

Dengue: A Serious Threat to Public Health around the World

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Abstract

In recent years, dengue fever cases have been reported from all around the world. Dengue fever is a viral infection that is transmitted to humans by the bite of infected Aedes mosquitos, particularly Aedes aegypti. The goal of this page is to provide information on many aspects of dengue. By reviewing peer-reviewed papers and acquiring access to internationally recognised scientific databases, a bibliographic search was done to retrieve accessible published content (Scopus, PubMed, SciELO, NISCAIR, Google Scholar and WHO Guidelines available during 1994-2016). Overall, 100 papers were thoroughly reviewed, but only 22 research from 1994 to 2016 were chosen for the study. Dengue criteria, transmission, laboratory diagnosis methods, clinical treatment (including a step-by-step approach to dengue management), and vector management are all covered on this page (including biological control). The study's main findings include the recently introduced Caripill tablets and the Dengvaxia immunisation. Caripill tablet has been shown to increase platelet count, which is a big accomplishment. This article will provide a roadmap for clinicians and other healthcare professionals. It will aid in raising public knowledge about dengue. More research on dengue fever is needed.

Keywords: *Dengue; Caripil; Aedes aegypti; Dengvaxia; Platelet count;*

INTRODUCTION

Dengue fever is a viral infection that is transmitted to humans by the bite of infected *Aedes* mosquitos, particularly *Aedes aegypti*. Dengue fever has grown by a factor of 30 in the last 50 years. Dengue fever has been discovered in previously unknown nations. Over 50 million new cases are reported each year. And the countries with dengue endemicity are home to about 2.5 billion people [1].

DENGUE CRITERIA

Probable dengue

A person either lives in or goes to dengue-endemic areas. Rashes, nausea, vomiting, tourniquet test positive, aches and pains, leucopenia, any warning sign (such as persistent vomiting, abdominal pain or tenderness, mucosal bleed, clinical fluid accumulation, liver enlargement >2 cm, lethargy, restlessness, increase in hematocrit concurrent with rapid decrease in platelet count) should be present in addition to fever.

Severe Dengue

- If there is significant plasma leakage resulting in fluid buildup, respiratory difficulty, or shock.
- If there is considerable bleeding, a clinician should be consulted.

- If there is serious organ involvement, such as the CNS (altered awareness), liver (ALT/AST $\geq$ 1000 U/L), and other organs, including the heart.

Transmission the virus

Dengue virus belongs to the Flavivirus genus and the Flavivirid *Aedes* family. It is an RNA virus of modest size (single-stranded). Dengue virus has four different serotypes, called DEN 1 to 4 [2-4].

The Vectors

Dengue virus is spread to humans through the bite of infected *Aedes* mosquitos, primarily *Aedes aegypti*. This mosquito is mostly found in tropical and subtropical regions of the earth between latitudes 350N and 350S. These locations equate to a winter isotherm of 100 degrees Celsius (approximately). *Aedes* mosquito larvae are found in water-filled environments, primarily in manmade containers. These containers are strongly related with human dwellings. The majority of female *Aedes aegypti* spend their lives near dwellings, where they eventually mature. This demonstrates that people, not mosquitos, spread the virus between human settlements. Several *Aedes* mosquito species, including *Aedes albopictus*, *Aedes polynesiensis*, and *Aedes scutellaris*, have been identified as being responsible for

Dengue epidemics. These species differ in terms of behaviour, ecology, and geographic distribution.

The host

The incubation period in humans lasts 4-10 days. The majority of infections are asymptomatic; nevertheless, different *Aedes* mosquito serotypes can induce a variety of clinical signs. Primary infection is expected to provide lifetime immunity to a single serotype and transitory immunity to many serotypes for up to 2-3 months. Dengue risk factors include age, ethnicity, secondary infection, and chronic diseases such as sickle cell anaemia, bronchial asthma, and diabetes mellitus. Children are more susceptible to dengue shock than adults because their ability to compensate for capillary leakage is poorer.

When an infected mosquito draws blood, the dengue virus enters the human body through the skin. During the acute phase of infection, the virus is present in the blood. Virus clearance is primarily accomplished by humoral and cellular immune systems. These systems produce neutralizing antibodies as well as stimulate CD4+ and CD8+ T cells, resulting in viral clearance. Severe dengue is distinguished by abnormalities in homeostasis, hemoconcentration, and plasma leakage.

Individual genetic make-up, immunological response, and viral features are all risk factors for severe dengue. According to recent research, plasma leakage is caused by endothelial cell activation. Thrombocytopenia is caused by changes in megakaryocytopoieses, which leads to platelet malfunction, increased consumption, or destruction. These processes will eventually result in haemorrhage.

Dengue Virus Transmission

Humans are the primary host of the dengue virus. Female mosquitos consume the dengue virus, which is spread by infected humans. This virus then infects the mosquito's midgut. It then spreads through systemic circulation over a period of 8-12 days. This is referred to as the extrinsic incubation time. Following that, this virus spreads to additional persons by successive feeding. The extrinsic incubation duration is influenced by environmental factors such as room temperature. After then, the mosquito is infectious for the rest of its life. The major vector for this virus is *Aedes aegypti*. It dwells in human-populated places because of its anthropophilic nature, and it bites several times before oogenesis is complete.

The following variables influence viral transmission: population immunological factors, climatic and environmental factors, and host-pathogen interactions. Climate has a direct impact on vector biology. As a result, climate influences the location and number of vectors, and thus is the primary cause of dengue outbreaks.

Material and Methods

A bibliographic research was conducted to extract accessible published material by evaluating peer-reviewed publications and gaining access to internationally recognized scientific databases (Scopus, PubMed, SciELO, NISCAIR, Google Scholar and WHO Guidelines available during 1994-2016). Overall, 100 publications were adequately examined, and only 23 studies from the years 1994 to 2016 were chosen for the study.

RESULTS AND DISCUSSION

Methods of laboratory diagnosis

Correct dengue diagnosis is critical for clinical treatment, pathophysiology, outbreak control, surveillance operations, academic research, vaccine development, and clinical trials. Methods of laboratory diagnosis to confirm dengue virus infection include the detection of the virus, viral nucleic acid, antigens, or antibodies. After the acute period of infection has

passed, serology is the primary technique of diagnosis. However, in the early stages of sickness, viral isolation, nucleic acid testing, or antigen detection are favoured methods of diagnosis. The antibody response to infection is determined by the host's immune state.

If a person has not previously been infected with a dengue virus, IgM is the first immunoglobulin to develop. IgM may be discovered in 50% of patients on days 3-5 of sickness; by day 5, it has increased to 80%, and by day 10, it has increased to 99 %. Peak levels of IgM antibodies are reached two weeks after disease start and thereafter drop to undetectable levels after 2-3 months. IgG antibodies reach measurable levels after the first week of sickness, then gradually grow, and IgG antibodies are detectable even after many months, and even for the rest of one's life.

If dengue infects a person who has been previously infected by a dengue virus, then IgG is the predominate immunoglobulin. Secondary infections have far lower IgM levels than initial infections. In comparison to the haemagglutination-inhibition test (HI), the IgM/IgG ratio is more routinely employed to identify primary and secondary dengue infections. The following factors are considered when

selecting acceptable laboratory diagnostic methods: the objective of the testing, the availability of laboratory facilities and technical knowledge, the time of sample collection, and the cost. Complex technology and technical knowledge are typically utilized for tests with high sensitivity and specificity. Rapid tests, on the other hand, sacrifice sensitivity and specificity in exchange for a quick answer. When compared to serological approaches for detecting antibodies, virus isolation and nucleic acid detection are more specific but also more labor-intensive and expensive.

Clinical Management

Dengue fever is a dynamic sickness that affects the entire body. The clinical appearance is quite diverse, encompassing both severe and non-severe clinical symptoms. Following the incubation phase, the sickness manifests itself

abruptly. The sickness has three stages: febrile, critical, and recovery. Even though the signs of dengue sickness are complicated, its care is simple, affordable, and capable of saving lives. However, correct action at the appropriate moment is required. Early illness detection and comprehension leads to methodical care of the case, which results in a positive clinical outcome. Patients are seen, examined, and evaluated for the first time in the primary and secondary care levels. Management decisions at this stage are critical in reaching a clinical conclusion. A prompt reaction reduces hospitalization and saves the patient's life. Dengue patients assessed in primary and secondary care should be reported as soon as possible. This will aid in the identification of epidemics, allowing for an early reaction. Table 1 summarizes the difficulties that arise during the various stages of dengue fever.

Table 1: Different phases of dengue

S. No	Name of Phase	Characteristics
1	Febrilephase	High fever, febrile seizuresand dehydration
2	Criticalphase	Shock due to organ impairment, plasma leakageand severe haemorrhage
3	Recoveryphase	Hypervolemia due toexcessive i.v. fluid therapy

Severe Dengue

A patient is said to have severe dengue if he or she lives in a dengue risk area and has a fever of 2-7 days, as well as any of the following symptoms: evidence of plasma leakage (such as a high haematocrit value, ascites or pleural effusions, shock or circulatory compromise), significant bleeding, impaired consciousness, severe involvement of the gastrointestinal tract (regular vomiting, excessive abdominal pain, jaundice), severe impairment of organs (acuity).

Case Management

Early detection, care, and referral (if necessary) of the disease helps minimize dengue mortality. This necessitates the provision of high-quality clinical services at all levels of health care, from primary to tertiary.

The vast majority of dengue patients recover without the need for hospitalization. Some of them, however, acquire a severe version of the condition. The implementation of management choices and effective triage concepts can identify severe patients at the primary and secondary care levels. Severe cases necessitate hospitalization at referral

centres, when all required treatment should be provided.

STEPWISE APPROACH TO THE DENGUE MANAGEMENT

First step - Overall assessment Complete history

It includes information such as when the fever/illness began, how much he/she is taking orally, an examination of warning signs, diarrhea, altered mental state/dizziness/seizure, urine output (volume, frequency, and last voiding), and other histories (like co-existing conditions, travel to areas where dengue has spreaded, family or neighborhood dengue, swimming in waterfall, jungle trekking and recent unprotected sex or drug abuse).

Physical Examination

It involves the following tests: mental well-being evaluation, hydration examination, haemodynamics examination, pleural effusion/ tachypnea examination, ascites/ tenderness examination, bleeding and rash examination, tourniquet test

Investigation

It consists of the following tests: complete blood count, hematocrit test, WBC count (decreasing), and platelet count (rapidly decreasing).

Laboratory testing confirm the diagnosis. Other tests include glucose, urea, creatinine, liver function, lactate, bicarbonate, serum electrolytes, cardiac enzymes, ECG, and urine specific gravity.

Second step - Diagnosis, assessment of phase of the disease and severity

Clinicians diagnose dengue following a thorough history, physical examination, haematocrit, and full blood count. Clinicians also identify the patient's dengue phase (febrile, critical, or recovery), haemodynamics, warning symptoms, and hydration. Clinicians also make decisions about the patient's hospitalization.

Third step – Management Notification of the disease

If cases of suspected, probable, and confirmed dengue are reported as soon as possible, appropriate public health measures may be launched in dengue-endemic nations. Before notification, laboratory confirmation is not required, although it should be done. Only confirmed instances in non-endemic countries are reported.

Suspected cases meet the following criteria: patient has been to or resides in a dengue-endemic location, has declining

white cell counts, has fever for three days or more, and/or has thrombocytopenia $\pm$ positive tourniquet test.

It is difficult to prevent dengue transmission in dengue-endemic regions if cases are not reported promptly.

Management Decisions

Patients are divided into three groups based on clinical manifestations:

- Group A (Patients who are sent back to home),
- Group B (Patients who require hospitalization),
- Group C (Patients who need emergency treatment and referral) [16].

Treatment for Group A – Patients who are sent back to home

Patients in this category do not exhibit any of the warning indicators. These individuals can tolerate a significant amount of oral fluids and can urinate at least once every six hours.

Patients who are not bedridden should be evaluated on a daily basis until they are no longer in the critical stage. WBC count, fever reduction, and warning symptoms are among the parameters examined. Patients with stable haematocrit values are discharged. They are, however, advised to

go to the hospital if they exhibit any of the warning indications.

They are instructed to follow these action plans:

- To restore the losses caused by vomiting and fever, urge the use of ORS, fruit juice, and fluids containing sugar and electrolytes. Oral fluid consumption reduces hospitalizations.

In cases of excessive fever, paracetamol should be administered. The period between doses should not be shorter than six hours. For chronic high fever, a lukewarm sponge should be used. Aspirin, ibuprofen, and other non-steroidal anti-inflammatory medicines (NSAIDs) should be avoided since they exacerbate bleeding or gastritis. Reye's syndrome can potentially be caused by aspirin. If there is no clinical improvement, the patient's condition worsens during the debatement of fever, continuous vomiting, abdominal pain (severe), extremities are cold and clammy, bleeding occurs, urine is not voided for more than 4-6 hours, irritability or restlessness, or lethargies, the patient should go to the hospital right away.

Patients who are gone home should be monitored on a daily basis. Monitoring metrics include urine output (frequency

and volume), temperature patterns, fluid intake and losses, warning signals, haematocrit value, WBC count, platelet count, and indicators of bleeding and plasma leakage.

Treatment for Group B – Patients who require hospitalization

Patients in the critical phase must be hospitalised for intensive observation. This category comprises patients who have warning signals, patients who have co-existing diseases, and patients who have social situations such as living alone.

The following is an action plan for dengue patients with warning signs:

- Haematocrit should be determined before starting the fluid therapy. Isotonic solutions (like normal saline, Ringer's lactate) should only be given. These solutions should be given at the rate of 5–7 ml/ kg/hour for 1–2 hours, then depending upon the clinical response, it should be reduced to 3–5 ml/kg/hour for 2–4 hours, and then it should be reduced to 2–3 ml/kg/hour or less.
- Clinical status should be reassessed and the haematocrit should be repeated. If the haematocrit is same or rises slightly, then same rate 2–3

ml/kg/hour for next 2–4 hours should be given. If the haematocrit is increasing very fastly and the conditions of vital signs are deteriorating, then increase the rate to 5–10 ml/kg/hour for next 1–2 hours. Again, clinical status should be reassessed, haematocrit should be repeated and fluid infusion rates should be reviewed accordingly.

- Minimum quantity of I.V. fluid should be given to keep optimum perfusion and output of urine should be around 0.5 ml/kg/hour. I.V. fluids are generally required only for 24–48 hours. I.V. fluids should be successively reduced, if the rate of leakage of plasma decreases.

Action plan for patients having dengue without warning signs, are as follows:

- Oral fluid intake should be encouraged. If oral intake is not tolerated, normal saline intravenous fluid treatment should be started. Because patients can take oral fluids after some time on I.V. fluid treatment, fluid infusion should be reviewed on a regular basis. A small amount of urine should be administered to maximize perfusion and output. I.V. fluids are usually only needed for 24 to 48 hours.

- Urine output (frequency and volume), temperature pattern, fluid intake and losses, warning symptoms, haematocrit value, WBC count, and platelet count are all monitored measures.

Treatment for Group C - Patients who need emergency treatment and referral

If the patient is in critical condition and has: significant plasma leakage, severe haemorrhages, severe organ impairment such as cardiomyopathy, renal impairment, encephalopathy or encephalitis, or hepatic damage.

Patients will then require emergency care and referral.

Patients with severe dengue should be admitted to a tertiary care hospital with blood transfusion and intensive care capabilities. The primary intervention required is intravenous fluid treatment. Before and after intravenous fluid treatment, haematocrit levels should be measured. To restore plasma losses, isotonic crystalloid solution is employed. In the event of hypotensive shock, however, colloid solutions are utilized.

Further plasma losses should be supplied on a continual basis to ensure good circulation over the next 24–48 hours. In the case of obese or overweight

individuals, ideal body weight is often utilized to establish fluid infusion rates. Cross match is commonly used for shock victims. Only in the case of serious bleeding should blood transfusion be performed.

Fluid resuscitation is not the same as fluid administration. Fluid resuscitation is a procedure in which 10-20 ml boluses of fluid are administered for a brief period of time. The patient's response is assessed in order to prevent the production of edoema in the lungs.

The goals of fluid resuscitation are to enhance circulation (both central and peripheral) and perfusion of end-organs, i.e. consciousness stability, urine output of ≥ 0.5 ml/kg/hour, and metabolic acidosis should be reduced.

Vector Management

The only way to prevent dengue virus transmission is to avoid human-vector interaction or to control mosquito vectors. Because *Aedes aegypti* is the primary vector, actions to limit transmission should focus on its natural habitat, which is in the home and near proximity. Other sites where human-vector interaction occurs, including as schools, hospitals, and workplaces, should be targeted as well.

Aedes aegypti develops in household containers when water is intentionally poured for purposes such as domestic water storage and aesthetic plants. It also thrives near rainwater-filled environments. In general, these mosquitoes cannot fly very far, and the majority of them remain within a 100-metre radius of where they were born. These mosquitoes are completely reliant on humans for food, primarily throughout the day and both outside and indoors.

WHO has developed integrated vector management, a systematic technique to controlling dengue vectors.

Aedes aegypti is mostly managed by removing container environments where eggs and aquatic stages grow. Management or destruction of larval habitats, use of insecticides for larviciding, biological agents, and the administration of adulticides are all means of vector control.

Before deciding on the best vector control strategy, consider the following factors: the target species' behavior and local ecology, the availability of resources for execution, the viability of approaches, the cultural background of the region, and the appropriateness of coverage.

Biological Control

It comprises the use of creatures that reduce target species populations by preying on, parasitizing, or competing with the target species. In appropriate container settings, some predatory copepods and carnivorous fish are effective at suppressing *Aedes* mosquitos. These species are seldom encountered on a wide basis.

The fundamental advantage of employing biological control is that it prevents chemical contamination of the environment. The limitations of this technology include the high cost and arduous effort of cultivating organisms on a large scale, the difficulty in their application, and their limited usage in aqueous medium. These treatments are capable of killing *Aedes* mosquito larvae. Because the organisms utilised in biological control cannot endure dry conditions, their usage is primarily restricted to container environments. Consent of local inhabitants is required for the incorporation of organisms into water containers for the purposes of distribution and monitoring [19].

Carica Papaya Leaf Extract

Carica papaya leaf extract can be used in conjunction with standard clinical therapy

for dengue. This extract can be used at any time, although it has the most impact if administered on the first day of the sickness. This extract is available as a syrup. Adults should take 30 mL thrice day before eating, while children should take 5-10 mL thrice daily till the illness is completely healed. Patients are encouraged not to discontinue treatment in the meantime. Cold water should be drunk after drinking the extract to disguise the harsh flavour. If the patient is allergic to papaya, avoid using this extract.

Caripill

Micro Labs, Bengaluru, recently developed Caripill tablet in the Indian market in 2015, which is claimed to improve platelet count in dengue patients. Caripill is a herbal medication made from *Carica papaya* leaf extract that has been approved by the Government of India's Department of AYUSH.

There was no specialised dengue tablet prior to Caripill tablet, only paracetamol pills (650 mg) to reduce fever. However, when the fever subsided, the platelet count decreased, causing serious complications. As a result, Caripill tablet is the first medicine with appropriate scientific evidence (a multicenter clinical study on 300 patients was done by the lab) to

enhance platelet count in dengue. Clinical research results reveal that Caripill tablet reduces haemorrhagic disease well. In addition, unlike previous dengue instances, the patient did not require blood transfusion to compensate for platelet loss. Caripill tablet costs only Rs 25 per tablet and is accessible in all major pharmacies in India. 1 tablet (1100 mg) thrice day for five days is the recommended dose. So, the whole cost of Caripill therapy is only Rs 375, which decreases the dengue patient's financial load while also relieving mental stress].

Dengvaxia: World's First Dengue Vaccine

According to Sanofi Pasteur (Sanofi's vaccine business), on December 9, 2015, Mexican authorities granted approval to distribute Dengvaxia, the world's first approved vaccine for dengue prevention.

Dengvaxia (tetravalent dengue vaccine) has been licenced by the COFEPRIS (Federal Commission for the Protection against Sanitary Risks) for dengue prevention caused by all four serotypes in people aged 9 to 45 living in dengue endemic regions.

Dengvaxia was approved based on a clinical trial that included almost 40,000

persons of varied ages, ethnic and socioeconomic origins, geographic and epidemiological situations, and living in 15 countries. People from dengue-affected areas in Mexico took part in this vaccine development experiment.

CONCLUSION

This research examines dengue fever, its transmission, laboratory detection methods, clinical care, and vector management. It will be interesting to examine how the recently available Caripill tablets and Dengvaxia vaccine influence dengue patients. The public has to be educated on vector control right now. More research is needed to develop new medications, herbal combinations, and vaccinations to combat this illness more successfully.

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