infected mosquitos *Aedes aegypti* and Aedes albopictus.

The dengue infection can produces several clinical manifestations from dengue fever to more severe forms such as dengue hemorrhagic fever and dengue shock syndrome. Dengue typically presents with symptoms such as fever, headache, muscle and joint pain, and a rash.

Infection with one serotype does not confer cross protection of infection from other serotypes, but instead, patients who acquire a second dengue infection with a different dengue serotype are at increased risk for severe dengue.

For the laboratory diagnosis of dengue, many methods are used to detect the DENV markers present in the serum of the patient. The most commonly used tests are serological methods that detect antibodies IgM and IgG against dengue virus. Serological tests are prone to cross reactivity due to antibodies against other related flaviviruses. Other methods that are used to detect dengue virus include antigen NS1 test and RNA detection methods.

There is no specific treatment of dengue. The prevention is based on personal protective measures and vector control. The recently developed vaccine will provide better prevention against the dengue virus.

The objective of this work is to make a general overview of dengue fever, its epidemiology, its clinical manifestations. Establish the diagnosis and give the measures of prevention and therapeutic management.

Brief History and geographical distribution of Dengue

2-Brief History and geographical distribution of Dengue:

The term "dengue" has its origins in the Swahili language, where it referred to an illness caused by malevolent spirits. Although a dengue-like disease was recorded in China as early as 992 A.D, the initial significant outbreaks of dengue fever were not reported until the late 17th century [1] .

Dengue epidemics were infrequent at that time. However, after World War II, the South-East Asia region experienced a significant increase in severe dengue cases, due to the proliferation of the virus in urban areas caused by urbanization [2] .

2.1-South Asia:

Dengue has been present in India for more than 200 years, typically with mild symptoms and self-limiting. However, as seen in other areas, there is now a rise in severe cases of dengue hemorrhagic fever (DHF) and dengue shock syndrome (DSS), as well as more frequent outbreaks. The initial significant outbreak of dengue in India was recorded in 1991, followed by the first epidemic of DHF in Delhi five years later [3] .

The predominant serotype during the epidemic of 1996 was DENV2 [4] .

However, During the 2003 epidemic, all four serotypes of dengue viruses were detected in co-circulation [5] .

A disease resembling dengue fever was documented in Sri Lanka during the 1960s [6,7] .

In 1989-90, Sri Lanka experienced its initial significant outbreak of DHF, followed by recurrent epidemics that have resulted in a rising number of cases each year. The major serotypes identified in Sri Lanka are DEN-3 and DEN-2 serotype [8,9] .

Pakistan, Bangladesh, and other countries in the area have also reported dengue outbreaks in recent times [10,11] .

2.2-South East Asia:

The first dengue fever outbreaks in the South-East Asia region were documented in 1954 and 1956 in Manila, Philippines, and in 1958 in Bangkok. Throughout the 1960s and 1970s, the disease caused epidemics in several countries, including India, Malaysia,

Singapore, Vietnam, Indonesia, and Myanmar. Currently, dengue has extended its reach westward into Pakistan, Sri Lanka, and the Maldives, as well as eastward into Taiwan and China [12] .

Indonesia has overtaken Thailand to become the country with the highest number of dengue cases in the region. According to serological surveys, DEN-3 has emerged as the primary serotype, superseding DEN-2 [13] .

The escalating burden and heightened transmission of the dengue virus in the region have been attributed to climatic conditions playing a significant role [14] .

2.3-The far East:

While the Republic of China is the most heavily impacted nation in this area, the prevalence and fatality rates of dengue fever/DHF epidemics in this region are comparatively lower than those in South East and South Asian regions [15] .

China's initial dengue fever outbreak surfaced in 1978, and was then succeeded by a DHF epidemic (DEN-2 serotype) on Hainan Island between 1985-86 [16] .

Hong Kong reported its inaugural case of locally contracted dengue infection in 2002 [17] .

Dengue fever and its mosquito vector are limited to the state of Queensland in Australia. Outbreaks occur when infected international travelers or overseas residents who return home transmit the virus to the local mosquito population [18] .

Fiji has also experienced significant dengue epidemics [19] .

2.4-The Americas:

In 1977-78, Cuba became the first Latin American nation to experience a significant epidemic of dengue fever caused by the DEN-1 serotype. The first DHF epidemic (DEN-2 serotype) was documented in 1981. Cuba maintained a dengue-free status for 16 years through effective vector control programs until 1997, when another DEN-2 epidemic emerged in the area. Children were mostly unaffected by this epidemic since they already had primary infections. The initial outbreak of dengue in Venezuela was documented in 1989 [20] .

Over the past twenty years, there has been a notable rise in the occurrence of dengue fever in Latin America, with over one million cases recorded across 30 countries in 2002. The current epidemiological pattern of dengue in the United States of America ressembles to what is observed in Asia, wherein epidemics of dengue hemorrhagic fever resurface every three to four years [21] .

2.5-Africa and the middle East:

Countries in East Africa, along with the Seychelles, have reported cases of epidemic dengue fever caused by all serotypes. These countries include Kenya (1982, DEN-2), Mozambique (1985, DEN-3), Djibouti (1991-92, DEN-2), Somalia (1982, 1993, DEN-2), and Saudi Arabia (1994, DEN-2). However, it remains unclear why many African and Middle Eastern countries have not reported any instances of epidemic dengue hemorrhagic fever [22] .

The existing evidence suggests that acute fever in eastern Africa is frequently attributed to DEN-1, -2, and -3. Instances of this include outbreaks in the Comoros during different years, such as in 1948, 1984, and 1993, which were caused by DEN-1 and -2. [23] and in Mozambique from 1984 to 1985, where DEN-3 was responsible [24] .

Samples obtained from humans in Nigeria in the 1960s led to the initial isolation of DEN-1, DEN-2, and DEN-3 in western Africa [25] .

Different countries have reported subsequent dengue outbreaks, such as Burkina Faso where DEN-2 was reported in 1982. [26] and in Senegal where DEN-2 was reported in 1999 [27] .

In Morocco, There have been no reported instances of DENV circulation. However, in 2016, the Department of Epidemiology and Disease Control (DELCM) identified Aedes albopictus in a small area within the upper Agdal district of Rabat.

Classification of dengue virus

3-Classification of dengue virus:

Dengue virus is an arbovirus belonging to the family Flaviviridae in the genus Flavivirus.

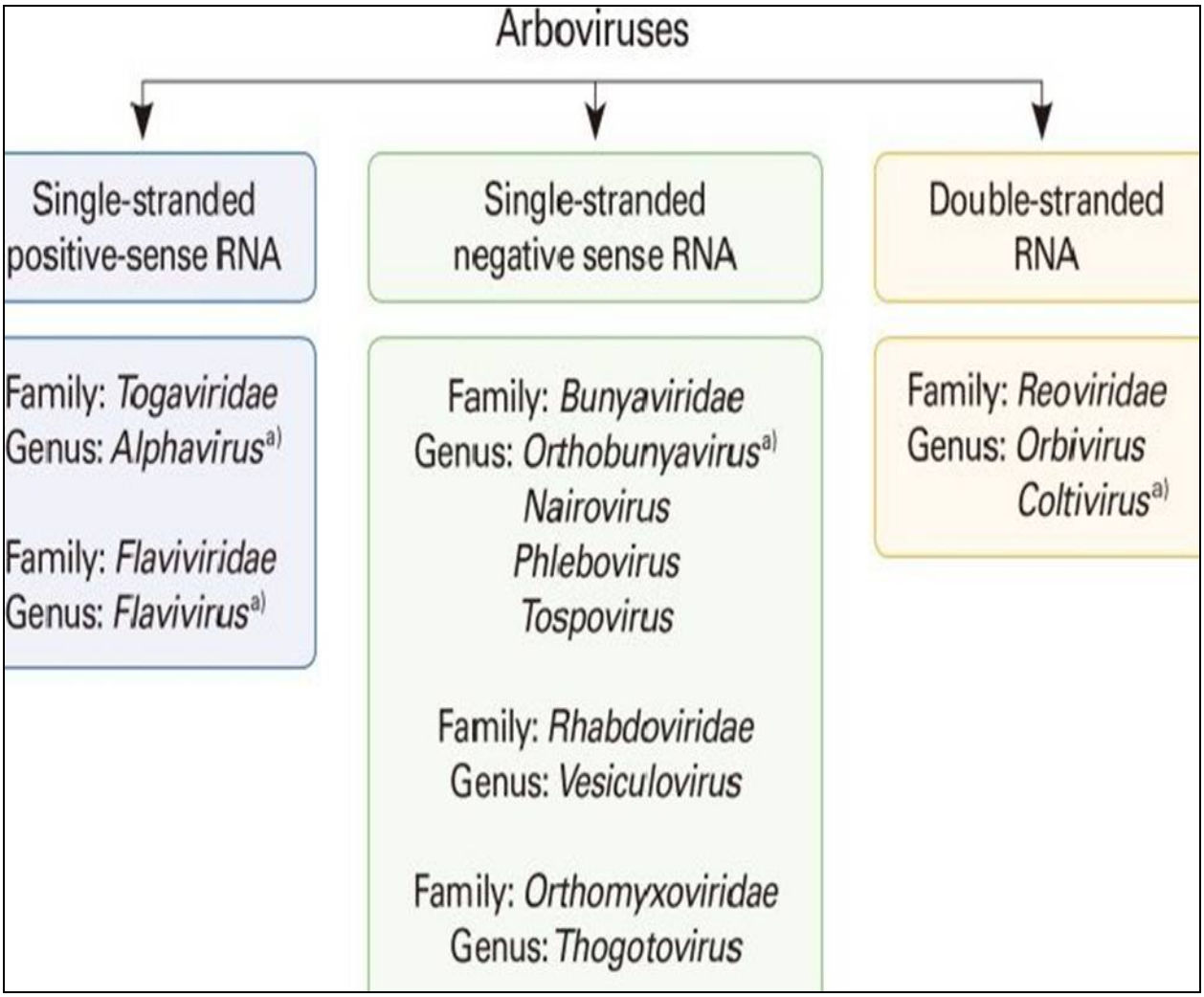

Figure 1: Classification of Arboviruses [28]

Characteristics of dengue virus

4-Characteristics of dengue virus:

4.1-Structure:

The mature particle of dengue virus has a diameter of about 50 nm. It consist of an outer glycoprotein shell and an internal host derived lipid bilayer. Within this bilayer is an RNA-protein core consisting of genome RNA and capsid proteins (C). The glycoprotein shell is well defined and consists of envelope (E) and membrane protein (prM/M) [29] .

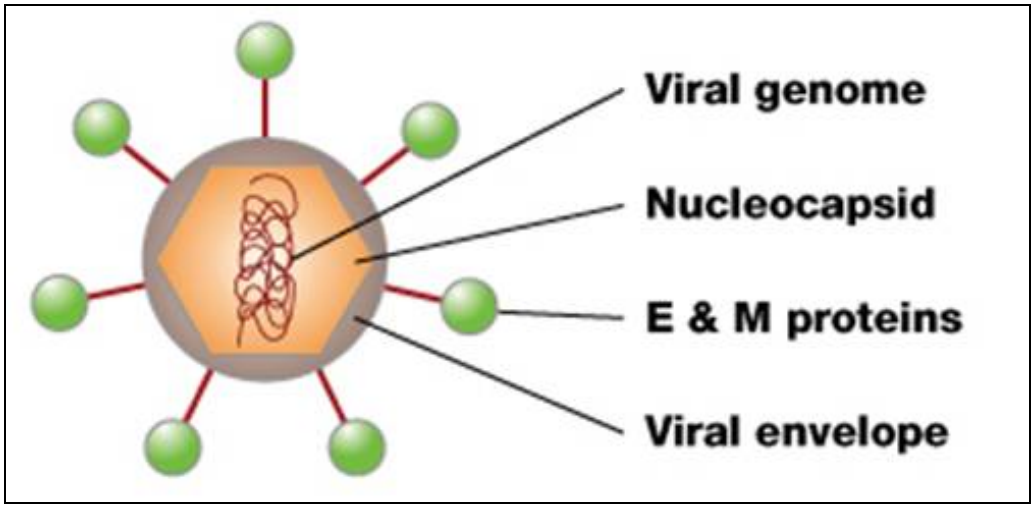

Figure 2: Structure of Dengue Virus. [30]

4.2-Genome:

The viral genome consists of a positive-sense RNA of 11 kb. This RNA encodes three structural proteins (C, prM and E) that form the components of the virion, and seven non-structural proteins (NS1, NS2A/B, NS3, NS4A/B, NS5) involved in viral RNA replication [29].

4.3-Non-structural proteins:

There is no structural information available for viral proteins NS1, NS2A and NS4A/4B. NS1 is a 45 kDa glycoprotein that is implicated in functions within the viral RNA replication [29] .

4.4-Structural proteins:

The structural proteins include capsid (C), membrane protein (prM/M) and envelope (E). The E protein provides the first point of contact between the virus and the host cell. The E protein interact with attachment factors and assist in receptor binding [29] .

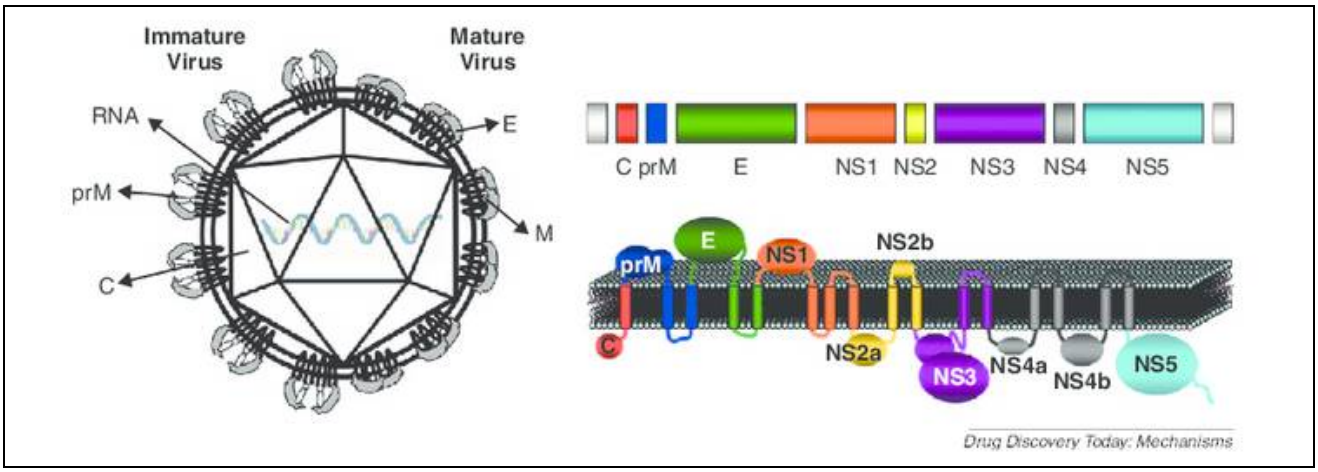

Figure 3: Flavivirus Genome Organization And Structural And Non Structural Proteins. [31]

Vector

5-Vector:

The most common vector of dengue is mosquito *Aedes aegypti.*

5.1-Life cycle of *Aedes aegypti* :

The *Aedes aegypti* mosquitos have four stages of life cycle: Egg, larva, pupa and adult. The entire life cycle takes about 8 to 10 days.

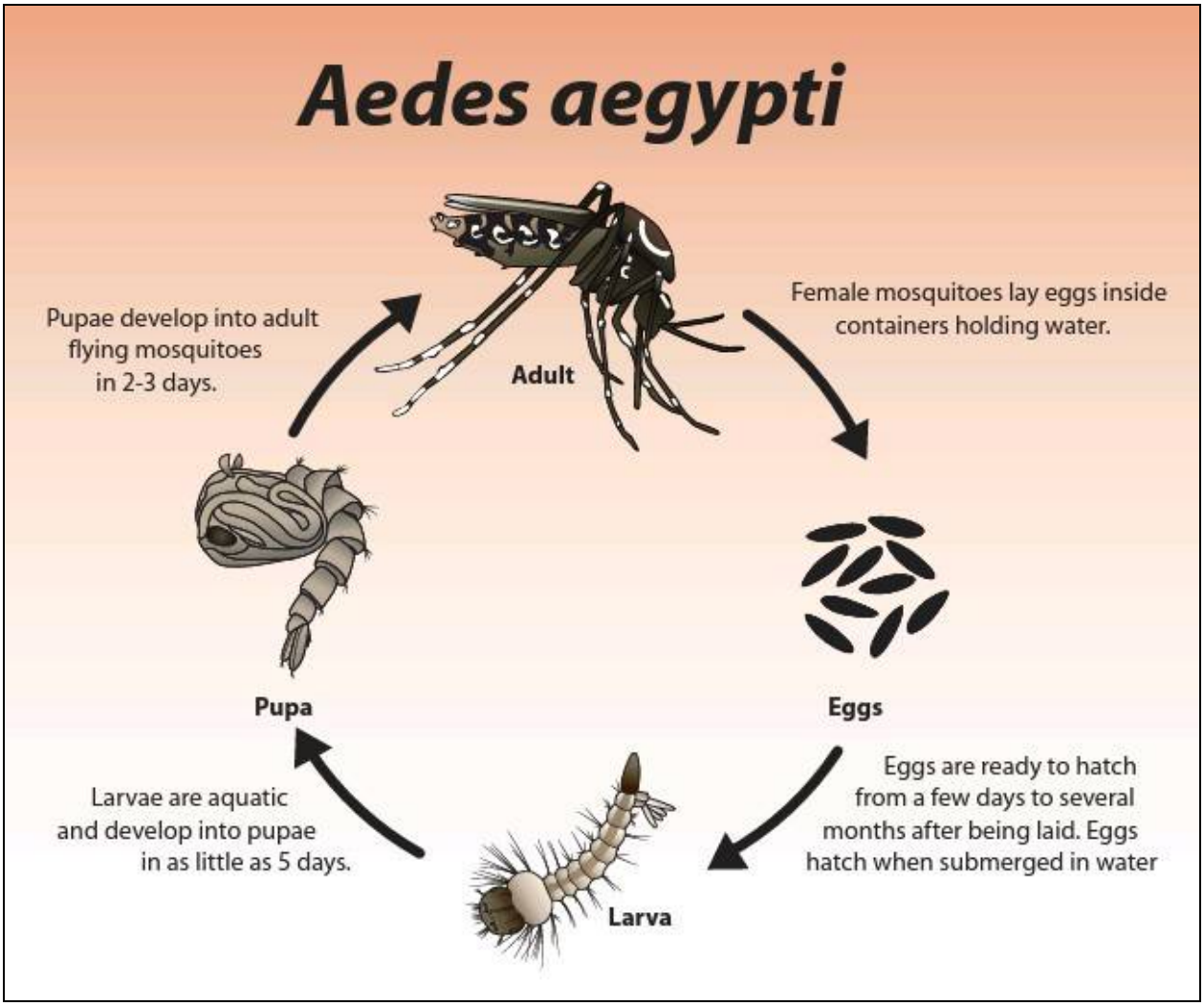

Figure 4: Life Cycle of *Aedes Aegypti* [32]

5.1.1- Egg:

Female *Aedes aegypti* lay eggs on damp surfaces just above the waterline. The eggs can withstand long periods of desiccation from 8 months to 1 year. Eggs are smooth and ovoid in shape [32] .

5.1.2- Larva:

Mosquito eggs hatch into larvae, but only when they are submerged in water. Thus, rain or human activities such as adding water to containers with eggs can prompt their emergence. The larvae subsist on microorganisms present in the water. Following three molts, the larva transforms into a pupa [32] .

Figure 5: Aedes Larva in water [32]

5.1.3- Pupa:

Pupae will develop until the body of the newly formed adult flying mosquito emerges from the pupal skin and leaves the water [32] .

Figure 6: Pupa In Water [32]

5.1.4- Adult:

Adult mosquitoes have different feeding behaviors. Male mosquitoes typically seek out nectar from flowers to provide them with the energy they need for survival. On the other hand, female mosquitoes will seek out humans or animals to feed on , because they require protein from blood to produce eggs. Once a female mosquito has finished feeding, she will typically search for a water source to lay her eggs [32] .

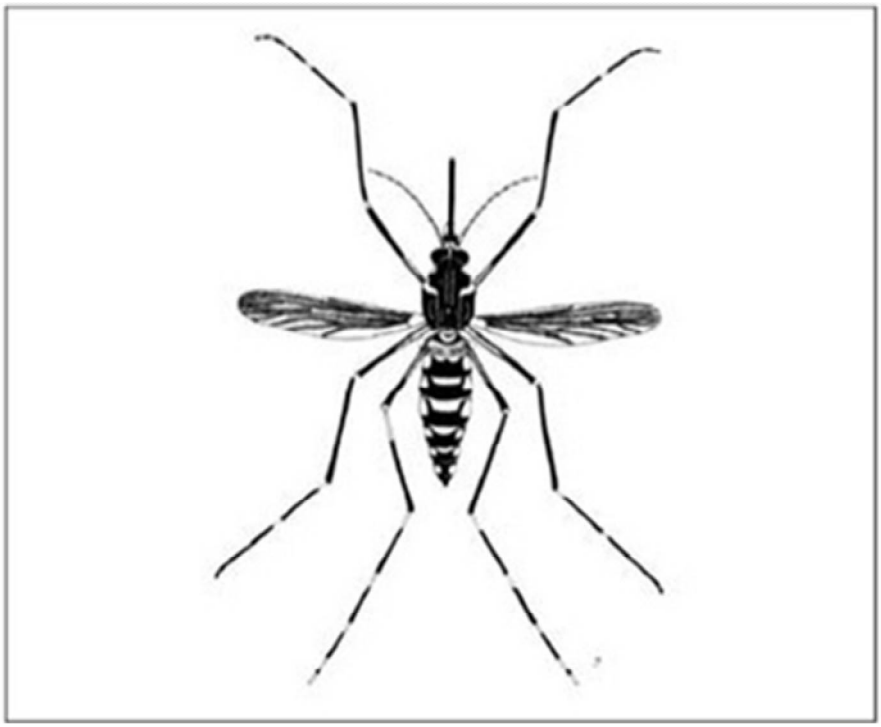

Figure 7: Adult *Aedes aegypti* [33]

Modes of transmission

6-Modes of transmission:

6.1-Human-to-mosquito transmission:

Humans serve as the primary host for the amplification of the dengue virus. When viraemic humans are bitten by female mosquitoes during feeding, the virus is ingested and infects the mosquito mid-gut. Over the next 8-12 days, the virus spreads systemically within the mosquito [34,35] .

6.2-Transmission through mosquito bite:

After the extrinsic incubation period, the mosquito can transmit the virus to other humans during subsequent feeding or probing. These mosquitoes prefer to bite people. They live both indoors and outdoors near people [34,36] .

6.3-Perinatal transmission:

DENV can also be transmitted from an infected woman to her fetus in utero or in infant during parturition [37] .

6.4-Transmission through blood transfusions:

The virus can be present in the blood of a person who has dengue fever and if that blood is transfused to another person, the virus can be transmitted to the recipient. To reduce the risk of dengue transmission through blood transfusion, blood banks may implement screening measures to detect the presence of the virus in donated blood [38] .

6.5-Transmission via organ donation:

The virus can be present in the blood or tissues of a person who has dengue fever, and if an organ from that person is transplanted to another person, the virus can be transmitted to the recipient. To reduce the risk of dengue transmission through organ donation, potential donors are typically screened for dengue infection using laboratory tests and medical history [35] .

6.6-Transmission via blood products:

Dengue virus can be transmitted through blood products such as plasma and platelets. The risk of dengue transmission through blood products is generally low. It is important for healthcare providers to screen blood for dengue infection before transfusion [38] .

Risk factors contributing to dengue

7-Risk factors contributing to dengue:

7.1-Risk factors linked to Host:

The incubation period for the virus is typically 4-10 days, after which infected host may experience a variety of symptoms. Primary infection with a dengue virus serotype is thought to provide lifelong immunity to that specific serotype to the host, but it does not provide long-term cross-protective immunity to other serotypes. Secondary infection with a different serotype may lead to severe dengue, especially in individuals with risk factors such as age, ethnicity, and chronic diseases. While most infections are asymptomatic or subclinical, some individuals may experience severe symptoms such as plasma leakage, hemorrhage, shock and abnormalities in homeostasis. Antibody-dependent enhancement (ADE) of infection is one proposed mechanism for severe dengue. In this model, non-neutralizing, cross-reactive antibodies from a previous infection or acquired passively at birth bind to epitopes on a heterologous virus and facilitate virus entry into cells. This results in a higher viral burden and robust host immune response that can contribute to capillary leakage and other severe symptoms. Endothelial cell activation could play a role in plasma leakage during severe dengue. Other factors such as activation of infected monocytes and T cells, complement system, and the production of mediators and cytokines may also contribute to endothelial cell dysfunction. Host genetic determinants may also influence the clinical outcome of dengue virus infection. Individuals of African ancestry may have lower rates of severe dengue compared to other ethnic groups. Thrombocytopenia and platelet dysfunction may be associated with impaired megakaryocytopoieses and progenitor cell growth. The transient and reversible imbalance of inflammatory mediators, cytokines, and chemokines likely plays a crucial role in the development of severe dengue. The virus enters the body through the skin when an infected mosquito takes a blood meal. During the acute phase of illness, the virus is present in the blood and is cleared with the help of neutralizing antibodies, CD4+ and CD8+ T lymphocytes and innate host defence mechanisms [39] .

7.2-Risk factors linked to virus:

The dengue virus (DEN) is a member of the Flaviviridae family and the Flavivirus genus, it is a small single-stranded RNA virus with four different serotypes DEN-1 to -4) . The mature virus particle is 50nm in diameter. The single-stranded RNA genome is cleaved into three structural proteins (capsid C, the precursor of membrane prM and envelope E) and seven nonstructural proteins (NS) by host and viral proteases. Genetic variability of the dengue serotypes is extensive with distinct genotypes within each serotype. Purifying selection is a major theme in the evolution of dengue viruses, allowing only viruses that are fit for both human and vector to persist. Asian genotypes of DEN-2 and DEN-3 are often commonly linked to severe disease accompanying secondary dengue infections [39] .

7.3-Risk factors based on vector and environment:

Dengue virus is transmitted to humans through the bites of infected Aedes mosquitoes, principally Ae. aegypti. Aedes aegypti is widely distributed around the world. But it is more common in tropical and subtropical regions. They are uncommon in colder regions. These mosquitos prefer higher and warmer climate. In recent decades Aedes albopictus has spread from Asia to other parts of the world due to international travelers. The particular reason of dengue spread is also the international trade in used tyres in which eggs are deposited when they contain rainwater. Breeding sites include the stagnant water in open containers, human dwellings and often indoor flower vases. Urbanization isassociated with dengue transmission. The mosquitos thrive in close proximity to humans. People rapidly move the virus within communities. Increase in population density anf human mobility leads to the increase of virus spread. poor waste management and garbage disposal near the houses also leads to the breeding of mosquito Aedes aegypti [39] .

Pathophysiology of dengue

8-Pathophysiology of dengue:

The pathophysiological mechanisms of the dengue virus can be explained by considering factors such as viral pathogenesis, viral genotypes and virulence, as well as the responses of the immune system including antibodies, cellular reactions, cytokines, and innate immunity.

When a mosquito carrying the dengue virus bites and feeds on blood, the virus gains entry through the skin. During the initial stage of the disease, the virus can be found in the bloodstream, and it is typically eliminated around the same time that the fever subsides [39] .

The severity of dengue infections is directly related to the peak plasma viraemia [40] .

Contracting infection a particular serotype of dengue provides immunity only against that specific serotype, while being infected by another serotype typically leads to a more severe infection due to antibody-dependent enhancement. It is possible that additional infections may contribute to the severity of secondary dengue infections [41] .

There is a 30% difference observed in the polyproteins of dengue viruses. Moreover, genetic variations exist within each serotype which causes the emergence of genetically distinct genotypes [42] .

Currently, four dengue virus serotypes have been identified with 3, 6, 4, and 4 genotypes, respectively. It is common for multiple genotypes to be present in the same geographic region. DEN-2 and DEN-3 serotypes, which originated in Asia, have become endemic in other continents. These genotypes are associated with higher viral titers [43] .

In cases of secondary dengue infections, the existing antibodies combine with the dengue virus to form complexes. These antibodies' Fc portion attaches to cells containing Fc RI and Fc RII receptors, leading to a significant number of cells being infected by the dengue virus [44] .

In DHF, thrombocytopenia results from multiple factors, including the presence of antiplatelet antibodies (IgM), dengue viral antibodies that cross-react with platelets, faulty platelet production, and peripheral destruction in the liver and spleen. Dengue virus-specific

IgM and IgG antibodies provide immune protection via different mechanisms, such as obstructing cellular attachment, viral fusion, or antibody-dependent cellular cytotoxicity (ADCC). Dengue viral epitopes targeted by neutralizing antibodies have been identified [45] .

The body's immune system plays a crucial role in clearing the virus from the bloodstream, with both humoral and cellular responses playing a role in generating neutralizing antibodies and activating T lymphocytes, including CD4+ and CD8+ cells. Additionally, the innate defense mechanisms of the body may help restrict the spread of the virus. Even after recovery from dengue infection, measurable levels of antibodies and T cells specific to the dengue virus can persist for many years [39] .

Different cytokines are produced by monocytes, B-cells, and mast cells when they are infected with the dengue virus. The types and amounts of these cytokines change over the course of the illness. During the initial 3 days of illness, tumor necrosis factor-α (TNF-α), interleukin (IL)-2, IL-6, and IFN-γ are at their highest levels, while IL-10, IL-5, and IL-4 appear later [46] .

Life cycle of dengue and virus replication

9-Life cycle of dengue and virus replication:

The replication of the dengue virus occurs in mononuclear cells such as skin dendritic cells, tissue macrophages, peripheral blood monocytes, and hepatocytes. It seems that endothelial cells are not suitable host cells for dengue virus replication [47] .

The process of dengue virus infection involves the attachment of the virus to a host cell, followed by its entry into the cell via endocytosis. Once inside the cell, the virus fuses with the endosomal membrane, releasing its genetic material into the cytoplasm. This genetic material is then used to produce ten proteins through a process of translation and cleavage of a single polypeptide. The viral genome is also replicated within the cell. The assembly of new virus particles takes place on the surface of the endoplasmic reticulum (ER), where structural proteins and newly synthesized RNA come together to form immature viral particles that bud out from the ER. These immature particles then travel through the trans-Golgi network (TGN), where they undergo maturation and become infectious. Finally, the mature viruses are released from the cell and can infect other cells [48] .

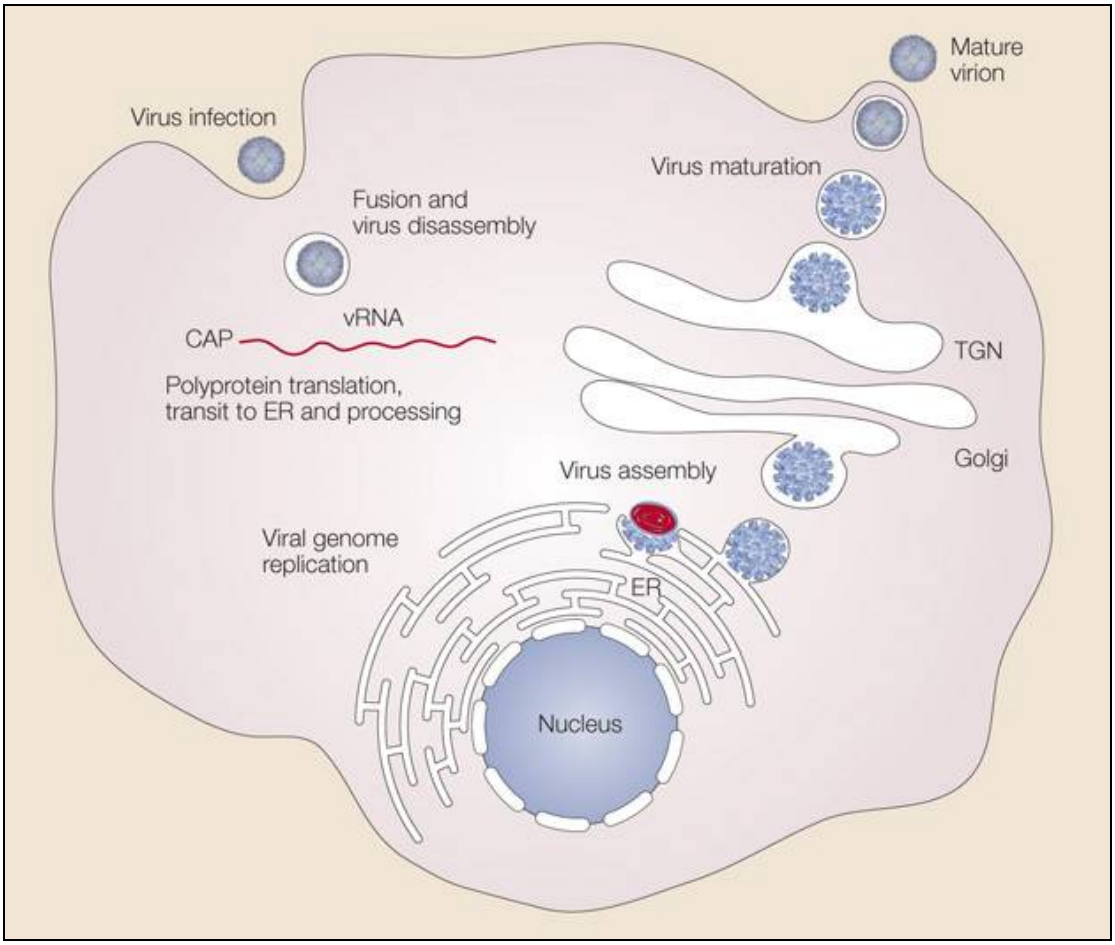

Figure 8: Dengue virus replication. [48]

Clinic

10-Clinic

10.1-Clinical characteristics of dengue:

After an incubation period of 3-4 days, the onset of disease is brutal and it evolves in three phases: febrile, critical and recovery phase.

10.1.1-Febrile phase:

Fever in patients typically persists 2−7 days and is often accompanied by facial erythema, myalgia, arthralgia, retro-orbital pain, skin rash, headache, minor hemorrhagic manifestations and leukopenia. Some patients may complain a sore throat and injected pharynx. Anorexia, nausea and vomiting are common [49] .

10.1.2-Critical phase:

The onset of critical phase of dengue occurs after the fever subsides and usually persists for a duration of 24-48 hours.

During the febrile to afebrile phase transition, if a patient doesn't experience increased capillary permeability they can recover without going through the critical phase. On the other hand, patients with increased capillary permeability may show warning signs, primarily due to plasma leakage, rather than getting better as their fever subsides. The onset of the critical phase is indicated by the warning signs. These warning signs include Abdominal pain or tenderness, Persistent vomiting, Lethargy, restlessness, Mucosal bleed, Liver enlargement > 2cm or tender enlarged liver , Clinical fluid accumulation, raised haematocrit levels concurrent with decreased platelet count [49] .

Around the time of defervescence, which typically occurs on days 3-8 of illness when the temperature drops to 37.5-38°C or less and remains below this level, these patients tend to experience a deterioration in their condition. Usually, before plasma leakage occurs, there is a progressive reduction in white blood cell count followed by a rapid drop in platelet count. One of the first additional indications may be an increase in hematocrit above the baseline. The duration of clinically massive plasma leakage typically lasts between 24 and 48 hours and the extent of plasma leakage can vary. An increase in hematocrit usually precedes modification in blood pressure and pulse volume [49] .

The severity of plasma leakage can be assessed by the degree of haemoconcentration above the baseline haematocrit, but early intravenous fluid therapy can help to decrease it. Therefore, it is crucial to perform frequent haematocrit measurements to identify the need to adjust the intravenous fluid therapy. Unless the plasma leakage is massive, pleural effusion and ascites may only become clinically evident after intravenous fluid therapy. Clinical detection may be preceded by a right lateral decubitus chest x-ray, ultrasound evidence of loose fluid in the chest or abdomen or oedema of gall bladder wall. Along with plasma leakage, haemorrhagic manifestations which includes simple bruising and bleeding at venepuncture sites [49] .

Shock is preceded by warning signs. shock occurs when a critical amount of plasma leaks out. Shock can cause body temperature to drop below normal. When shock becomes severe or prolonged, it leads to hypoperfusion which causes metabolic acidosis, progressive organ dysfunction and disseminated intravascular coagulation. This may result in severe bleeding and a decrease in hematocrit in profound shock. Unlike dengue's typical leukopenia that occurs during this phase, patients experiencing severe bleeding may exhibit an increase in their total white cell count as a stress response. Moreover, severe organ damage such as severe hepatitis, encephalitis, myocarditis, and severe haemorrhage may develop even when plasma leakage or shock is not apparent [49] .

In certain patients, the critical stage of plasma leakage and shock may occur before defervescence. For such patients, an increasing haematocrit and sudden onset of thrombocytopenia or warning signs serve as an indication of the beginning of plasma leakage. Intravenous rehydration can usually lead to recovery in dengue cases with warning signs. However, dengue may progress to a severe form in some instances [49] .

10.1.3-Recovery phase:

Following the critical phase of 24-48 hours, as the patient begins to recover, there is a gradual reabsorption of fluid from the extravascular compartment that occurs over the next 48-72 hours. During this time, the patient's overall health improves, their appetite recovers, gastrointestinal symptoms improve, their hemodynamic status stabilizes, and they begin to experience diuresis. Some patients may develop erythematous or petechial rash with small patches of normal skin, also known as isles of white in the sea of red. While others may

experience generalized itching. Bradycardia and electrocardiographic changes are common during this stage. The patient's hematocrit stabilizes or may decrease because of the dilutional impact of the reabsorbed fluid. The white blood cell count begins to increase followed by the recovery of platelet count. Excessive intravenous fluid administration during the critical or recovery phase can lead to shortness of breath due to pleural effusion, ascites, pulmonary edema or congestive heart failure. Typically laboratory results show low white blood cell and platelet counts, decreased sodium levels, increased levels of aspartate aminotransferase and alanine aminotransferase, along with a normal erythrocyte sedimentation rate [49] .

10.2-Complications during febrile, critical and recovery phase: [49]

Febrile phase: Dehydration, high fever may cause neurological disturbances and febrile seizures in young children.

Critical phase: Shock from plasma leakage: severe hemorrhage, organ impairment.

Recovery phase: pulmonary edema, Hypervolemia (if excessive IV fluid therapy).

10.3-Clinical Classification of dengue by Severity:

By clinical severity, dengue can be classified into dengue fever, dengue hemorrhagic fever and dengue shock syndrome.

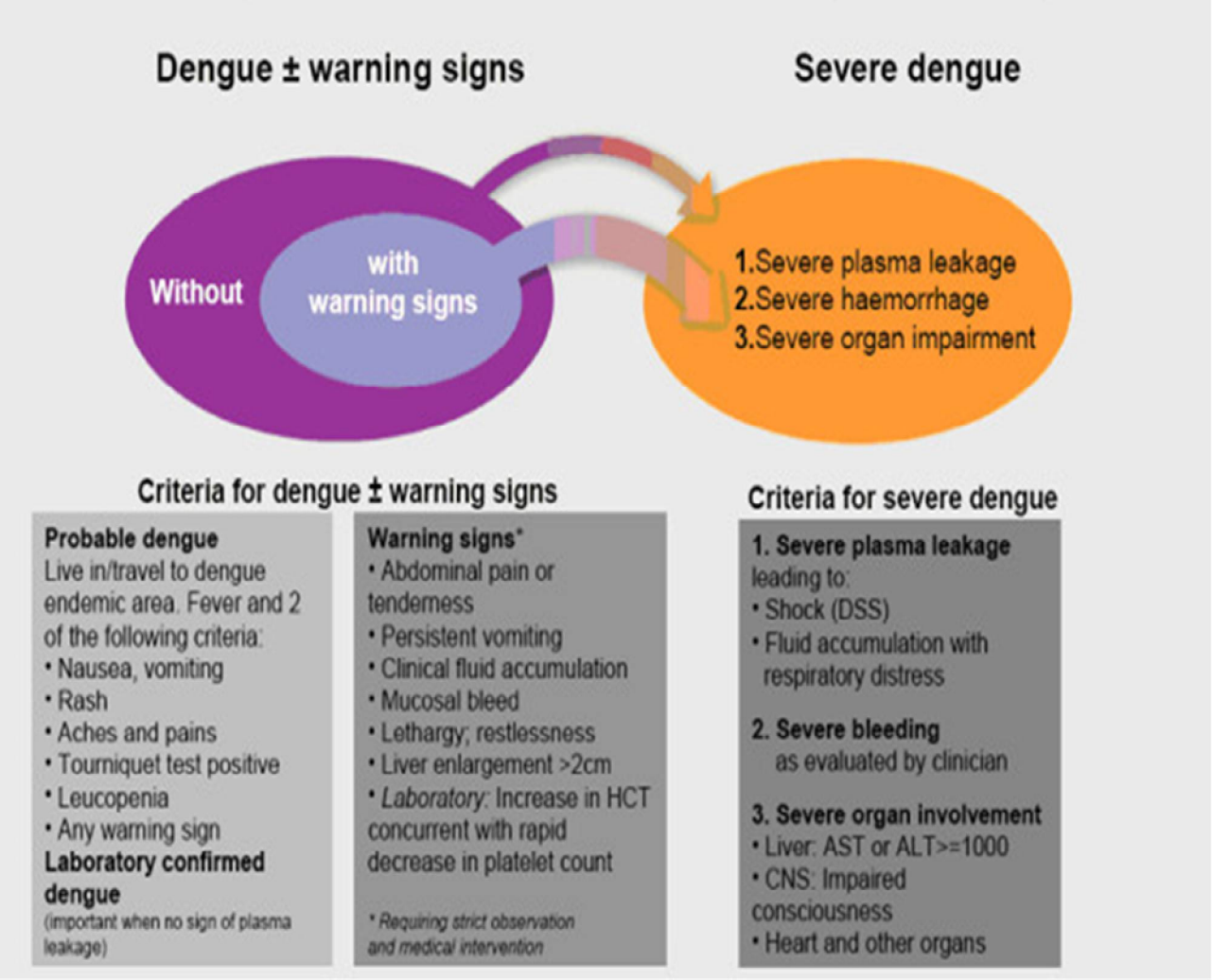

Figure 9: Dengue classification by severity: [49]

10.3.1-Dengue fever:

It can occur in any age group. But it is most common among older children, adolescents and adults. After an incubation period of 4–6 days clinical signs may develop. It is characterized by sudden onset of biphasic Fever that ranges between 39 °C and 40 °C. It is usually associated with flushed face, headache, retro-orbital pain, myalgia, arthralgia and rash. In DF, unusual hemorrhagic manifestations can occur. Leucopenia, mild thrombocytopenia, mild hematocrit rise may develop [50] .

10.3.2-Dengue hemorrhagic fever:

DHF is more common in children less than 15 years of age as well as in infants. It is characterized by the acute onset of high fever that may continue from of two to seven days of duration and is associated with signs and symptoms similar to DF such as anorexia, vomiting, constipation, diarrhea, headache, muscle or joint pains and hepatomegaly. Hemorrhagic manifestations such as such as positive tourniquet test, petechiae, gastrointestinal bleeding, hypermenorrhea and epistaxis. Signs of plasma leakage may begin at the transition from the febrile to the afebrile phase. The plasma leakage signs include rising hematocrit and hemoconcentration ≥20% from baseline, pleural effusion, ascites, hypoproteinemia or albuminemia . Significant Plasma leakage may lead to hypovolemic shock (DSS). Abdominal pain is a frequent complaint before the onset of shock. Other signs of DHF include thrombocytopenia and abnormal hemostasis [50] .

10.3.3-Dengue shock syndrome (DSS):

It is the most severe form of dengue and it is characterized by the symptoms of DHF with signs of shock. it is a form of hypovolemic shock and results from continued plasma leakage. This usually takes place after 4−5 days of illness. The signs of shock include tachycardia, cold extremities, delayed capillary refill time (superior to 3 seconds), restlessness, narrow pulse pressure ≤20 mmHg with an increased diastolic pressure (100/80 mmHg) or hypotension (systolic pressure 80 to 90 mmHg in adults). Prolonged shock can lead to cardiorespiratory collapse, multiple organ failure, bleeding, metabolic acidosis and electrolyte imbalance. If untreated, it can lead to coma and death [50] .

Table I: Grading Of Severity Of Dengue [50]

DF/ DHF	Grade	Signs and symptoms	Laboratory
DF		Fever with two of the following: •Headache. •Retro-orbital pain. •Myalgia. •Arthtralgia/bone pain. •Rash. •Haemorrhagic manifestations. •No evidence of plasma leakage.	•Leucopenia (wbc ≤5000 cells/mm3). •Thrombocytopenia (Platelet count <150 000 cells/mm3). •Rising haematocrit (5% – 10%). •No evidence of plasma loss.
DHF	I	Fever and hemorrhagic manifestation (positive tourniquet test) and evidence of plasma leakage	Thrombocytopenia <100 000 cells/ mm3; HCT rise ≥20%
DHF	II	As in Grade I plus spontaneous bleeding.	Thrombocytopenia <100 000 cells/mm3; HCT rise ≥20%.
DHF (DSS *)	III	As in Grade I or II plus circulatory failure (weak pulse, narrow pulse pressure (≤20 mmHg), hypotension, restlessness).	Thrombocytopenia <100 000 cells/mm3; HCT rise ≥20%.
DHF (DSS*)	IV	As in Grade III plus profound shock with undetectable BP and pulse.	Thrombocytopenia < 100 000 cells/mm3; HCT rise ≥20%.

Differential diagnosis

11-Differential diagnosis:

Many infectious and non-infectious diseases imitate dengue.

Table II: Differential Diagnosis Of Dengue Fever [49]

Conditions that mimic the febrile phase of dengue infection	
Flu-like syndromes	Influenza, measles, chikungunya, infectious mononucleosis, HIVseroconversion illness
Illnesses with a rash	Rubella, measles, scarlet fever, meningococcal infection, chikungunya, drug reactions
Diarrhoeal diseases	Rotavirus, other enteric infections
Illnesses with neurological manifestations	Meningoencephalitis Febrile seizures
Conditions that mimic the critical phase of dengue infection	
Infectious	Acute gastroenteritis, malaria, leptospirosis, typhoid, typhus, viral hepatitis, Acute HIV-seroconversion illness, bacterial sepsis, septic shoc k
Malignancies	Acute leukaemia and other malignancies
Other clinical pictures	Acute abdomen ,Acute appendicitis , Acute cholecystitis, Perforated viscus, Diabetic ketoacidosis, Kawasaki syndrome, Lactic acidosis, Leukopenia, thrombocytopenia and bleeding, Platelet disorders, Renal failure, Respiratory distress (Kussmaul's breathing), Systemic lupus erythematosus.

Dengue during pregnancy

12-Dengue during pregnancy:

There is limited knowledge of adverse effects of dengue on pregnancy outcomes, such as; preterm birth, low-birth weight, caesarean deliveries and spontaneous abortion risks. The clinical symptoms of dengue in pregnant women are similar to those of non-pregnant women. Dengue in Pregnancy may be asymptomatic. The symptoms are fever, mild to severe bleeding, abdominal pain, ascites or pleural effusion and increased hematocrit in plasma leakage, Leukopenia, thrombocytopenia and mildly raised liver enzymes.

Impact of dengue on pregnancy and delivery are early abortion, antepartum hemorrhage (APH), preterm birth, low-birth weight, intrauterine growth restriction, fetal distress and still birth ,increased incidence of caesarean deliveries and postpartum Hemorrhage (PPH) [51] .

Other complications of pregnancy, often misdiagnosed are severe pre-eclampsia (PE) , HELLP syndrome, placental abruption or concealed hemorrhage [52] . Severe bleeding may complicate delivery and surgical procedures performed during the critical phase [53] .

During dengue Fever in pregnant women, the body temperature is usually between 39 °C and 40 °C, the fever may be biphasic, that can last from 2-7 days. Headache, Retro orbital pain, muscle pain and bone pain are also presenting symptoms [54] .

During the initial 2 to 3 days of dengue in pregnant women, one may notice a widespread redness or short-lived skin eruptions on the face, neck, and chest. By the third or fourth day, a rash consisting of petechiae that encircle small, pale, circular areas of unaffected skin may develop on the feet, legs, hands, and arms. Additionally, skin itching may be present [55] .

Dengue Hemorrhagic Fever during pregnancy is characterized by a persistent fever lasting 2-7 days, along with hemorrhagic symptoms such as a positive tourniquet test, petechiae, epistaxis, hematemesis, Par vaginal bleeding, an enlarged liver and shock. Laboratory findings indicating plasma leakage include a hematocrit increase of >20%, along with the presence of pleural effusion, ascites, and hypoalbuminemia.

In pregnant women, Dengue Shock Syndrome is characterized by various clinical symptoms, including delayed capillary refill, a weak and rapid pulse, lethargy, restlessness, cold and clammy skin, undetectable blood pressure and pulse, thrombocytopenia, and an increase in hematocrit and hemoconcentration [56] .

Two distinguishing characteristics of dengue hemorrhagic fever and dengue shock syndrome are plasma leakage & abnormal hemostasis that may lead to severe complications and death [57] .

During dengue in pregnancy, certain physiological changes can complicate the diagnosis and evaluation of plasma leakage. For instance, in dengue fever, the elevation of hematocrit levels may be disguised by hemodilution, particularly in the second and third trimesters [58] .

Detecting the accumulation of third space fluid can be challenging because of the gravid uterus. Additionally, the baseline blood pressure tends to be lower and the pulse pressure wider, further complicating the diagnosis.

Causes of maternal death due to dengue during pregnancy include Severe Antepartum Hemorrhage, severe Post-Partum Hemorrhage, Dengue Shock Syndrome and Multi Organ Failure [59] .

There is possibility of risk of vertical transmission among women with dengue during the perinatal period. Vertical transmission rates appear low. The risk of dengue transmission from mother to fetus may be linked to the timing of the dengue infection during the pregnancy [34] .

Pregnant women should protect themselves from dengue. The preventing measures include avoid travel to areas with risk of dengue, Use an insect repellent, Wear long-sleeved shirts and long pants. Stay in a house with screens on windows and door. Take steps to control mosquitoes in and around your home [60] .

For pregnant women with dengue, Only Paracetamol can be given for fever. Normal saline 0.9% should be used for initial resuscitation. Fresh blood transfusion is only indicated if there is overt blood loss nearing 500 cc. There is no role of IV immunoglobulin or prophylactic antibiotics. Measures to postpone labor to a suitable time may be considered during the critical phase of dengue illness. Delivery should take place in a hospital where a team of skilled obstetricians and a neonatologist are available.

13-Dengue in Neonates:

In pregnant women with dengue, the risk of vertical transmission is well established during the perinatal period. The dengue virus can be transmitted to the foetus in utero or to the infant at parturition. Some newborns may be asymptomatic. The clinical manifestations in neonates are high fever, skin rash, petechiae, thrombocytopenia and hepatomegaly. The signs of severe illness include febrile seizure, sepsis, pleural effusion and gastric bleeding. Raised hematocrit may be noted.

A study was conducted in Thailand for transmission of dengue from mother to two new born infants. The study stated that on their sixth day of birth, two infants developed a mild case of dengue, which progressed to dengue hemorrhagic fever. They both exhibited symptoms such as low-grade fever, hepatomegaly, and a generalized petechial rash. The first baby had a hematocrit ranging from 40 to 46 percent, along with a minimal amount of right pleural effusion. Their lowest platelet count was 19,000 cells/mm3, and the mother of the baby had dengue shock syndrome, which caused her to experience massive postpartum bleeding. The second baby also contracted dengue, while their mother had dengue fever. The baby's hematocrit increased from 52 to 61 percent, and they had right pleural effusion, with the lowest platelet count being 7,000 cells/mm3. All of the individuals, including the mothers and their babies, made a complete recovery, although the first baby experienced prolonged thrombocytopenia for two months [61] .

14-Dengue in the older People:

The clinical symptoms in elderly dengue patients include fever, flushed face, headache, retro-orbital pain, myalgia and arthralgia. Other more common clinical manifestations in elderly patients are Gastrointestinal tract bleeding, microhematuria, bacteremia, acute renal failure, pleural effusion, prolonged prothrombin time and lower hemoglobin levels. While, skin rash, hepatomegaly and muco-cutaneous hemorrhage are less frequent.

15-High risk patients:

People who live in or travel to tropical and subtropical areas where dengue is endemic are at high risk of dengue. Dengue is most common in Southeast Asia, the Caribbean, Central and South America, and Africa.

Infants, children, and the elderly are more susceptible to develop severe forms of dengue fever. People with weakened immune systems such as those with HIV/AIDS, cancer, organ transplantation or other conditions that weaken the immune system are at increased risk to dengue fever.

Individuals who have previously been infected with one of the four dengue virus strains. They are at risk of developing severe dengue if they are re-infected with a different serotype of the virus.

Pregnant women are at higher risk of developing severe dengue, which can lead to complications for both the mother and the baby. People living in areas with poor sanitation and standing water. These conditions provide breeding grounds for the mosquitoes that transmit dengue, thus increasing the risk of dengue [50] .

Diagnosis

16-Diagnosis:

16.1-Sample collection:

venous and capillary blood samples could be collected from patients suffering from dengue symptoms. Serum obtained from patient by intravenous puncture could be used for viral diagnosis, isolation on Aedes cells and serological diagnosis. Capillary blood samples could be obtained from a finger and absorbed on filter paper for analysis by molecular and serological methods. The drop of capillary blood deposited on a strip of Whatman filter paper should be immediately placed in a tube at room temperature (20 to 25°C) until it is taken to the laboratory for analysis [62] . Samples can be obtained from tissues during biopsy or autopsy. Liver, spleen and lymph nodes are the sites of choice for tissue samples [63,64] .

16.2-Virus isolation:

The gold standard for identification of dengue infection is virus isolation, but it has limitations, such as its lengthy procedure, requirement for viability of the virus in specimens, and inability to differentiate between primary and secondary infections. For successful isolation of the virus, Samples should be collected early in the disease, usually within the first 5 days of onset of fever. Common specimens used for virus isolation include plasma, serum and peripheral blood during febrile phase, and also from postmortem specimens such as cerebrospinal fluid, pleural fluid, liver, lung, spleen, lymph nodes, thymus. There are three methods of DENV cultivation: inoculation of specimens into mosquitoes, in vitro cultured cell lines or intra-cerebrally in mice. Inoculation of Toxorhynchites splendens and C6/36 (Aedes albopictus) mosquitoes is the most sensitive method, but it requires excellent facilities and strict adherence to health and safety protocols. Alternatively, specimens may be inoculated into mosquito lines (such as AP61, TRA-284, C6/36, AP64 and CLA-1) or mammalian cell lines (such as LLCMK2, Vero and BHK21) which are widely available but less sensitive than mosquito inoculation. A new approach under development combines RT-PCR with culture of whole peripheral blood to reduce the time needed for detection [65] .

16.3-Serological diagnosis:

Specific IgM antibodies are produced transiently in both primary and secondary infections. In the case of dengue fever, anti-dengue IgM can usually be detected from the fifth day of the disease and persists for 60 to 90 days. The detection of anti-dengue IgM in any serum sample indicates an active or recent infection that occurred within the last two to three months. The generation of antibodies against DENV is typically distinct between primary and secondary infections. During a primary infection, IgM antibodies can be detected from the fifth day after the onset of infection, while IgG antibodies are typically present at low levels, usually from the seventh day of the infection. on the other hand, during a secondary infection, IgG antibodies are detected at high levels during the acute phase, while IgM antibodies are typically present at lower titers as compare to those observed during primary infections [66] .

During primary infection, there is a detection of relatively monotypic neutralizing antibodies. On the other hand, in secondary infections, there is a production of high levels of neutralizing antibodies targeting two or more of the four DENV serotypes. In some subsequent dengue virus (DENV) infections, the phenomenon of “original antigenic sin” can lead to the production of higher levels of neutralizing antibodies against the serotype of the virus that infected earlier, rather than the serotype currently causing the infection. This can complicate the interpretation of serological tests [67] .

16.3.1- IgM capture enzyme linked immunosorbent assay (MAC ELISA):

MAC-ELISA has gained widespread use in recent years. It is a quick and simple test that doesn't require sophisticated equipment. This test detects dengue-specific IgM antibodies in the serum by capturing them from a solution that contain anti-human IgM pre-bound to a solid phase [68] .

When a patient's serum contains anti-dengue IgM antibodies, it will bind with the dengue antigen added in the next step. This binding can then be detected by adding an enzyme-labelled anti-dengue antibody (human or monoclonal). The addition of an enzyme-substrate results in a color reaction. The anti-dengue IgM antibodies typically appears slightly earlier than IgG and they can be detected around Day 5 of the illness. However, the time it

takes for IgM antibody to appear can varies greatly among patients. They are not usually detectable during the first five days of illness. In primary infections, IgM antibody titers are significantly higher than in secondary infections, although IgM titers of 320 can still be obtained in some secondary infections. In some cases of primary infections, IgM can persist and remain detectable for over 90 days. However, in most patients, it drops and becomes undetectable after 60 days [50] .

MAC-ELISA has proven to be an extremely useful tool in monitoring cases of DF, DHF, and DSS. Even in non-endemic areas, it can be utilized for clinical surveillance of viral diseases or for sero-surveys of the general population, with the added assurance that any positive result indicate recent infections [69] .

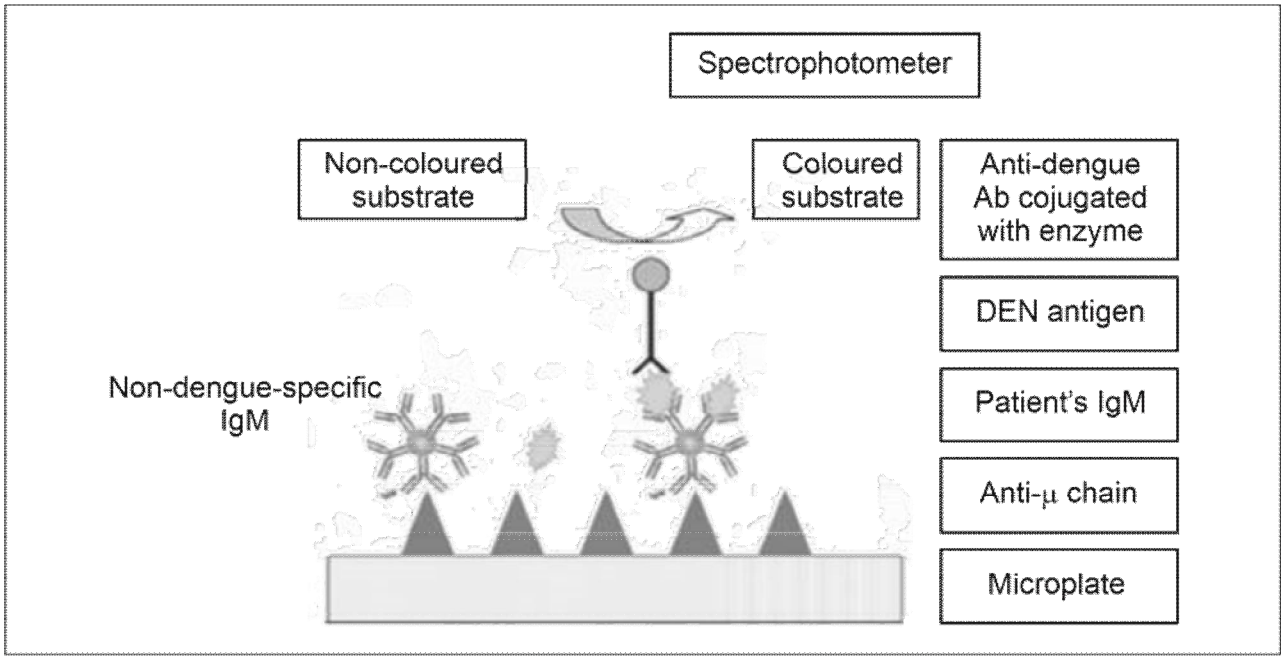

Figure 10: Principle of MAC-ELISA Test. [39]

16.3.2- IgG ELISA :

An indirect IgG-ELISA has been created and it demonstrates good similarity to the Hemagglutination inhibition test. Additionally, this test can help distinguish between primary and secondary dengue infections. It is a user-friendly, simple and easy test, which makes it ideal for conducting a high volume of tests. However, the IgG-ELISA is not very specific and has broad cross-reactivity with flaviviruses similar to the HI test. It cannot be used to determine the exact dengue serotype responsible for the infection. These tests can be used alone or in combination, depending on the sample type and the tests available to confirm the diagnosis [50,70] .

16.3.3- IgM/IgG ratio:

The IgM/IgG ratio helps to differentiate between primary and secondary dengue infections. A primary dengue infection is characterized by a capture IgM/IgG ratio greater than 1.2, while a secondary infection is defined as a ratio less than 1.2 [71] .

16.3.4- Hemagglutination Inhibition (HAI):

The Hemagglutination Inhibition (HI) test is a widely used protocol for the diagnosis of dengue, due to its simplicity, low cost, and rapidity, which allows it to be applied to a large number of samples. HI antibodies are long lasting, making it a best test for sero-epidemiological studies. This test requires the examination of paired sera obtained from an individuals during acute infection and convalescent phase, collected over an interval of seven days. The HI test is used to detect DENV and to distinguish between primary and secondary dengue infections. In primary infections, HI antibody titres increase slowly, while secondary infection is characterized by rapid and elevated anamnestic responses. One major drawback of the HI test is its inability to differentiate between members of the closely related Flaviviridae, such as dengue and Japanese encephalitis, which can be compounded by prior vaccinations against Japanese encephalitis and yellow fever. To yield a positive result, there should be above four-fold raise in antibody titres between acute and convalescent sera. Titres above 2560 indicate secondary infection, while titres below 1280 indicate primary infection. Hence, by this test alone, the diagnosis of dengue infection may not be reliable [65] .

16.3.5- Complement fixation test (CFT):

The complement fixation test is not commonly utilized in routine dengue serology diagnostics due to its difficulty in execution and the need for highly skilled personnel. This test operates under the principle that complement is depleted during interactions between antigens and antibodies. It includes two systems; a test and an indicator system. Antigens used in CF test are produced similarly to those used in the HI test. While CF testing is helpful for identifying patients with ongoing infections, it has limited value in sero-epidemiological investigations where the detection of persistent antibodies is vital [50] .

16.3.6- Neutralization test (NT):

The neutralization test is the most sensitive and specific serological assay used to determine immune protection against dengue viruses. The most commonly used protocol in dengue laboratories is the serum dilution plaque reduction neutralization test (PRNT). However, the major drawbacks of this technique are its cost and time requirements, as well as its associated technical complexity which necessitates the use of a cell culture facility. As a result, it is not routinely employed in most laboratories. Nonetheless, it is extremely useful in the development of vaccines and their efficacy studies [50] .

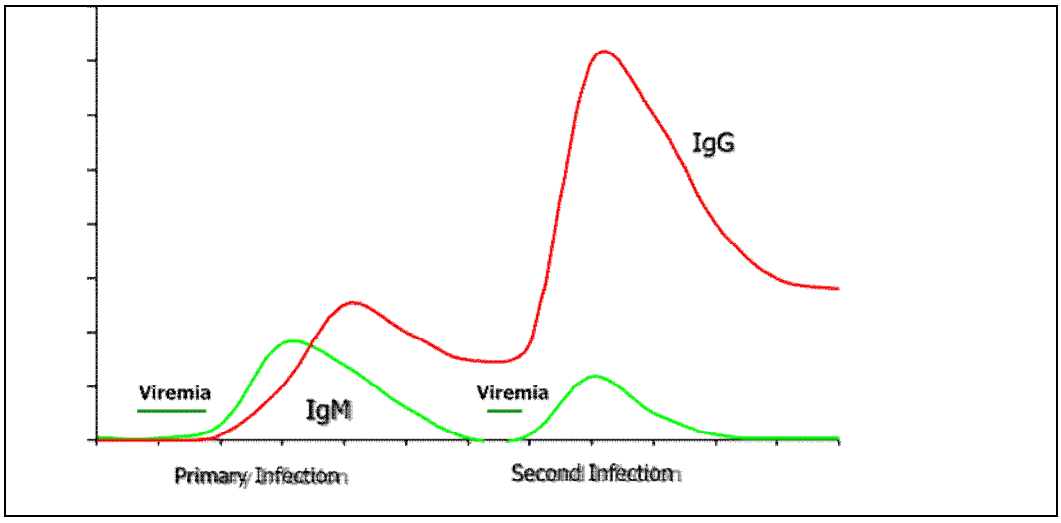

Figure 11: Virological and Serological Markers of dengue infection according to time of illness: [49]

16.4- Antigen NS1 detection:

The viral non-structural protein (NS1) is an effective diagnostic target. The NS1 glycoprotein is produced by all flaviviruses and it is secreted from mammalian cells. For up to six days after the onset of the symptoms, NS1 can be detected in the sera of patients with primary and secondary dengue infections. NS1 can be detected concurrently with viral RNA and prior to an antibody response in primary infections and it can be considered a surrogate marker for viremia, as its level correlates with viral titer. The first description of detecting NS1 in patient blood using an antigen-capture ELISA method was reported in 2000, and further studies utilizing quantitative-capture ELISA have revealed NS1 secretion at high levels, ranging from low nanograms per milliliter to micrograms per milliliter. Some infected individuals exhibiting up to 50 µg/mL in circulation. Further investigations of NS1 kinetics in secondary infections have shown that NS1 levels ≥600 ng/mL within the first 72 hours of disease indicate a high likelihood of progression to more severe disease. These early findings led to the development of commercial NS1 capture ELISAs and rapid strip tests [40,72,73] .

16.5- Rapid diagnostic tests:

Many rapid format serological test-kits for NS1 antigen and anti-dengue IgM and IgG antibodies are commercially available. They can give results within 15 minutes. The accuracy of these tests is not certain. Rapid diagnostic tests are less specific and less sensitive than the equivalent laboratory-based assays. Rapid tests can produce false positive results because of cross-reaction with other flaviviruses, malaria parasite and diseases such as rheumatoid and lupus. Rapid tests can give false negative results due to the fact that serum samples taken in the first five days after the onset of illness lack detectable IgM antibodies [70] .

16.6- Nucleic acid detection:

16.6.1- RT-PCR:

RT-PCR assays offer better sensitivity and specificity than virus isolation and it can be performed more rapidly. The laboratory and personnel carrying out the test should be equipped and trained properly to avoid false positive results. The three basic steps involved in nucleic acid detection assays are: extraction and purification of the nucleic acid, amplification of the nucleic acid and detection of the amplified product. Properly separating each step and

following strict decontamination procedures are important for minimizing the risk of contamination and false positive results. The sensitivity of RT-PCR varies from 80 to 100% than the virus isolation method [39] .

16.6.2- Nested RT-PCR:

The nested RT-PCR assay utilizes universal dengue primers that target the C/prM region of the viral genome to perform the first step of reverse transcription and amplification. This is then followed by a serotype-specific nested PCR amplification [74] .

16.6.3- One step Multiplex RT-PCR:

This test offers an alternative to nested RT-PCR for identifying dengue serotypes. It uses a combination of four serotype-specific oligonucleotide primers in a single reaction step to detect and discriminate between the serotypes. Following amplification, the resulting products are separated by electrophoresis on an agarose gel, and the different molecular weight bands are visualized by staining with ethidium bromide dye and compared to standard molecular weight markers. By comparing the size of the resulting bands, the dengue serotypes present in the sample can be identified [39,75] .

16.6.4- Real-time PCR:

Real-time PCR has become the preferred method for rapidly diagnosing dengue virus infection using acute-phase serum samples, replacing conventional PCR. The real-time RT-PCR assay is a one-step assay that utilizes primer pairs and probes specific to each dengue serotype. By utlizing a fluorescent probe, the assay is capable of detecting reaction products in real-time within a specialized PCR machine. Thus, eliminating the need for electrophoresis. Real-time RT-PCR assays are either singleplex or multiplex. Singleplex real-time PCR can detect only one serotype at a time. While, a multiplex real time PCR can detect all four serotypes from a single sample. The TaqMan real-time PCR is highly specific due to the sequence-specific hybridization of the probe. However, the primers and probes previously reported in publications cannot detect all dengue virus strains. In fact, the sensitivity of the primers and probes available depends on their homology with the target gene sequence of the virus being analyzed. Therefore, it is recommended to use multiple primers and probes targeting at different gene regions to avoid false-negative results caused by sequence

differences between different strains and potential mutants. Unlike TaqMan assay, the SYBR Green real-time RT-PCR assay is less specific, but it has the advantage of simplicity in primer design and uses universal RT-PCR protocols suitable for the detection of multiple target sequences [39,76] .

16.6.5- Isothermal amplification methods:

NASBA (nucleic acid sequence based amplification) assay is used to amplify RNA molecules without the need for thermal cycling instrumentation. This isothermal amplification method uses RNA as a template to create a double-stranded DNA molecule, which in turn acts as a template for RNA transcription. The amplified RNA can then be detected by using fluorescent-labelled molecular beacon probes or electrochemiluminescence. The sensitivity of NASBA in detecting dengue virus has been shown to be comparable to that of virus isolation in cell cultures, which is the gold standard for dengue virus detection. Therefore, NASBA has the potential to be a useful method for studying dengue infections in field studies [77] .

Loop Mediated Amplification (LAMP) is a PCR-based method that was developed as an alternative to traditional PCR methods such as RT-PCR and real-time PCR assays. It is a simple and cost-effective method [78] .

16.7- Hematological tests:

Standard hematological parameters including platelet count and hematocrit play a crucial role in the biological diagnosis of dengue infection. Thrombocytopenia is typically detected during the third to eighth day of illness. A decrease in platelet count below 100 000 per µl, may sometimes occur in dengue fever but is constantly observed in the cases of Dengue Hemorrhagic Fever (DHF). Elevated hematocrit with hemoconcentration is considered definitive evidence of increased vascular permeability and plasma leakage [39] .

16.8- Future tests:

There are many new dengue diagnostic methods which are currently under development. Micro/paper fluidics, microsphere based immune assays (MIAs), in vivo micro-patches, isothermal PCR , electrochemical and piezoelectric detection, Biosensor technology, microarray technology and many other approaches are in the early stages of development [39] .

Table III: Dengue Diagnostics And Sample Characteristics [49]

	Clinical sample	**Diagnostic method**	**Methodology**	**Time to results**
Virus detection and its components	Acute serum (1–5 days of fever) and necropsy tissues	Viral isolation	Mosquito or mosquito cell culture inoculation	One week or more
		Nucleic acid detection	RT-PCR and real time RTPCR	1 or 2 days
		Antigen detection	NS1 Ag rapid tests	Minutes
			NS1 Ag ELISA	1 day
			Immuno-histochemistry	2–5 days
Serological response	Paired sera (acute serum from1–5 days and second serum 15–21 days after)	IgM or IgG seroconversion	ELISA HIA	1–2 days
			Neutralization Test	Minimum 7 days
	Serum after day 5 of fever	IgM detection (recent infection)	ELISA	1 or 2 days
			Rapid tests	Minutes
		IgG detection	IgG ELISA HIA	1 or 2 days

Treatment

17- Treatment:

There is no specific antiviral treatment for dengue illness. Clinical management is based on supportive therapy. According to the severity of the disease, Patients are divided into three groups:

Group A (ambulatory management)

Group B (inpatients management)

Group C (intensive care unit)

17.1- Group A :

These patients do not have any of the warning signs. They are able to take oral fluids and they have normal urine output. For ambulatory management, advice the patient to take bed rest and good hydration. Adequate oral fluids intake should cause the patient to urinate at least 4 to 6 times per day. For fever, the recommended dose of paracetamol is 10 mg/kg/dose, maintain a 6 to 8 hours interval between each dose. Do not prescribe acetylsalicylic acid (Aspirin), ibuprofen or other NSAIDs. Patient should be brought to the hospital if there is no clinical improvement, persistent vomiting, cold extremities, lethargy or restlessness, severe abdominal pain, bleeding, breathing difficulties or absence of urine output. If the symptoms cannot be monitored at home or certain social circumstances such as living alone or living very far away from hospital, then admission during the febrile period should be advised [49] .

17.2- Group B:

These are the patients with warning signs and those with co-existing conditions such as diabetes, hypertension, infants, old age, pregnancy, chronic hemolytic, heart and renal diseases and those with certain social circumstances. For fever and pain, prescribe paracetamol 500 mg every 6 to 8 hours. If the patient has poor oral intake then place an intravenous line and administer ringer Lactate 2 to 3 ml/kg/hour. Then reassess the clinical status and encourage the patient for oral intake as soon as possible. Give the minimum volume required to maintain good perfusion and urine output. Intravenous fluids are usually needed only for 24−48 hours. Monitor Patients status such as warning signs, vital signs, peripheral perfusion (1−4 hourly), urine output (4−6 hourly), hematocrit, blood glucose, Liver and renal function tests [49] .

17.3- Group C:

These are patients with severe dengue who require emergency treatment and urgent referral because they are in the critical phase of the disease and have:

- severe plasma leakage leading to dengue shock and/or fluid accumulation.
- severe hemorrhages.
- severe organ impairment.

Hospitalization is necessary for patients suffering from severe dengue, and intravenous fluid resuscitation should be administered. To replace plasma losses, an isotonic crystalloid solution should be administered without delay. If hypotensive shock occurs, it is advisable to use colloid solution. It is recommended to obtain hematocrit levels before and after fluid resuscitation. To maintain proper circulation, additional plasma losses should be replaced continuously for 24-48 hours. In the case of overweight or obese patients, the fluid infusion rates should be calculated using their ideal body weight. It is recommended that all patients in shock have their blood group determined and undergo cross-matching. Blood transfusions should only be administered to patients with confirmed severe bleeding or suspected severe bleeding combined with unexplained hypotension. It is crucial to distinguish between fluid resuscitation and basic fluid administration. Fluid resuscitation involves administering larger volumes of fluids, typically 10-20 ml/kg boluses, over a limited period of time while closely monitoring the patient's response to prevent the onset of pulmonary edema. Glucose should not be present in these fluids. The level of intravascular volume deficit in dengue shock can vary, and the input/output ratio is not useful in determining the necessary fluid resuscitation during this stage as input tends to be much greater than output [49] .

The goals of fluid resuscitation include:

- improving central and peripheral circulation. For example; decreasing tachycardia, improving BP and pulse volume, warm and pink extremities, a capillary refill time < 2 seconds;
- improving end-organ perfusion. For example; achieving a stable conscious level (more alert or less restless), and urine output ≥ 0.5 ml/kg/hour or decreasing metabolic acidosis.

Table IV: Hospital Admission Criteria For Dengue Fever Patients: [39]

Warning signs	Any of the following warning signs: Abdominal pain or tenderness ,Persistent vomiting, Lethargy, restlessness , Mucosal bleed, Liver enlargement > 2cm or tender enlarged liver, Clinical fluid accumulation, Increase in haematocrit level concurrent with rapid decrease in platelet count.
Signs and 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/shortness of breath (deep sighing breaths)
Bleeding	Spontaneous bleeding, independent of the platelet count
Organ impairment	Renal, hepatic, neurological or cardiac. *enlarged, tender liver, although not yet in shock *chest pain or respiratory distress, cyanosis
Findings through further investigations	Rising haematocrit , Pleural effusion, ascites or asymptomatic gall-bladder thickening.
Co-existing conditions	Pregnancy, Co-morbid conditions, such as diabetes mellitus, hypertension, peptic ulcer, hemolytic anemias and others. Overweight or obese (rapid venous access difficult in emergency) Infancy or old age.
Social circumstances	Living alone, Living far from health facility, Without reliable means of transport.

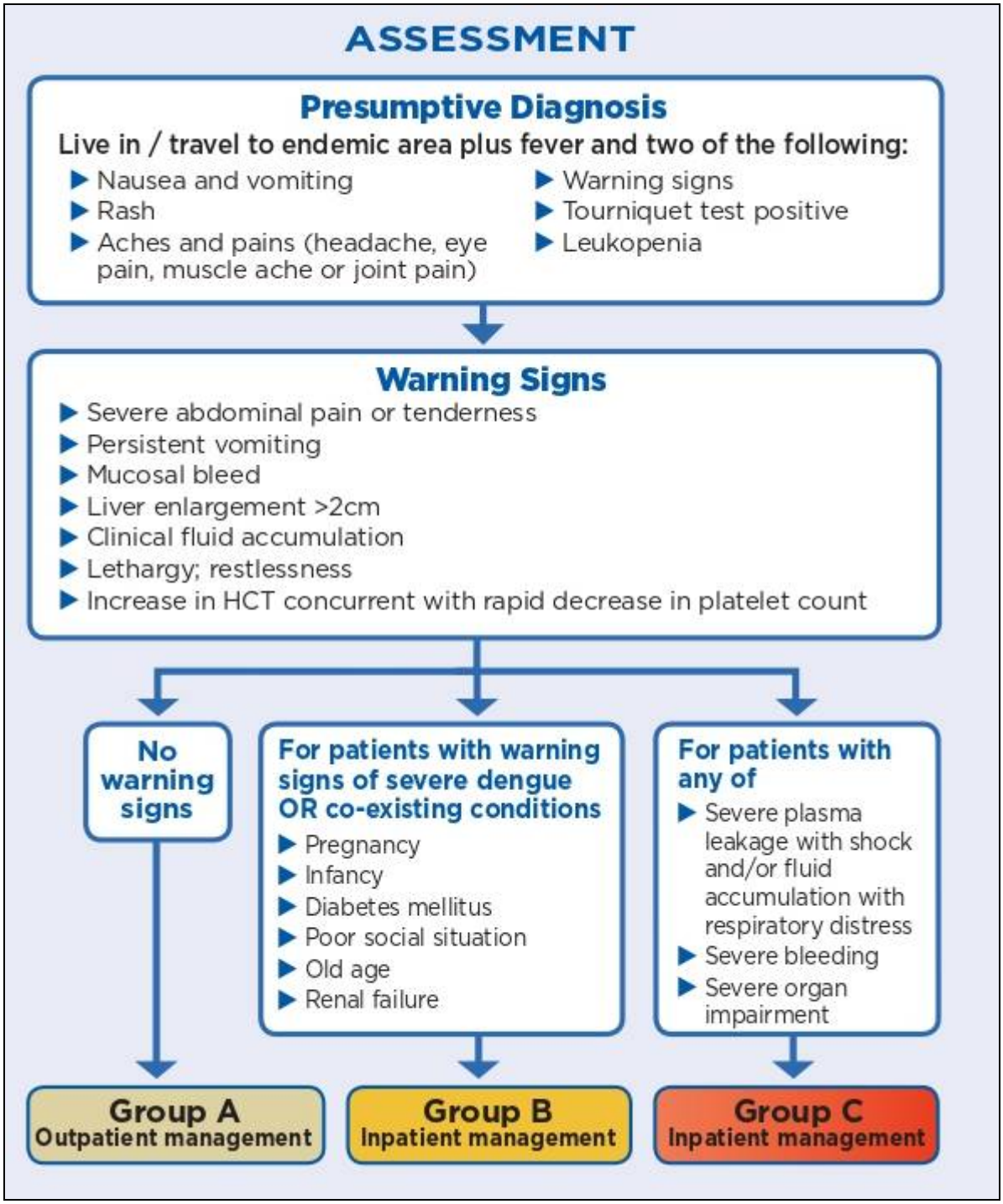

Figure 12: Dengue Case Management: [79]

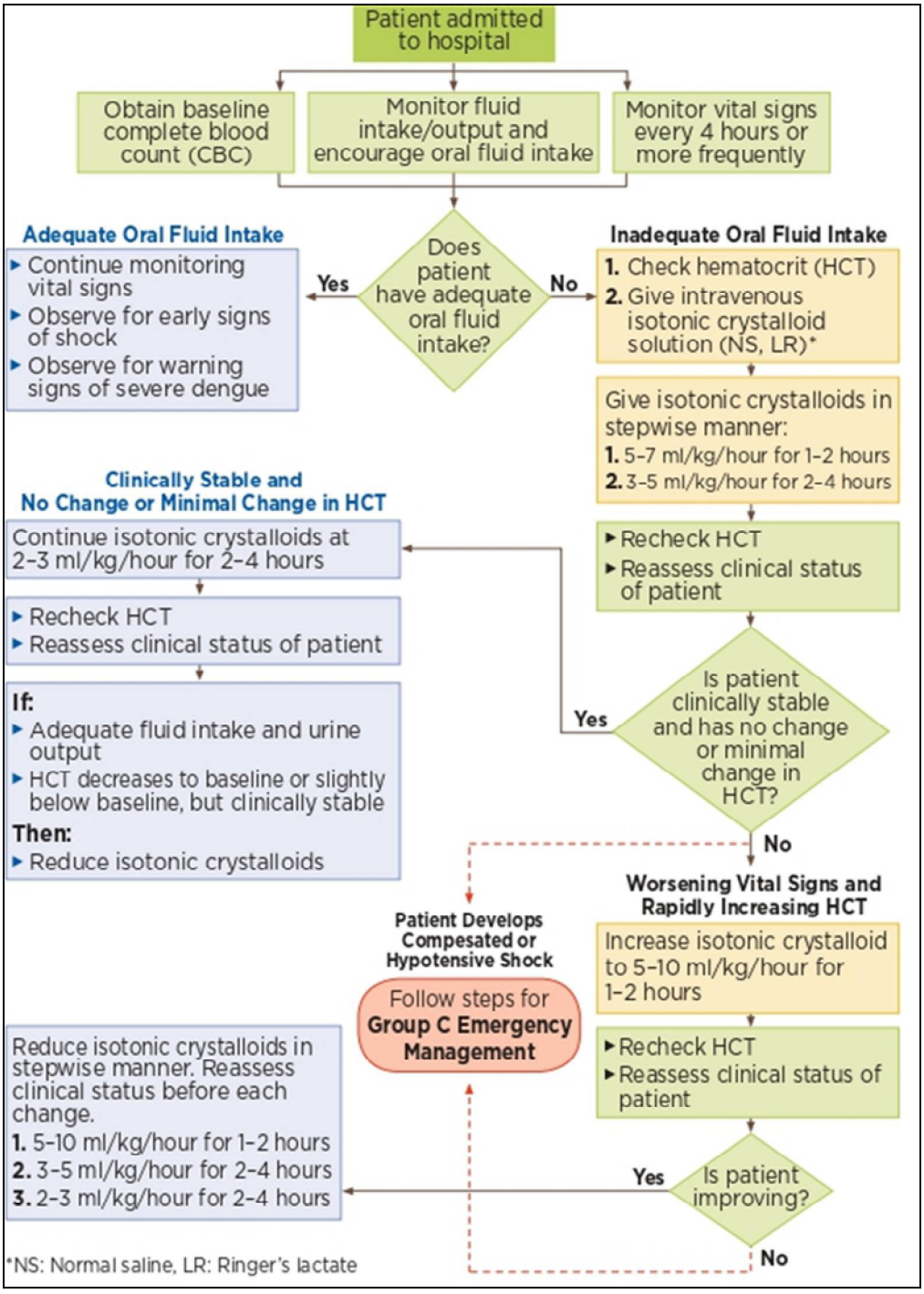

Figure 13: Group B: Inpatient Management for dengue patients with warning signs [79]

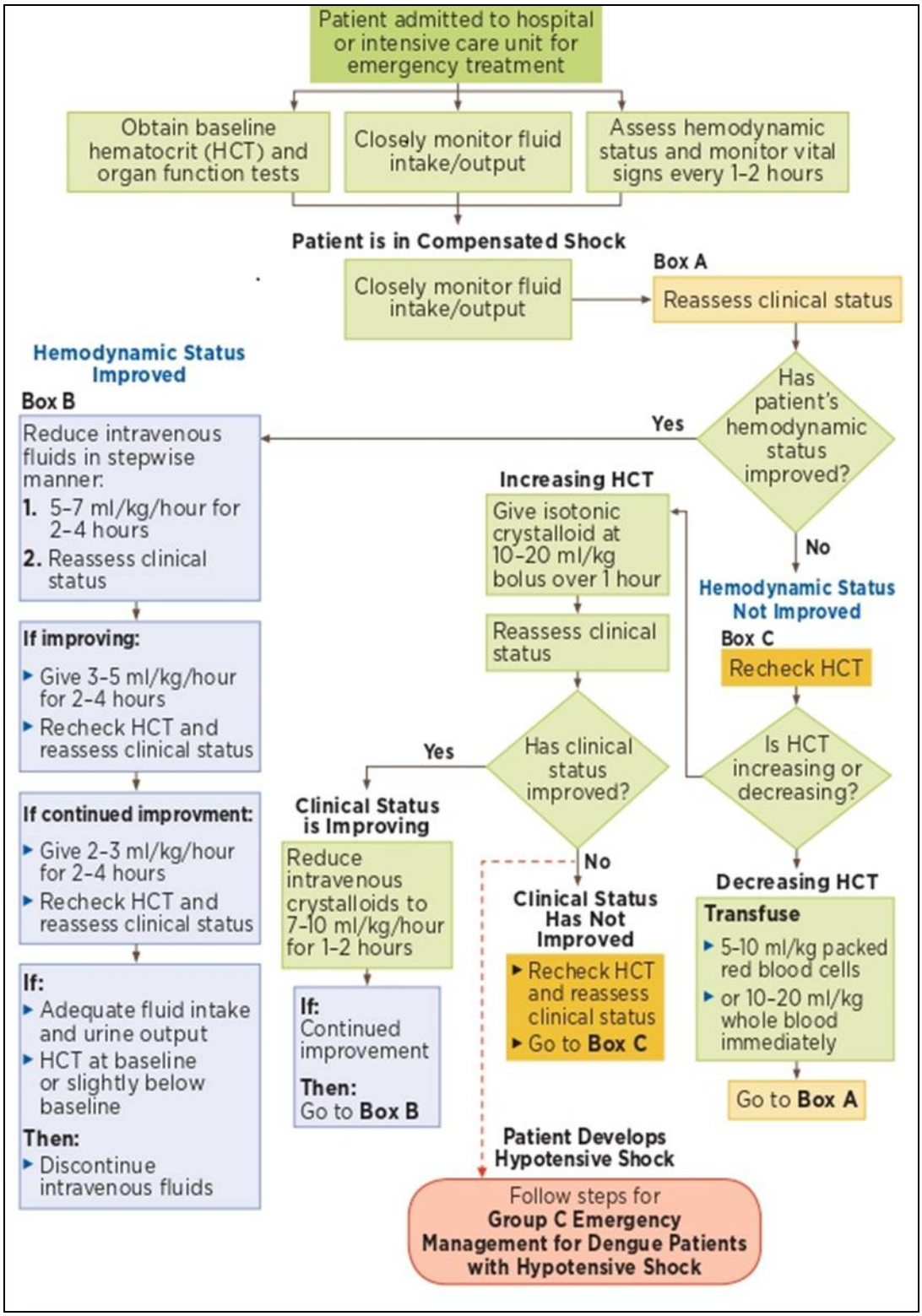

Figure 14: Group C: Management for dengue patients with compensated shock: [79]

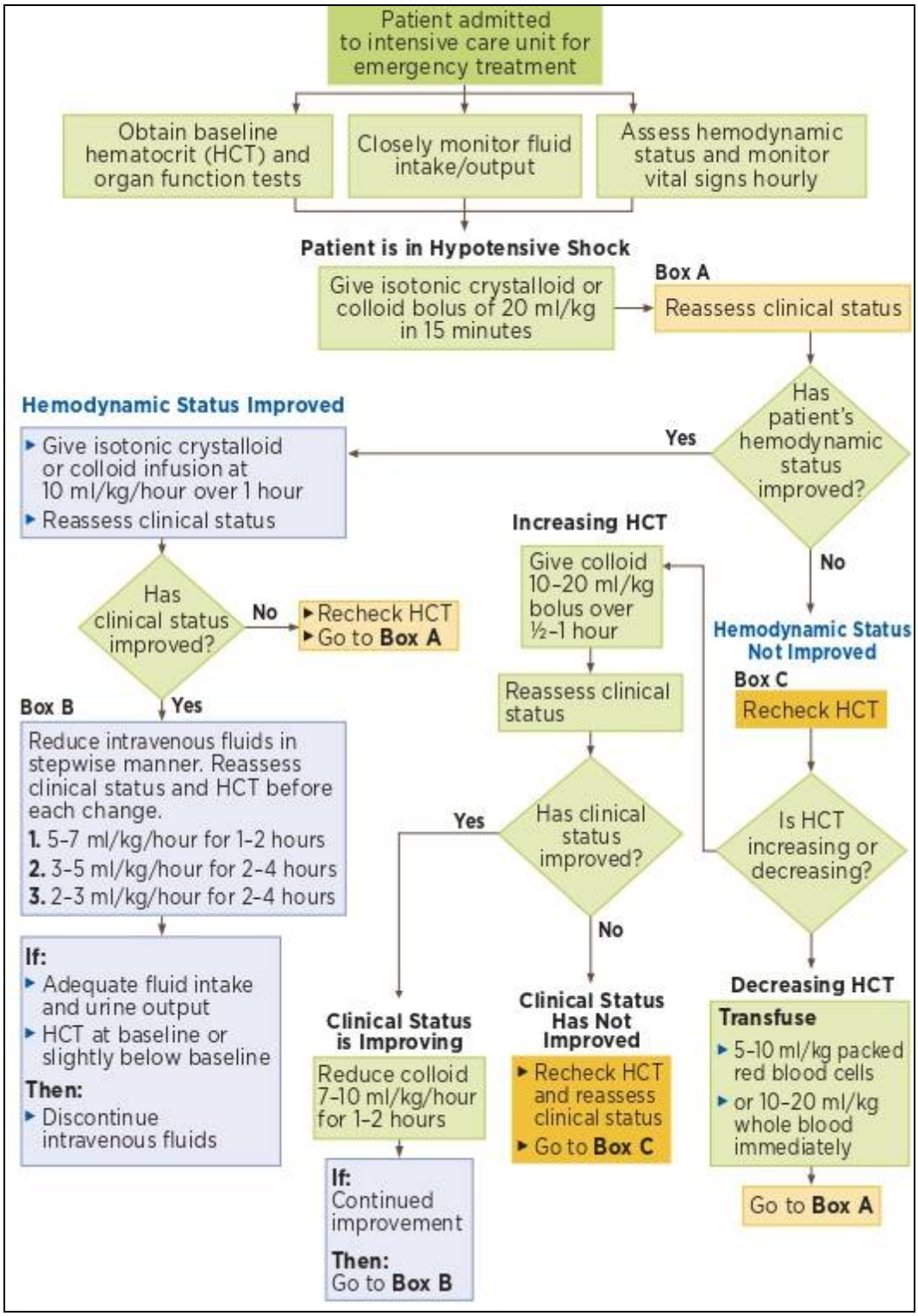

Figure 15: Group C: Management for dengue patients with hypotensive shock: [79]

Prophylaxis

18- Prophylaxis:

18.1- Environmental protection:

prevention of mosquito breeding sites by:

-Covering water containers.

-Empty water containers in the house.

-Cleaning domestic water storage every week.

-Dump standing water.

-Better designed water supply lines.

-Clear debris that may block water flow in drain or roof gutters.

-Dispose of waste items that can collect rain water (tyres, bottles, buckets and cans).

-Weekly change of stagnant water (Pet bowls, flower vases).

-Proper disposal of garbage and clean surrounding areas near the houses.

-Cover trash cans and rain barrels.

-Proper management of rooftops and sunshades.

18.2- Personal protection:

-minimise skin exposure to mosquitoes by wearing long sleeved shirts and pants. Wear clothes that cover arms and legs. Treat clothing with 0.5% permethrin. Do not use permethrin products directly on the skin.

-Use of mosquito repellents such as, DEET, Picaridin (KBR 3023 and icaridin), IR3535, Oil of lemon eucalyptus, Para-menthane-diol and 2-undecanone. Do not apply insect repellent to a child’s hands, eyes, mouth, cuts, or irritated skin.

-Liquid vaporizers.

-Use mosquito coils.

-Electrical mosquito mat.

-Use screens on room windows and doors.

-Sleep under a mosquito net.

-Avoid going to the dark places in the house where there is no light or wind.

18.3- Blood screening before transfusion:

By performing these tests before a transfusion, healthcare providers can reduce the risk of transfusion-related complications and ensure that the recipient receives safe and compatible blood.

18.4- Social mobilization:

Educate the community on the risks of dengue and engage with the community for vector control activities.

18.5- Health Education:

The sensitization can be done by audiovisual media or mass awareness campaigns.

18.6- Biological methods:

Biological methods are used to kill or reduce larval mosquito populations in water containers. Viviparous species of fish and Predatory copepods have been used in large water tanks and freshwater wells.

18.7- Chemicals methods:

Use insecticidal sprays on dark places of the house.

There are three insecticides that can be used for treating containers that hold drinking water.

18.7.1- Temephos 1% sand granules:

To administer a dosage of 1 ppm, graduated plastic spoons are used to apply one per cent temephos sand granules into containers. Regular monitoring of the susceptibility level of Aedes mosquitoes is necessary to ensure the insecticide's effectiveness. This treatment has been proven effective for 8-12 weeks, especially in porous clay jars with normal water usage [50].

18.7.2- Insect growth regulators (IGRs) and Pyriproxyfen:

The development of immature mosquito stages can be disrupted by insect growth regulators (IGRs), which interfere with chitin synthesis during larval moulting or the pupal and adult transformation processes. Pyriproxyfen, an insect-juvenile hormone analogue, is particularly effective against Aedes. aegypti, with concentrations as low as 1 ppb having a significant impact. High concentrations of pyriproxyfen do not appear to inhibit oviposition, and even very low doses can reduce the fecundity or fertility of adult mosquitoes. Contaminated female mosquitoes can transfer effective doses of pyriproxyfen to breeding sites they subsequently visit. A new formulation of pyriproxyfen can remain effective for up to six months. However, disadvantage is that the mecanism of action prevents hatching, so treated larvae and pupae remain visibly active. This can lead to suspicion and doubts about the effectiveness of IGR treatment within communities, particularly in domestic water treatment contexts [50] .

18.7.3- Bacillus thuringiensis H-14 (Bt.H-14):

Bacillus thuringiensis H-14 is an environmentally safe and effective larvicide for controlling mosquito populations. It is available under various trade names. A briquette formulation is commercially available with greater residual activity. The larvicide is completely safe for humans when used at normal doses in drinking water. The parabasal body of Bt.H-14 contains a toxin that is activated solely in the alkaline environment of the mosquito midgut. However, the toxin is photolabile and is destroyed by sunlight. This specificity ensures that only mosquito larvae are affected while protect any entomophagus predators and non-target species that may be present. Bt.H-14 formulations tend to settle rapidly at the bottom of water containers, requiring frequent applications [50] .

18.7.4- Space sprays:

Space spraying, the process of spraying insecticide droplets into the air to kill adult mosquitoes. It has been widely used as a primary method of control for dengue fever and dengue hemorrhagic fever in the Southeast Asia Region for 25 years. However, recent studies have shown that this method is largely ineffective at controlling the mosquito population and dengue transmission, as evidenced by the significant increase in DHF cases in these countries

during the same period. While it is politically desirable due to its visibility and the perception that the government is taking action, this is not a valid reason for using space sprays. Therefore, space spraying of insecticides should only be used in epidemic situations. In addition, space spraying can create a false sense of security among residents and hinder community-based source reduction programs. Undiluted technical grade malathion or a mixture of one part technical grade diluted with 24 parts diesel can be used for ultra-low volume (ULV) spray and thermal spray, respectively. Organophosphate insecticides such as malathion, fenitrothion, and pirimiphos methyl have been used to control adult Aedes albopictus vectors. For undiluted technical grade ULV malathion applications from vehicles, the area based dosage is 0.5 liters per hectare. Several companies produce pyrethroid formulations containing permethrin, deltamethrin, lambda-cyhalothrin, or other compounds that can be used for space spray applications in addition to the above-mentioned formulations [50] .

18.7.5- Thermal fogs:

Thermal fogging, which involves the use of insecticides, is typically created by condensing a suitable formulation that had been vaporized at high temperatures. The resonant pulse principle is commonly employed in thermal fogging machines to produce hot gas that reaches temperatures over 200 °C and moves at high velocities. Two types of thermal fogging formulations exist: oil-based (diesel or kerosene) and water-based. Oil-based formulations produce dense clouds of white smoke, whereas water-based formulations produce a fine mist that is colorless. This gas quickly atomizes the insecticide formulation, causing it to vaporize and condense rapidly, but with the little formulation breakdown. Typically, the droplet size of a thermal fog is less than 15 microns in diameter. Despite attempts to achieve uniform droplet size in normal fogging operations, it remains challenging to achieve [50] .

18.7.6- Ultra-low volume (ULV), aerosols (cold fogs) and mists:

Ultra-low volume (ULV) refers to the application of insecticides in concentrated liquid form in small quantities. Aerosols, mists, and fogs can be applied using portable machines, vehicle generators, or aircraft equipment. Typically, using less than 4.6 liters of concentrated insecticide per hectare is considered an ULV application. Although ULV is determined by the

application volume, still the size of droplets produced is also important. To ensure the appropriate droplet size, monitoring can be done by exposing Teflon or silicone-coated slides and examining them under a microscope. Ideally, equipment should be capable of producing droplets ranging from 10-15 microns, but even droplets within the 5-25 micron range can be effective [50,80] .

18.8- Harmful effects of insecticides: [79]

Harm to beneficial insects: Bees, butterflies, and other pollinators may be harmed due to insecticides. Insecticides should be applied only when beneficial insects are not active. for example; during early morning or late evening.

Harm to the environment: inappropriate application of insecticides, which can negatively impact the environment.

Risk of exposure to insecticides: insecticide may be harmful if inhaled. Neighbors, landscaper, children and pets could be exposed unintentionally when insecticides are sprayed. The mist can coat furniture and children's toys that can lead to additional exposure to insecticides.

Insecticide resistance in mosquitoes: Over time and repeated use of insecticides can lead to insecticide resistance in mosquito populations that can reduced the ability of an insecticide to kill mosquitoes.

18.9- Vaccination:

The first licensed dengue vaccine, CYD-TDV (Dengvaxia), is a live attenuated, recombinant tetravalent vaccine employing the attenuated YF virus 17D strain as the replication backbone. Several other dengue vaccine candidates are in clinical development: 2 vaccine candidates currently under evaluation in Phase 3 trials are also live attenuated (recombinant) tetravalent vaccines [81,82] .

World health organization has developed recommendations for assessing the quality, safety, and efficacy of live attenuated tetravalent dengue vaccines.

18.9.1- Vaccine characteristics and content:

CYD-TDV is a live attenuated, prophylactic, tetravalent viral vaccine. The vaccine contains four live attenuated recombinant dengue viruses, each representing one of the four serotypes. The vaccine is formulated with 4.5–6.0 $\log^{10}$ median cell-culture infectious doses (CCID50) of each of the four live attenuated dengue viruses [83] .

18.9.2- Vaccine dosage and administration:

The package contains a vial of lyophilized vaccine antigen and a vial of saline diluent. The preparation requires mixing of diluent (0.4% Nacl) and lyophilized vaccine antigen in single use vials. To reconstitute Dengvaxia, withdraw 0.6 mL from the diluent vial and inject it into the vial of lyophilized vaccine antigen. Then Swirl the vial gently. After reconstitution, you should administer Dengvaxia immediately or otherwise it should be refrigerated at 2°C to 8°C and use within 30 minutes. Reconstituted vaccine should be discarded if it is not used within 30 minutes. The vaccination schedule consists of 3 doses of 0.5 mL, given subcutaneously at 6-months intervals [84] .

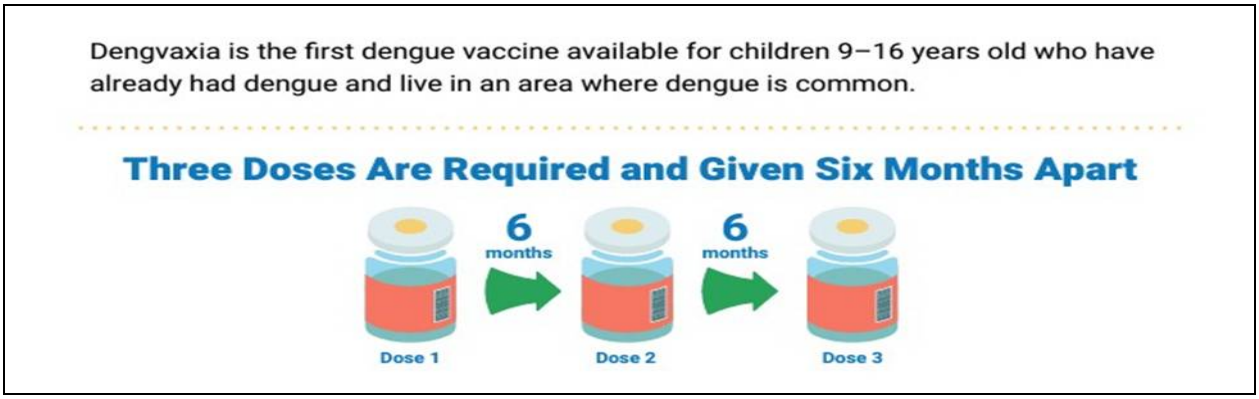

Figure 16: Vaccine Doses [79]

18.9.3- Vaccine storage:

The vaccine does not contain any adjuvants or preservatives. The vaccine should not be freezed. When stored between 2 °C and 8 °C and protected from light, CYD-TDV has the shelf- life of 36 months [85] .

18.9.4- Vaccine Eligibility:

Children aged 9–16 years with laboratory confirmation of previous dengue virus infection and who are living in dengue-endemic areas are eligible for the Dengvaxia dengue vaccine [84] .

18.9.5- Immunogenicity:

In vaccinees who were seropositive before vaccination, titres of neutralizing antibodies detectable by PRNT50 were higher to each dengue serotype following vaccination than in baseline seronegative vaccinees [86] .

Some correlation has been described between high vaccine induced neutralizing antibody titres and protection from dengue infection for a given serotype [87] .

18.9.6- Vaccine efficacy:

The Phase 3 trials of CYD-TDV included participants with an age range of 2–16 years. In trial participants aged 2–16 years, 9–16 years and those younger than 2–8 years, Vaccine efficacies against symptomatic virologically confirmed dengue illness (VCD) of any severity were 60.3% , 65.6% and 44.6% respectively. Hence, Vaccine efficacy was higher in the older age groups [88] .

But according to CDC, The dengue vaccine protects against all four types of dengue. For children aged 9–16 years with laboratory confirmed history of dengue infection, Dengvaxia is approximately 80% effective against virologically confirmed symptomatic dengue, for dengue hospitalization and severe dengue [84] .

18.9.7- Vaccine efficacy by serotype:

In trial participants aged 2–16 years, efficacy was 54.7% , 43.0% , 71.6% and 76.9% against serotype 1, 2, 3 and 4 respectively. In the pooled trial population aged 9 years and older, efficacies were 58.4% , 47.1% , 73.6% and 83.2% for serotype 1,2,3 and 4 respectively [88] .

18.9.8- Vaccine efficacy in preventing hospitalizations:

During trials, the vaccine had higher efficacy against hospitalization due to dengue and severe dengue than in preventing the symptomatic virologically confirmed dengue (VCD) illness of any severity [87] .

18.9.9- Vaccine safety:

The CYD-TDV encodes YF (vaccine strain) non-structural proteins including NS1, replacing those for dengue; the new test can differenciate between immune responses generated by prior dengue infection from those elicited due to vaccination. The anti-dengue NS1 IgG ELISA has estimated sensitivity of 95.3%, and the specificity to be 68.6% [89] .

According to CDC, the Dengvaxia vaccine is very safe, when used in individuals with laboratory confirmed past dengue infection. The dengue vaccine protects against all four types of dengue. Individuals who have tested positive for previous dengue infection, dengue vaccination can provide them protection against future dengue infections and reduce the risk of developing severe disease. People without a previous dengue infection should not be vaccinated because the dengue vaccine will increases the risk of severe disease and hospitalization if the individual is later infected with dengue. Although dengue vaccine is safe but it has few side effects. The most commonly reported adverse reactions of dengue vaccination include headache, injection site pain, malaise, asthenia and muscle pain [84] .

18.9.10- Duration of vaccine protection:

According to CDC, Dengvaxia provides protection against dengue hospitalization and severe disease for at least 6 years after the last dose of the series [84] .

18.9.11- Vaccination precautions:

Laboratory confirmation of a previous dengue infection is required for vaccination with Dengvaxia. Evidence of prior acute dengue virus infection with Positive dengue RT-PCR test result or Positive dengue NS1 antigen test result. “OR” positive results on BOTH of the following anti-dengue virus immunoglobulin G (dengue IgG antibody) tests in a two-step testing algorithm: EUROIMMUN Anti-Dengue Virus NS1 Type 1-4 ELISA (IgG)external icon and CTK BIOTECH OnSite Dengue IgG Rapid Testexternal icon [84] .

The World health organization Global Advisory Committee on Vaccine Safety (GACVS) has recommended against administering CYD-TDV vaccination to individuals who have not been previously infected with wild dengue virus (seronegatives), due to increased risk of hospitalized dengue among seronegative trial participants [90] .

18.9.12- Contraindication of Vaccination: [83]

Vaccination is contraindicated in:

-People who have a a history of severe allergic reactions to any ingredients of the dengue vaccine or have experienced such reactions after previously administration of the dengue vaccine.

- People who have congenital or acquired immune deficiencies that compromise their cell-mediated immunity should not receive the vaccine.

- People who have symptomatic HIV infection or asymptomatic HIV infection with evidence of compromised immune functionshould not receive vaccine.

- women with pregnancy or breasfeeding women should not be administered vaccine.

Conclusion

Dengue fever is a major public health concern in tropical and subtropical regions worldwide, caused by the mosquito-borne flavivirus, dengue virus (DENV), which has four serotypes (dengue 1, 2, 3, and 4). It is prevalent in Southeast Asia, South America, Mexico, and the Caribbean. Travelers to these regions should be advised to take precautions against mosquito bites. Dengue is transmitted mainly by the *Aedes aegypti* mosquito and is a leading cause of hospitalization and death in some countries. Diagnosis is challenging as the symptoms are non-specific. The typical symptoms include sudden onset of fever, headache, retro-orbital pain, muscle pain, and rash. For diagnosis, it is recommended to use several techniques and not be limited to a single diagnostic method. Treatment is mainly supportive, including oral rehydration and analgesia, with intravenous rehydration for severe cases. Control measures include reducing mosquito populations by eliminating breeding sites using insecticides and larvicides. A comprehensive approach involving collaboration between public health officials, doctors, nurses and the community is important in controlling the vector. The first licensed dengue vaccine, Dengvaxia, is a live attenuated, recombinant tetravalent vaccine administered over a year via three injections, targeting all four serotypes of the virus.

Résumés

Résumé

Titre: Les Méthodes de diagnostic et de traitement de la dengue

Auteur: Umer Farooq Bhatti

Mots clés: Aedes, Fièvre, PCR, Re-emergence, Vaccin.

La dengue est une maladie virale transmise par les moustiques causée par une infection par l'un des quatre sérotypes du virus de la dengue (DENV-1-4). Le diagnostic précoce en laboratoire du DENV est essentiel pour une prise en charge efficace des patients. Pour la confirmation de la dengue par des tests de laboratoire, il est généralement recommandé d'utiliser plusieurs techniques et de ne pas se limiter à une seule méthode de diagnostic. Parmi les méthodes de diagnostic existantes, les tests sérologiques sont les plus largement utilisés et ils sont considérés comme le pilier du diagnostic de cette maladie. Parce qu'ils sont sensibles, rapides et bon marché. NS1 ELISA et IgM ELISA sont utiles pendant la phase aiguë de l'infection par la dengue. Les tests de diagnostic rapide pour la détection de l'antigène NS1 et des anticorps IgM sont une bonne alternative aux tests ELISA. L'isolement du virus est le method de reference du diagnostic de la dengue. Mais son utilisation est limitée car elle est longue, prend du temps et nécessite des travailleurs de laboratoire qualifiés. D'autres méthodes de diagnostic moléculaire comprennent la RT-PCR en temps réel (TaqMan ou SYBR green), le test NABSA et le RT-LAM. Ils ont une sensibilité et une spécificité élevées. La prévention de la dengue peut être obtenue par la lutte antivectorielle. Il n'existe pas de traitement antiviral spécifique pour la maladie de la dengue. La prise en charge clinique repose sur une thérapie de soutien. Le premier vaccin homologué contre la dengue, CYD-TDV (Dengvaxia), est un vaccin vivant atténué recombinant tétravalent. Le vaccin contient quatre virus vivants atténués recombinants de la dengue, chacun représentant l'un des quatre sérotypes.

Summary

Title: Diagnostic methods and treatment of dengue

Author: Umer Farooq Bhatti

Key words: Aedes, Fever, PCR, Re-emergence, Vaccine.

Dengue is a mosquito borne viral disease caused by infection from any of the four serotypes of dengue virus (DENV-1-4). Early laboratory diagnosis of DENV is essential for effective patient management. For confirmation of dengue through laboratory tests, it is usually recommended to use several techniques and not be limited to a single diagnostic method. Among existing diagnostic methods, serological assays are the most widely used and they are considered as mainstay of diagnosis of this disease. Because they are sensitive, rapid and cheap. NS1 ELISA and IgM ELISA are useful during acute phase of dengue infection. Rapid diagnostic tests for NS1 antigen and IgM antibody detection are a good alternative to ELISA based assays. Virus isolation is a gold standard of dengue diagnosis. But it is of limited use because it is lengthy, time consuming and requires skilled lab workers. Other molecular diagnostic methods include Real time RT-PCR (TaqMan or SYBR green), NABSA assay and RT-LAM. They have high sensitivity and specificity. The prevention of dengue can be achieved by vector control. There is no specific antiviral treatment for dengue illness. Clinical management is based on supportive therapy. The first licensed dengue vaccine, CYD-TDV (Dengvaxia), is a live attenuated, recombinant tetravalent vaccine. The vaccine contains four live attenuated recombinant dengue viruses, each representing one of the four serotypes.

ملخص

العنوان: طرق تشخيص وعلاج حمى الضنك.

المؤلف: عمر فاروق بهاتي

الكلمات الأساسية: الزاعجة، الحمى، تفاعل البوليميراز المتسلسل، عودة الظهور، لقاح

حمى الضنك هي مرض فيروسي ينقله البعوض وينتج عن العدوى بأحد الأنماط المصلية الأربعة لفيروس حمى الضنك (DENV-1-4).

يعد التشخيص المختبري المبكر لـ DENV ضروريًا للعلاج الفعال للمرضى. لتأكيد الإصابة بحمى الضنك، يوصى عمومًا باستخدام العديد من التقنيات وعدم الاقتصار على طريقة تشخيص واحدة.

من بين طرق التشخيص الحالية، تعتبر الاختبارات المصلية، هي الأكثر استخدامًا وتعتبر الدعامة الأساسية لتشخيص هذا المرض، لأنها حساسة، سريعة ورخيصة مفيدان خلال المرحلة الحادة من عدوى حمى الضنك.

تعد الاختبارات التشخيصية السريعة للكشف عن مستضد NS1 ELISA والأجسام المضادة IgM ELISA بديلاً جيدًا لاختبارات ELISA. عزل الفيروس هو المعيار الذهبي لتشخيص حمى الضنك. لكن استخدامه محدود لأنه يستغرق وقتًا طويلاً ويتطلب عمال مختبرات مهرة.

تشمل طرق التشخيص الجزيئي الأخرى RT-PCR في الوقت الفعلي (TaqMan أو SYBR green) واختبار NABSA و RT-LAM. لديهم حساسية عالية.

يمكن تحقيق الوقاية من حمى الضنك من خلال مكافحة ناقلات الأمراض، لا يوجد علاج محدد مضاد للفيروسات لحمى الضنك. تعتمد الإدارة السريرية على العلاج الداعم. أول لقاح مرخص لحمى الضنك، ((Dengvaxia)CYD-TDV) ، هو لقاح حي موهن رباعي التكافؤ. يحتوي على أربعة فيروسات حية لحمى الضنك ، يمثل كل منها واحدًا من أربعة أنماط مصلية.

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Hippocratic Oath

At the time of being admitted as a member of the medical profession, I solemnly swear that:

- *I will devote my life to serving humanity.*
- *I will treat my teachers with due respect and appreciation.*
- *I will practice my profession with conscience and dignity, with my patient's health as my first consideration.*
- *I will not betray the secrets that are confided in me.*
- *I will maintain by all the means in my power, the honour and the noble traditions of the medical profession.*
- *My colleagues will be my brothers.*
- *I will not permit considerations of religion, nationality, race, political or social standing to intervene between my duty and my patient.*
- *I will maintain the utmost respect for human life from the time of conception.*
- *Even under threat, I will not use my medical knowledge in a manner contrary to the laws of humanity.*
- *I pledge this freely and on my honour.*

Serment d'Hippocrate

Au moment d'être admis à devenir membre de la profession médicale, je m'engage solennellement à consacrer ma vie au service de l'humanité.

- *Je traiterai mes maîtres avec le respect et la reconnaissance qui leur sont dus.*
- *Je pratiquerai ma profession avec conscience et dignité. La santé de mes malades sera mon premier but.*
- *Je ne trahirai pas les secrets qui me seront confiés.*
- *Je maintiendrai par tous les moyens en mon pouvoir l'honneur et les nobles traditions de la profession médicale.*
- *Les médecins seront mes frères.*
- *Aucune considération de religion, de nationalité, de race, aucune considération politique et sociale ne s'interposera entre mon devoir et mon patient.*
- *Je maintiendrai le respect de la vie humaine dès la conception.*
- *Même sous la menace, je n'userai pas de mes connaissances médicales d'une façon contraire aux lois de l'humanité.*
- *Je m'y engage librement et sur mon honneur.*

قسم أبقراط

بسم الله الرحمان الرحيم

أقسم بالله العظيم

في هذه اللحظة التي يتم فيها قبولي عضوا في المهنة الطبية أتعهد علانية:

- بأن أكرس حياتي لخدمة الإنسانية.
- وأن أحترم أساتذتي وأعترف لهم بالجميل الذي يستحقونه.
- وأن أمارس مهنتي بوازع من ضميري وشرفي جاعلا صحة مريضي هدفي الأول.
- وأن لا أفشي الأسرار المعهودة إلي.
- وأن أحافظ بكل ما لدي من وسائل على الشرف والتقاليد النبيلة لمهنة الطب.
- وأن أعتبر سائر الأطباء إخوة لي.
- وأن أقوم بواجبي نحو مرضاي بدون أي اعتبار ديني أو وطني أو عرقي أو سياسي أو اجتماعي.
- وأن أحافظ بكل حزم على احترام الحياة الإنسانية منذ نشأتها.
- وأن لا أستعمل معلوماتي الطبية بطريق يضر بحقوق الإنسان مهما لاقيت من تهديد.
- بكل هذا أتعهد عن كامل اختيار ومقسما بالله.

والله على ما أقول شهيد.

المملكة المغربية
جامعة محمد الخامس بالرباط
كلية الطب والصيدلة
الرباط

سنـة : 2023

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طرق تشخيص وعلاج حمى الضنك

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من طرف

السيد عمر فاروق بهاتي

لـنـيـل دبلوم

دكـتـور فـي الطب

الكلمات الأساسية : الزاعجة؛ الحمى؛ تفاعل البوليميراز المتسلسل ؛ عودة الظهور؛ لقاح

أعضاء لجنة التحكيم:

السيد ميمون زوهدي أستاذ في علم الأحياء الدقيقة	**رئيس اللجنة**
السيد ياسين سخسوخ أستاذ في علم الأحياء الدقيقة	**مدير الأطروحة**
السيد أحمد كاوزي أستاذ في طب الأطفال	**عضو**
السيدة سعيدة طلال أستاذة في الكيمياء الحيوية	**عضو**
السيدة مريمة الشادلي أستاذة في علم الأحياء الدقيقة	**عضو**