Dengue: A Review of Its Clinical Manifestations, Diagnostics, and Treatment Strategies

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***Abstract*—Dengue fever, a mosquito-borne viral disease, is a major global health concern, particularly in tropical and subtropical regions. It is transmitted primarily by Aedes aegypti and Aedes albopictus mosquitoes and caused by four Dengue virus serotypes (DENV-1 to DENV-4). The disease presents with a spectrum of symptoms, ranging from mild fever to severe complications such as Dengue Shock Syndrome (DSS) and Dengue Hemorrhagic Fever (DHF). Since no specific antiviral treatment exists, supportive care, including fluid resuscitation and symptomatic relief, remains the primary management approach.**

Dengue pathology is characterized by thrombocytopenia, immune dysregulation, and endothelial dysfunction, which worsen disease severity. The review explores different therapeutic approaches, including allopathic, Ayurvedic, and homeopathic treatments. While NSAIDs are contraindicated due to bleeding risks, allopathic management relies on paracetamol and intravenous fluids. Ayurvedic remedies such as giloy, papaya leaf extract, and basil leaves are used to enhance immunity and platelet recovery, while homeopathy is explored as an adjunct therapy.

Preventive measures like vector control, insecticide spraying, elimination of breeding sites, and personal protection are critical for reducing disease spread. Public awareness initiatives, larvicide use, and surveillance is essential for effective dengue management. Given the increasing prevalence of dengue due to urbanization and climate change, an integrated approach combining modern medicine, traditional therapies, and public health strategies is necessary to mitigate its impact.

***Index Terms*—Dengue fever, Dengue virus, Vector-borne disease, Allopathy, Ayurveda, Homeopathy, Epidemiology, Dengue treatment, Dengue prevention.**

I. INTRODUCTION

In order to stop dengue outbreaks, preventive actions—including public awareness campaigns and vector control strategies like larviciding—remain crucial. Recent outbreaks and epidemiological trends are also highlighted in the review, highlighting the necessity of coordinated vector management strategies and enhanced surveillance. Given the predicted geographic spread of dengue as a result of urbanisation and change in climate, reducing the disease's impact requires an all-encompassing strategy that incorporates contemporary medicine, conventional wisdom, and strong public health campaigns. Aside from supportive care and adequate hydration therapy, dengue does not currently have a specific cure. Over the past 50 years, various treatment options have been evaluated in clinical trials, but with limited success.[2] Based on WHO clinical case definitions, the children in the study were classified as DF, DHF, or DSS, and the WHO criteria for the severity of dengue infection were used to grade the severity of their illness. Every child with thrombocytopenia or leucopenia was monitored until their blood counts returned to normal. [4] A marked increase in vascular permeability is a defining characteristic of Dengue Shock Syndrome (DSS), the most severe manifestation of Dengue Hemorrhagic Fever (DHF)[17] In a single study conducted in India, we identified two cases of dual infection involving the DENV-1 and DENV-3 serotypes.[18] Because of regional diversity In vector habitat, climate variations, and climatic Patterns, along with subsequent human intervention and control measures, vector-borne illnesses are known to exhibit spatial heterogeneity. [20] It's noteworthy that the 2023 dengue fever virus (DENV) outbreak spread to developed countries where the illness was previously uncommon or infrequent. the danger is about half of the world's population, with dengue being predominantly found in urban and semi-urban areas within tropical and subtropical climates worldwide. Between 100 and 400 million cases are reported to occur each year, according to the World Health Organisation. [22]

According to a recent study, approximately 390 million dengue virus (DV) infections occur annually, 100 million symptomatic cases, and 25,000 fatalities. Arthropods carry dengue viruses, which pose a serious threat to world health. They are indigenous to tropical and subtropical regions of the planet, and they can infect up to 400 million individuals. [24] Many experts anticipate that dengue will continue to expand geographically, become more prevalent, and be reported to the WHO more frequently in the coming years. Therefore, it is essential to explore in greater detail some of the potential factors driving dengue activity as well as the global strategy to combat this expansion. Estimated that by 2085, between 50% and 60% A significant portion of the global population is expected to live in areas where dengue transmission is possible. [25]

II. CLINICAL SYMPTOMS AND SIGNS

CONSTITUTIONAL
1. Fever
2. Chills
3. Myalgia
4. Arthralgia
5. Lethargy

GASTROINTESTINAL
1. Vomiting
2. Nausea
3. Diarrhea
4. Anorexia
5. Ascites

MUCOCUTANEOUS
1. Rash +
2. Pruritus
3. Exanthema

CARDIORESPIRATOR
1. Cough
2. Pleural effusion
3. Myocarditis
4. Hypotension
5. Respiratory disorder

NEUROLOGICAL
1. Headache
2. Dizziness
3. Seizure
4. Shock
5. Convulsion

HEMORRHAGIC MANIFESTATIONS
1. Epistaxis
2. Hematuria
3. Melena
4. Petechiae [3]

III. OUTBREAK OF DENGUE FEVER

In the 1780s, nearly simultaneous outbreaks of dengue in Asia, Africa, and North America were the first to be clinically identified. After the first major outbreak of Dengue Hemorrhagic Fever (DHF) was documented in the Philippines between 1953 and 1954, DF/DHF epidemics quickly expanded around the world. While DHF was prevalent in neighboring countries, India remained largely unaffected for unknown reasons, despite having all the necessary risk factors. However, by 1988, DHF cases began to surface in various parts of India. In 1996, the country witnessed its first major widespread epidemic of and Dengue Shock Syndrome (DSS) and DHF, initially affecting regions near Delhi and Lucknow before spreading across the nation [1].
According to unpublished data from our study on dengue in Pune from 2002 to 2008, DENV-1, DENV-2, and DENV-3 were all co-circulating in the city. The multiplex RT PCR test was able to serotype 56 instances between May 2009 and September 2010. We found 13 instances of DENV-1, 21 cases of DENV-2, 20 cases of DENV-3, and two cases of DENV-4. [5] Using a licensed version of www.indiastat.com, reported dengue cases and mortality in Indian states during the past 20 years were carefully examined. Between 1996 (16,517 cases) and 2015 (99,849 cases), there was a more than 500 percent increase in dengue cases. Delhi (15,867) had the most dengue cases reported in 2015, followed by West Bengal (8516), Punjab (14,128), and Haryana (9921). Recorded the highest number of dengue-related deaths (60), followed by Kerala (25), Maharashtra (23), and Punjab (18).[11] The WHO reported 0.4 million dengue cases between 1996 and 2005; between 1996 and 2005, that number rose to 1.3 million, and in 2015, it hit 3.2 million. However, a significant percentage of dengue cases remain unreported to the WHO and other national health systems. [13]

IV. HISTORY

For centuries, dengue has existed. Although they were first Originally documented hundreds of years prior, during the Chin Dynasty (265–420 AD), the earliest symptoms resembling dengue were later included in a 992 AD Chinese medical encyclopaedia before undergoing full revision. The disease was referred to as "water poison" and was associated with flying insects." Epidemics similar to dengue were documented, with similar disease course and spread. Cases were documented in Central America as early as 1699 and in the West Indies as early as 1635. Epidemics became widespread in the United States Continuing into the early 20th century after a significant outbreak in Philadelphia in 1780. The most recent outbreak took place in New Orleans in 1945. It wasn't until the 20th century that the viral aetiology and mosquito transmission were eventually identified. [16] Although dengue has become a global disease, about 75% of those exposed to the virus reside in Asia-Pacific.

As of December 20, 2023, over 80 countries and territories worldwide reported more than five million cases of dengue fever, according to the Centers for Disease Control and Prevention (CDC).[23] Ibrahim Idris, Olalekan Chris, and Akinsulie. "Global re-emergence of dengue fever: The need for a rapid response and surveillance." 100107 in The Microbe (2024). [23] The National Vector Borne Disease Control Program (NVBDCP) is in charge of managing vector-borne disease prevention and control, including dengue, in affected regions forecasts that in 2022, there were 233,251 dengue cases in India overall. This syndrome was more common in a number of States such as West Bengal, Uttar Pradesh, Rajasthan, and Bihar.[26] India experienced a severe dengue epidemic in 2017 (1.8 lakh cases), which was followed by a notable decline in cases in 2020 (50 thousand cases). Up to 80000 instances of dengue have been documented to date, with the majority of these cases being of the DENV 2 serotype. Later in 2021, there was a twofold increase in dengue incidence (1.9 lakh cases). Furthermore, compared to the previous year, more adults than children died in 2022, which may indicate a shift in strain or genotype or a replacement event of a genotype or clade. The epidemiology of dengue varies in regarding common strains, geographic spread and severity of the disease infection in India is highly complex and has changed significantly during the previous 60 years. Following the first documented outbreak on the east coast in 1963, DENV 4 was discovered in Kanpur in 1968, and in the year 50 that followed, both DENV 4 and 2 were found coexisting.

In the neighbouring region of Hardoi, DENV4 was completely replaced by DENV 250 in 1970. In 1966, Myers et al. Reported an outbreak of DENV3 in Vellore, Southern India, affecting both patients and Ae. Aegypti. This epidemic in 1968 was linked to all four forms of DENV and its isolation from both vectors and patients. In 1988 and 1989, the western Indian state of Gujarat reported an epidemic of DENV 253 in both urban and rural areas,In both urban and rural regions, while the neighboring state of Rajasthan had an outbreak of DENV1 and DENV3. The northern Indian states of Delhi, Haryana, Lucknow, and Gwalior were the main areas where the DENV 2 virus was prevalent. In the meantime, during the 1997 Delhi outbreak, the DENV1 serotype was identified. Molecular epidemiology research may provide information on DENV genotype and lineage turnover (replacement and/or extinction). A single lineage or genotype may emerge in a particular region, persist for a while, and then be eradicated and replaced by a completely other genotype. [29]

V. TRANSMISSION OF DENGUE FEVER

Transfer. After the first midgut infection, DENV spreads systemically in the body cavity of Aedes vectors, also known as hemocels. It then moves on to secondary tissues. The extrinsic incubation period is the interval of 7-14 days at 25–30°C between the initial infection of the mosquito's midgut and the subsequent transmission of DENV by its vector, such as Aedes aegypti. Perhaps because the viral DNA is stable in the midgut of the vectors, DENV stays there. Finally, virions are released into the saliva and the salivary glands become infected during The extrinsic incubation period refers to the process in which the dengue virus initially infects the mosquito's midgut and subsequently spreads within its vector, such as *Aedes aegypti* disease has rapidly expanded throughout the world in recent decades (World Health Organisation, 2021a) [12].

VI. MODE OF ACTION

Every dengue serotype is classified according to the antigen on its surface, which has a 60%–70% sequence similarity. The non-structural protein of RNA helps the single-stranded RNA dengue virus multiply on the endoplasmic reticulum membrane. Out of all of them, NS5 is the biggest non-structural. A few live attenuated virus-based vaccines have been developed; however, the main issues are the lengthy dosage schedule, the vaccine's reactivity, and its seroconversion rate. [13] When someone gets bitten the virus and the insect's saliva enter the body through the skin when a mosquito carrying the dengue virus bites. As the white blood cells move throughout the body, it attaches itself to them, enters, and grows inside of them. In response, the white blood cells (WBC) respond by releasing various signaling proteins, including Among other cytokines, interferons, which trigger nonspecific symptoms such as headaches, fever, muscular soreness, and joint discomfort. The body produces a lot more viruses when the infection is severe, Additionally, a number of organs, such as the bone marrow and liver, may be affected. Endothelial dysfunction leads to fluid leakage from the bloodstream into body cavities through the tiny blood vessel walls. Less blood flows as a result, and shock could happen. Additionally, thrombocytopenia, this increases the risk of bleeding, another major complication, which arises due to bone marrow failure caused by stromal cell infection.[28]

PATHOLOGY

Pathological analyses of skin lesions from patients with classical dengue fever have revealed perivascular oedema, mononuclear cell infiltration, and swelling of small artery endothelial cells. However, biopsy specimens have not been found to contain any virus or viral antigen. According to the results, immune globulins or some other mechanism other than a direct viral infection of the skin may be responsible for the maculopapular rash associated with dengue fever. [6] Around the world, Urban and semi-urban areas, as well as tropical and subtropical climates, typically have higher levels of DENV. Individuals of all age groups exposed to infected mosquitoes are at risk of contracting the virus. Dandy fever, breakbone fever, and dengue hemorrhagic fever are among the symptoms brought on by DENV infection; in extreme situations, dengue shock syndrome may result. The best time of year for DENV virus Outbreaks occurring in tropical nations In regions of Asia and South America is during the rainy season. [10]

DRUGS USED IN DENGUE TREATMENT

Regretfully, the primary diagnostic tools for DENV infection are currently the signs and symptomsThe initial symptom of DENV infection is fever or a flu-like illness. [10] Patients with symptomatic fever may be treated with paracetamol and fluid replacement. [8] Antiviral medications are being developed to treat dengue illness. These substances typically affect the dengue virus's RNA genome. The antiviral drugs celgosivir and balapavir, designated NCT02569827 and NCT01096576, respectively, are undergoing phase clinical studies. Using in vitro and in silico techniques, studies have been conducted to determine the effectiveness of sofosbuvir, a medication used to treat hepatitis, in treating dengue fever. [13]

TREATMENT MODALITIES

While severe cases necessitate hospitalisation or intensive care unit care, mild cases only require oral rehydration; IV fluids are given for one to two days, if necessary, with dosages adjusted based on urine output and vital signs. [15] Larvicides are used to prevent vector breeding in many Western Pacific Region countries and regions, and since 2000, Cambodia has adopted a short-term intervention strategy that includes timely larviciding in certain densely populated areas before the dengue season [19].

AYURVEDA

Dengue can be effectively treated with a number of ayurvedic medications. Natural ingredients are used to make medications, which have been proven to be entirely safe, free of adverse effects, and effective in treating thousands of dengue cases. An herb called giloy, also known as amrita, has anti-inflammatory and antipyretic properties that lower fever. Papaya leaves have recently shown great efficacy and utility In the control of dengue fever, particularly In boosting platelet levels in patients with hemorrhagic dengue fever and those with low platelet counts. Not only do basil leaves help with dengue fever, but they also boost immunity in general. Oranges are rich in antioxidants and vitamins that aid in alleviating secondary symptoms of dengue, while chewing five to six basil leaves is believed to enhance immunity and is Suggested as an effective Ayurvedic remedy for dengue fever. Neem leaves are also recommended for

a number of ailments due to their medicinal properties [9].

ALLOPATHY

About 20% of cases of dengue are symptomatic, while it can also be asymptomatic. In general, three to ten days after a mosquito bite, dengue fever appears as a self-limiting febrile disease. In its early stages, dengue sickness might seem as a moderate A "sickness that has symptoms similar to the flu, resembling those of influenza, chikungunya, Zika, and other viral infections prevention of DENV infection, there is currently no approved vaccination. Acetaminophen (paracetamol) and enough hydration are the only medications that can lower body temperature and pain. Because they can worsen bleeding, when treating dengue-related pain, nonsteroidal anti-inflammatory medications (NSAIDs) should be avoided. Most patients recover within two weeks. As hydration plays a crucial role in dengue fever treatment, the clinician must adhere to certain recommendations for rehydration or water replacement therapy that have been produced and authorised by the World Health Organisation. Bed rest, antipyretics or sponging to lower fever, analgesics or mild sedatives for pain relief, and fluid or electrolyte therapy to maintain hydration are recommended strategies for managing dengue.[14]

HOMEOPATHY

According to the WHO, homoeopathy has been effectively used to prevent and cure a variety of infectious diseases, such as diarrhoea and influenza. It has also been shown to significantly reduce the symptoms of dengue fever. Homoeopathic treatments can help reduce the disease's severity and progression or shorten its clinical course. [8] The homoeopathic treatment used in this study included ten herbal and mineral remedies, such as pure tinctures of Bryonia alba, Rhus toxicodendron, Gelsemium sempervirens, Aconitum napellus, Eupatorium perfoliatum, China boliviana, Hamamelis, Citrullus colocynthis, Crotalus horridus, and Phosphorus. The original tinctures were diluted 1:100 in a water-alcohol solution and diluted thirty times to reach the 30C potency of the used homoeopathic combination. One millilitre of the original tincture Was mixed with 99 milliliters of a water-alcohol solution mixture to complete this procedure.

VII. DENGUE FEVER AND PREGNANCY

Among the major pregnancy outcomes associated with the dengue virus are severe maternal problems in the second and third trimesters and abortion in the first trimester. Haemorrhage, hypertension, and eclampsia are among the negative effects of caesarean deliveries, which are more common. Although there are no known foetal abnormalities, dengue is equally dangerous to the foetus (increased chance Leading to risks of miscarriage, stillbirth, and neonatal death). Transmission from mother to foetus has been documented. The most frequent Adverse pregnancy outcomes included low birth weight and preterm birth (less than 37 weeks). [21]

AUTOMATIC DETECTION OF DENGUE

A major threat to world health, Dengue fever is a rapidly spreading mosquito-borne disease, particularly prevalent in tropical and subtropical regions. It's still difficult to detect dengue cases accurately and effectively. The application of deep learning (DL) methods for automatic dengue identification from peripheral blood smear (PBS) pictures is investigated in this work. Utilising transfer learning (TL), pre-trained convolutional neural networks (CNNs)—ResNet50, MobileNetV3Small, and MobileNetV3Large—were used to differentiate dengue-infected blood smears from healthy samples.

A fivefold cross-validation framework was employed to train and validate the models on a dataset of 100x magnified microscopic PBS pictures. Critical areas in the photos that affected model predictions were highlighted using Gradient-weighted Class Activation Mapping (GradCAM), an explainable artificial intelligence (XAI) technique.

The accuracy of all three CNN models was good (above 98%), but MobileNetV3Small stood out as the best model because of its effectiveness and reduced processing requirements. MobileNetV3Small obtained strong recall, F1 score, specificity, precision, and AUC values, along with a 98.2% accuracy rate. The study comes to the conclusion that by automating the interpretation of PBS pictures, these AI-powered models can help haematologists and increase productivity in low-resource and hospital settings. [30]

VACCINES DEVELOPMENT

A tetravalent vaccine designed to provide long-term protection against all Dengue virus serotypes is imminent, although dengue vaccinations have been

developed since the 1940s.[1] The first tests of dengue vaccines were conducted in 1929. However, a number of problems have hindered the development of vaccines. First, developing a vaccine has become extremely difficult due to DENV's four complex serotypes, each of which has a unique antigen. Second, the development of the DENV vaccine has been hampered by DHF and DSS, which are caused by a second heterotypic infection with an uncertain immunological response and pathophysiology. Third, the exact nature of immune reactions (pathogenic or protective) to the virus is confusing the development of a vaccine, and the adaptive immunological reaction to the virus is not well understood. [7]

One of the main preventive strategies for fighting infectious diseases is vaccination. Several vaccinations have been developed to combat dengue fever, but as of right now, only one vaccine is authorised for sale in certain nations where dengue is endemic. Dengvaxia, a tetravalent chimeric vaccine, was developed by removing the progenitor yellow fever 17D strain's membrane and envelope proteins and replacing them with proteins from all four dengue serotypes. The tetravalent Sanofi Pasteur created the Dengvaxia vaccine, which is authorised for sale in more than ten dengue-endemic nations, including Mexico, the Philippines, El Salvador, Paraguay, Thailand, Singapore, Brazil, Costa Rica, Guatemala, Peru, and Indonesia. The vaccine is intended to offer protection against all four dengue virus serotypes. This vaccine is administered to people aged 9 to 45 who reside in dengue-endemic areas in a three-dose schedule spaced six months apart. [13] The two currently licensed Dengue vaccines, Dengvaxia (Sanofi Pasteur Inc., France) and Qdenga (TAK-003, Takeda, Japan), are tetravalent live attenuated vaccines designed to provide protection against all four Dengue virus serotypes. These tetravalent live attenuated vaccines are approved for use in endemic areas in persons 9 years of age and older. They are made to target all four Dengue serotypes. locations, with previously confirmed Dengue infection. Qdenga has been incorporated into the Brazilian Ministry of Health's public health policy from December 2023. Vaccine-related side effects in the perioperative phase are still debatable. Nonetheless, there is a single recommendation to wait seven days after surgery to get vaccinated and to delay elective procedures for three weeks following vaccination with an attenuated virus. However, this is not a formal recommendation, and surgery does not prevent vaccination programs. [21]

Sanofi Pasteur's Dengvaxia brand is used to sell Dengvaxia CYD-TDV. A live attenuated chimaera vaccine is what this tetravalent immunisation is. The most sophisticated kind was created by substituting the PrM and E structural genes from each of the four DENV serotypes for those from the attenuated yellow fever 17D strain vaccination using recombinant DNA technology. This vaccine, after undergoing extensive testing, and multiple studies, obtained clearance to be released further on May 1, 2019. Nearly 35,000 children aged 2 to 16 participated in placebo-controlled clinical trials to test the safety and effectiveness of protocols. These tests were conducted in 10 countries identified as dengue-endemic regions, yielding promising results gained were mixed. Nearly 65.5% of 9-year-old children received the vaccine's protection against hospitalization three years after the first dose. However, a protection rate of approximately 44.6% was observed in children aged 8 years and younger.[27]

PREVENTIVE STRATEGIES

Dengue, a disease transmitted by mosquitoes, can be prevented by reducing the risk of mosquito bites. This can be accomplished with applying insect repellents, dressing in long sleeves, using window and door screens, and removing stagnant water to prevent mosquito breeding typically use nets, air-conditioned spaces, and repellent on our skin both indoors and outdoors. However, numerous plant extracts can currently be applied to attack the Ae population. Egypt. Recently, plant-based products such as essential oils, plant extracts, and isolated metabolites have been explored for their potential ovicidal properties against mosquito vectors. [13]

FUTURE SCOPE IN DENGUE TREATMENT

Future developments in dengue treatment will encompass vaccine development, with mRNA-based vaccines and better candidates like TAK-003 providing wider protection. Antiviral medication research focuses on compounds like Celgosivir and nanotechnology-based drug delivery. Monoclonal antibodies, such as DN59 and 1C19, show potential in lowering viral load. Gene-editing technologies like CRISPR are being researched for mosquito control, alongside Wolbachia-infected mosquitoes. Phytopharmaceuticals, including papaya leaf extract

and andrographolides, are under investigation for their effect in boosting platelet count. Drug discovery and dengue prediction are being transformed by AI and machine learning. The goal of rapid diagnostics, including biosensor and CRISPR-based tests, is to enhance early detection. Immunomodulators are being researched to prevent severe dengue sequelae. Vector control innovations, including RNA interference and nanotechnology-based larvicides, provide new methods to curb mosquito populations. These advancements have a great deal of promise for successful dengue prevention and therpy with multidisciplinary research.

VIII. CONCLUSION

Dengue fever is still a serious global health issue, particularly in tropical and subtropical areas. The cornerstones of treatment continue to be supportive care, hydration, and symptom management in the absence of a specific antiviral medication. Developments in antiviral medications, vaccines, and complementary therapies like homoeopathy and Ayurveda hold promise for bettering patient outcomes. In order to reduce the spread of disease, preventive measures such as vector control, public health awareness, and early diagnosis are essential. Future studies should concentrate on creating potent vaccinations, specialised antiviral treatments, and fusing conventional medicine with contemporary therapeutic modalities. To address the increasing global dengue burden, a thorough, interdisciplinary approach is required.

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