Review Article Biotechnology

International Journal of Pharma and Bio Sciences

A REVIEW ON MAJOR ASPECTS OF DENGUE

HARDEEP KAUR*[1] AND REEMA SHARMA[2]

[1]*Assistant professor of chemistry, Department of Biotechnology Chandigarh University Gharuan, Mohali (Punjab), India*
[2] *Research Scholar, Department of Biotechnology Chandigarh University Gharuan, Mohali (Punjab), India*

ABSTRACT

Dengue is a viral illness caused by a RNA virus belonging to family Flaviviridae. This virus is further classified into four distinct serotypes. Dengue is spread by the bite of mosquito - *Aedes aegypti*. Symptoms of Dengue from moderate fever to extreme conditions such as dengue hemorrhagic fever and shock syndrome, which have significant distress and mortality. The disease has a huge percentage of clinically asymptomatic cases observed till now. Some common symptoms are frontal headache, fever, and severe musculoskeletal pain. Dengue is also responsible for many highly complex pathophysiological, economical and ecological problems. Dengvaxia is the first vaccine approved by FDA for the prevention of dengue disease caused by all serotypes of dengue virus Preventive measures should be taken to avoid disease extent and diminish epidemic flash up as it has turned out to be a major public health problem.

KEYWORDS: ***Dengue, Aedes aegypti, DF/DHF, Pathophysiology, Vaccine***

HARDEEP KAUR *

Assistant professor of chemistry, Department of Biotechnology, Chandigarh University Gharuan, Mohali (Punjab), India

Received on: 09-05-2019
Revised and Accepted on: 26-06-2019
DOI: http://dx.doi.org/10.22376/ijpbs.2019.10.3.p46-57

INTRODUCTION

Dengue refers to a mosquito-borne viral disease brought about by a virus known as dengue virus, which is an associate of the family Flaviviridae of genus Flavivirus and is an arthropod –borne virus [1,2]. Flavivirus is further classified into four strongly correlated serotypes i.e. DEN-1, DEN-2, DEN-3, DEN-4, each serotype is sufficiently distinct in such a way that there is no possibility of cross-protection and epidemics caused by various serotypes (hyperendemicity) can take place [3]. Infection by any of the strain of dengue virus will provide lifelong immunity for that distinct strain only but not for other remaining strains of this virus [4,5]. Dengue virus is carried by female anopheles mosquito *Aedes aegypti* . Manifestation are observed within 3 to 14 days after the infection whereas recuperation generally takes two to seven days [1,6].These majorly involve high fever, headache, nausea, joint and muscle pain and distinct skin rashes[1] . In few percentages of manifestations, the disease develops into the lethal dengue hemorrhagic fever, consequential bleeding, blood plasma leakage and low levels of blood platelets, also into dengue shock syndrome, where severely low blood pressure occurs[6] . According to WHO dengue is observed as a paramount worldwide public health issue in tropical and subtropical nations. Dengue has perceived 30-times upturn worldwide in the time span of 1960-2010 and this was majorly due to idle mosquito control, increased population expansion rate, spontaneous urbanization, global warming, regular air travel, and inadequate health care services [7,8,9]. Currently dengue is prevalent in 128 countries, mostly developing countries, posturing jeopardy to roughly 3.97 billion populations yearly. A latest dengue distribution model has discovered that there are about 390 million dengue infections per annum, out of these 96 million cases occurred apparently[10, 11] . India is the epicentre of dengue and however there are many cases which have been profoundly underestimated[12,13]. Transmission occurs between human and mosquito (*Aedes)* vector species in endemic, hyper endemic or epidemic pattern. Aedes is a day biting mosquito[8]. Though there is no approved anti-DENV therapeutic drug to cure or treat dengue. However a number of vaccine candidates are in clinical and preclinical development phase but none have been licensed yet. However a vaccine for dengue is approved and is available in many countries[14.] Mild and moderate type of dengue can be treated by giving fluids orally or intravenously on the other side blood transfusion might be helpful in rigorous cases[15]. For the confirmation of diagnosis various tests are available including detection of antibodies to the virus or its RNA[16].

EPIDEMIOLOGY

Dengue is the most established emerging mosquito borne viral disease in tropical and sub tropical regions of the world. There is a 30-fold raise in dengue cases in the last five decades[17]. Dengue is reported in 110 countries till now[18]. Dengue viruses are known to be fully acclimatized to humans, and the well reclaimed primary vector *Aedes aegypti is* widely spread long ago from sylvatic cycles relating to non-human primates and canopy-dwelling Aedes mosquitoes in the rainforests of Asia and Africa [19].. Epidemic motion of dengue virus considerably leaped in the 1970s and 1980s, resulting in global geographical expansion of dengue viruses and mosquito vectors, and the resulting prevalent transmission of DENV across the tropical and subtropical areas[20,21]. The prime reasons for twentieth century widespread of dengue were various global trends like population growth, urbanization, modern transportation, global trade and the lack of effective mosquito control[22-24] .It has been reported that maximum cases of DENV virus occurred among the age group of 5 to 15 years in Asia which is followed by American tropics where 19 to 40 years was the general age of infection [25.] In India the existence of dengue fever was first observed in 1946 [26]. Initial epidemics of Dengue in Eastern Coast of India was seen in 1963-1964, subsequently reaching Delhi and Kanpur in 1967 and 1968 respectively and at the same time it was also prevalentin the southern part of India [27-35]. First case of Dengue haemorrhagic fever was observed in Calcutta city in 1963. The epidemiology of DENV and its widespread serotypes has been always altering. In 1968 the serotype responsible for dengue epidemics was DV-4 whereas in 1969 DV-2 and DV-4 were isolated [34, 36]. Then during the epidemics of 1970 it was completely replaced by DV-4 in Hardoi. [37] The prominent type of serotype prevalent in northern India including Lucknow, Delhi, Gwalior was DV-2 whereas during epidemic of 1997 at Delhi DV-1 was isolated [38,39,40]. DV-2 was the most prominent serotype of dengue in Delhi till 2003 but later on all the serotypes of dengue were isolated hence changing the hyperendemic state whereas in 2005 it again changed to DV-3[41,42] . DV-4 was reported in Andhra Pradesh, Mumbai and Pune and the outbreak was rigorous in nature[43,44]. The simultaneous infection in some patients with multiple serotypes was the upshot of co-circulation of various type of dengue virus[45.] Currently dengue fever is the cause of major illness and death in comparisonto any other type of human arbovirus[46]. According to recent estimates of dengue disease burden more than half of the world's inhabitants are reported to be living in areas that place them at high risk of DENV infection, with 390 million overall DENV infections, 96 million symptomatic infections, 2 million cases of severe dengue and an approximate 21,000 deaths per year [13, 21.In] 2007 Intergovernmental Panel on Climate Change warned that due to climate change 1.5 to 3.5 billion people will be facing the risk of dengue by 2080's[149.] In 2003, 2005, 2006, 2008 and 2009, the dengue incidence exceeded 10 per million population[150]. Since 2010, a dengue incidence of greater than 15 per million populations has been reported annually[150]. From 2010 onward, the states of Assam, Bihar, Jharkhand, Orissa and Uttarakhand and some union territories including Andaman and Nicobar Islands, Dadra and Nagar Haveli, and Daman and Diu have become endemic for dengue. India experienced the highest dengue incidence in 2012 (about 41 per million population), 2013 (61 per million population) and 2014 (32 per million population)[150].

VECTOR

Female Aedes mosquito is the reason for the transmission of different serotypes of dengue virus in humans. *Ae.aegypti* is the most significant epidemic vector in tropical and sub-tropical regions. Some other species has been reported to act as secondary vectors such as *Ae.polynesiensis, Ae.albopictus, Ae.niveus* and

member of *Ae.scutellaris* complex[15,47]. But *Ae.niveus* is regarded as the only sylvatic vector[48]. The life cycle of Aedes mosquito lasts for 8–10 days at room temperature based on the level of feeding but in some cases mosquitoes are reported to live for 2 weeks or more[49]. There are two phases of lifecycle of mosquito: (i) aquatic (larvae, pupae) and (ii) terrestrial (eggs, adults) phase[50]. Currently, *Ae albopictus* has been reported as the most progressively significant vector because it has the ability to simply adapt to new-fangled environments, including temperate regions. *Ae.aegypti* is a day biting mosquito and only female *Aedes* bites. Life span of Aedes mosquito is approximately 2 weeks only. Roughly after seven days of biting a virus infected person, the mosquito becomes infective or virulent. It has been reported that the mosquito lays its eggs in clean and stagnant water i.e. free of any organism. Every species has its own ecology, behaviour and geographical distribution. Eggs of this mosquito can stay feasible for few months in the absence of water[48, 50, 51,52] . Life cycle of this mosquito is-

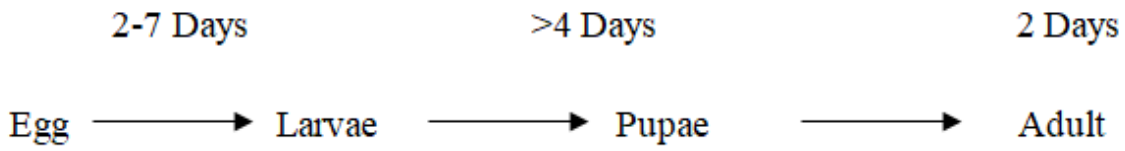

Figure 1

MODE OF TRANSMISSION

Transferral of dengue virus principally takes place through *Aedes* mosquito specifically through *A.aegypti*[11]. It is reported that mosquitoes primarily attain DENV by consuming the blood of already infected individual[48]. Initially it infects and duplicates in the mosquito's midgut epithelium. Afterwards it propagates with the help of hemolymph and reaches to increase its number in other organs like fat body and trachea of lungs and at the end eventually infects the salivary gland after 10 to14 days after the meal[50]. Hence DENV can be transferred in human as mosquito acquires blood meal from the infected person resulting in dissemination of the disease[53,54]. The mosquitoes become infected when they feed on humans during the five day period of viremia. After an external incubation period the virus gets transferred from intestinal tract to the salivary gland of mosquito during ambient high temperatures in approximately 10 days[52]. After the bite of mosquito a person can suffer an acute arrival of fever along with some non specific signs and symptoms[53]. Reasons for the expanding transmission of this disease can be global warming, urban sprawl, increased travel. An infected mosquito is capable of spreading virus throughout its life. Infected symptomatic and asymptomatic humans are also carriers and multipliers of this virus because if another *A. aegypti* mosquitoes acquires blood meal from the sick person during this feverish viremic stage, those non-infected mosquitoes may become infected and consequently pass on the virus to other healthy persons, after an extrinsic incubation time span of 8 to 12 days[10,54] . Vector is a day time feeder and its peak time is early morning and evening before dusk[55,56] . Virus does not tend to affect the mosquito in which it lives[21]. The Aedes species of mosquito is commonly involved because of its tendency to grow in artificial water containers so as to live in close contact to humans[57]. Some other reasons for the transmission of dengue virus occurs viaproducts of infected blood, donation of organ and vertical transmission during pregnancy has also been observed in some cases along with a few cases of person to person transfer [58-61].

DENGUE VIRUS AND ITS PATHOPHYSIOLOGY GENOME

Dengue fever virus [DENV] is an RNA virus of genus flavivirus and family Flaviviridae[62]. Dengue virus is transmitted by mosquito hence it is also known as arbovirus i.e. arthropod borne virus[63]. Virion of dengue comprises of spherical particles of 40 to 50 nm in diameter and an envelope of lipopolysaccharide[64]. Genome of dengue virus is 11000 nucleotide bases long single stranded RNA with single open reading frame which codes for three different protein molecules i.e. capsid, membrane and envelope(C, prM and E) that forms virus particals and other seven non-structural molecules such as NS1, NS2a, NS2b, NS3, NS4a, NS4b and NS5, which are found in only host but are essential for viral replication[50]. Viral proteins are synthesized in cytoplasm specifically on rough endoplasmic reticulum whereas the structural proteins get assembled and matured onluminal side[60]. Further there are five different and distinct serotypes of virus i.e. DENV-1,DENV-2,DENV-3,DENV-4 and the fifth serotype of dengue was first proclaimed in 2013[61]. Antigenicity is the basis of the distinctions between these serotypes[62]. Genome of dengue virus also consists of some non-coding regions on both the 5' and 3' ends[63].

STRUCTURE AND IT'S FUNCTION OF DENGUE VIRUS (Table 1).

Dengue virus consists of an outer protein shell, a less characterized nucleocapsid core with RNA complex and a lipid bilayer that contains M protein and E protein, which mutually coordinate host–viral interactions during entry[64]. Dengue virus bears different structure of surface during its maturation. The envelope proteins of dengue virus are made up of three subsets i.e. EDI, EDII, EDIII and a hinge motion takes place between EDI- EDII and EDI- EDIII[65]. E protein is majorly introduced part of dengue virus antigen against which antibodies develop immune response during natural infection[66,67] . All the dengue serotypes have similar E protein to the extent of 60 to 70%[68]. The E-protein is an arrangement of 90 monomers that lie flat on the surface of DENVs and assists the entry of virus into cells of host by binding to cellular receptors and hence mediating the combination

of cellular and viral membranes[69, 66.] The E-protein is made up of transmembrane region and an ectodomain which are divided into three functional domains : [66]

1. EDI (envelope domain I)
2. EDII (envelope domain II)
3. EDIII (envelope domain III)

Apart from this these three domains differ in their immunogenicity and EDIII of all the serotypes generate sturdily neutralizing antibodies which are strictly serotype specific[70]. Such serotype particular antibodies have been reported to be majorly involved in the trigger against the EDI/EDII hinge region, complex quaternary epitopes displayed on the E protein dimer and the whole virion[71,72] .It has been reported that these are not cross reactive neutralizing antibodies instead they are serotype specific neutralizing antibodies that confer immunity against infection. It has also been reported that most of the immune response is obtained against the domains of EDI, EDII, and prM (yellow domain in the virus image) [62,63] . Anti-EDI/II antibodies are largely weak or non neutralizing heterotypic type, whereas prM antibodies are cross-reactive and nonneutralizing. The virus utilizes these weak cross-reactive antibodies in getting hold of access into the host cell via Fc receptor as an alternative pathway at the time of a secondary infection with a heterologous serotype, leading to intensification of infection[73,74] . This process is referred to as antibody-dependent enhancement (ADE)[75]. When a virus infects a new cell by the mechanism of receptor mediated endocytosis the E molecules transform its conformation into trimeric conformation in acidic compartment of endosome which further protrudes from the virus surface resulting in membrane fusion resulting in viral RNA release into the cytoplasm[76]. NS1 proteins are firstly synthesized as soluble monomers and after dimerization in the lumen of ER these proteins become associated with the membrane[77]. The intracellular NS1 protein plays a significant function in initial viral replication and is established in virus induced vesicular compartments that accommodate the viral replication complexes[78,79] . The crystalline structure of NS1 protein is recently reported to expose hydrophobic domains in dimer that probably mediate the membrane fusion. NS1 can be isolated from the blood sample of infected person from the first day of infection and their amounts can vary from ng/ml to mg/ml at the sensitive phase of infection and further their levels in the blood are also an indication for severity of infection [80,81].

Table 1
Functions of viral proteins

Protein	Function
1. Capsid (C)	It binds and stabilizes viral RNA
2. Premembrane/membrane (prM/M)	(i) Pr peptide acts as a cap that protects the fusion peptide on E, hence preventing premature fusion (ii) M forms ion channel
3. Envelope (E)	(i)Helps in recognition and binding to the host cell (ii) Involved in uncoating of virus by enabling fusion of viral and endosomal membranes
4. NS1	(i) Helps in viral RNA replication (ii) Viral defence through inhibition of complement activation
5. NS2A	Helps in viral replication and assembly
6. NS2B	It is a NS3 protease cofactor
7. NS3	(i) Serine protease-cleaves viral polyprotein (ii) RNA helicase and RTPase/NTPase-viral RNA replication (iii) Induction of apoptosis in infected cells
8. NS4A	It induces membrane alterations and autophagy to enhance virus replication
9. NS4B	(i) Interacts with NS3-viral replication (ii) Blocks IFN-α/β-induced signal transduction and helps virus to escape host's innate immune response
10. NS5	(i) Methyl transfer as domain (ii) RNA-dependent RNA polymerase

PATHOPHYSIOLOGY

Dengue infection is both systemic and viral, which includes both severe and non severe clinical symptoms[82]. After incubation period the infection spreads immediately and leads to different phases of disease[83]. When the mosquito bites a human, DENV probably enters the bloodstream and then flows over the epidermal and dermal layers causing the consequential infection of undeveloped epidermal and keratinocyte[84]. The infected cells then drift from the site where infection is present to lymph nodes where macrophages and monocytes become target of infection[85]. Because of this prime meet of various cells of single nuclear ancestry, including blood derived monocytes, myeloid, splenic and macrophages of liver becomes damaged[86]. It has been reported that at the time of initial infection with heterologous dengue virus, high concentration of DENV definite immunoglobulin G (IgG) will form a complex with newly formed viruses that attaches to and is occupied by single nucleus cells hence following the infection these mononuclear cells ultimately dies by the process of apoptosis i.e. programmed cell death[87,88] . In this aspect, factors that affect the number of infected target cells, and therefore the extent of viremia, may also help in estimation of the ratio of unlike proinflammatory and anti-inflammatory mediators such as cytokines, and chemokines. It also helps to know the approach in which the inflammatory reaction affects the hemostatic system[89,90] . Stromal cells of bone marrow have also

been reported to have susceptibility to dengue infection[91]. Liver is the major organ which is commonly concerned in DENV infections in humans[92, 93] . Organ tropism has also been observed which indicates the higher levels of virus isolated from skin and lower levels from spleen, thymus and lymph node [94, 95]. Generally the most severe clinical appearance during the infection course is not related with a high viral load [96]. Once the incubation period is over, the illness starts immediately which is accompanied by the three phases i.e. Febrile, critical and recovery phase.[94, 95,96,97,98]

FEBRILE PHASE

In this phase a sudden high grade fever is developed by patients. Febrile phase lasts from 2-7 days along with manifestations like skin redness known as facial flushing, skin burns, general body ache, myalgia, headache and arthralgia. Symptoms like sore throat, injected pharynx and conjunctival injection can also be observed in this phase whereas anorexia, nausea and vomiting are the most common symptoms. There is a possibility of misinterpretation of dengue infection during its febrile phase with a non-dengue febrile disease. In this phase a positive tourniquet test indicates the existence of DENV. Moderate symptoms such as mucosal membrane bleeding and petechiae e.g. nose and gums can also be observed. Liver becomes tender and enlarged after few days of infection. The preliminary irregularity in the full blood count is a gradual reduction in total leukocyte count, which specifies the maximum chances of dengue infection.

CRITICAL PHASE

During the period of abatement of fever, when temperature falls to 37-38 °C or even below this level, an increase in permeability of capillaries takes place in correspondence with increased haematocrit levels. This connotes the onset of critical phase. The time period of plasma leakage generally lasts for 24 to 48 hours. Plasma leakage is preceded by subsequent leucopenia followed by prompt decrease in platelet count. According to the intensity of plasma leakage, pleural effusion and ascites can be clinically detected. Along with this the extremity of plasma leakage can be reflected by the degree of increase above the baseline haematocrit. When paramount volume of plasma is lost shock occurs. With long-lasting shock, subsequent organ hypoperfusion results in continuous impairment of organs, disseminated intravascular coagulation and metabolic acidosis. Along with this, extreme organ destruction such as rigorous hepatitis, encephalitis or myocarditis and/or ruthless bleeding may also occur devoid of any noticeable plasma leakage or shock.

RECOVERY PHASE

In recovery phase, a steady reabsorption of extracellular compartment fluid takes place in the next 48 to 72 hours if the patient manages to endure the critical phase of one or two days. The haematocrit becomes stabilized or may be minor because of the dilutional outcome of reabsorbed fluid. Normally leukocytes count start to increase shortly after abatement of fever but the recuperation of platelet count is characteristically seen after the count of leukocytes become normal. Throughout the critical and/or recovery phase, excessive fluid therapy is allied with congestive heart failure or pulmonary oedema.

DENGUE FEVER AND ITS CLASSIFICATION

According to WHO dengue fever is primarily categorized into two major groups: uncomplicated and severe[99] . Extreme cases are correlated to severe plasma escape, disproportionate hemorrhage, organ impairment and some other remaining cases are regarded as uncomplicated[11,100] . Dengue can also be categorised as undifferentiated fever, Dengue Fever [DF], and Dengue hemorrhagic fever [DHF] [22].DHF is further classified into four grades:[101]

Grade I- Only mild ecchymosis or a positive tourniquet test

Grade II- Impulsive bleeding into some parts of body but mainly skin.

Grade III- Clinical sign of shock.

Grade IV: Severe shock - feeble pulse and blood pressure cannot be recorded.

In the above mentioned, grades III and IV includes Dengue shock syndrome [DSS] [11]. Undifferentiated fever, DF, DHF are likely to represent the increasingly severe stages of a constant dengue disease scale[102].

UNDIFFERENTIATED FEVER

This phase is often observed in the primary stage of infection whereas it can also befall occur after the initial secondary stage of infection. It often remains undiagnosed because it is difficult to distinguish it from various other viral infections.

DENGUE FEVER

In this case initiation of manifestations is categorized by a dual phase, high-grade long term fever of 3 days to 1 week [103,104]. Dengue is associated with myalgia and pain in joints therefore it is also known as breakbone fever[105, 59]. Cases of skin rashes have also been reported[152]. Occasionally, distinct lesions may combine and they will be presented as extensive confluent erythematous areas with isolate bleeding spots giving a characteristic manifestation of “white islands in a sea of red”[106,107]. The cutaneous rash is generally asymptomatic, and pruritus is reported in few cases [108,109]. Bleeding incident is uncommonly seen in DF, even though gingival bleeding, epistaxis, petechiae/purpura, gastrointestinal tract (GIT) hemorrhage and substantial menstruation can take place[103, 110]. It is also identified by the abrupt inception of fever and a range of unclear signs and symptoms, together with body aches, retro-orbital pain, frontal headache, weakness, joint pains, nausea and vomiting, and rash [11,10,53,107,111]. Thrombocytopenia is frequent in dengue fever[112].

DENGUE HEMORRHAGIC FEVER AND DENGUE SHOCK SYNDROME

Dengue Hemorrhagic Fever is often indicated by a secondary dengue infection. It may also occur during a primary infection in infants because of maternally inherited dengue antibodies [113]. It is a disease of children under 15 but can also occur in adults[11,113] . Because of late diagnosis and improper supervision, some patients may experience shock from loss of blood that can be mild or rigorous[114-116]. In patients suffering

from severe DHF or DSS some imprecise signs and symptoms are observed which results in the rapid worsening of the patient's health condition [10]. A recurrent severe pain in abdominal area soon before the beginning of shock is experienced [115-117] . Once the shock is overcome, even patients with unnoticeable pulse and blood pressure will generally get better within 2 to 3 days[117]. Hepatomegaly is a common but not regular verdict[10,115,116] . The most important pathophysiologic irregularity observed in DHF and DSS is a sharp rise in vascular permeability that results in leakage of plasma into extravascular section, resulting in hemoconcentration and a reduction in blood pressure[117,118] . Hemostatic alterations in DHF and DSS include 3 factors i.e. vascular changes, coagulation disorders and thrombocytopenia[117] . The most recognized factors include deficiency and dysfunction of platelets Vasculopathy and defects in the blood coagulation pathways[119]. Increased damage of platelets and decreased production of platelets can cause effect in thrombocytopenia in DHF[120-122] . The blood vessels become fragile due to impaired platelet function and this result in hemorrhage[21] . The clinical path of DHF is identified by three phases: Febrile, leakage, and convalescent phase. The initiation of the febrile illness is characterized by high-grade fever along with legitimate signs and facial erythema[104]. The primary febrile illness is identified by a morbilliform rash and hemorrhagic tendencies[123]. The fever continues for 2 days to 1 week and then falls to normal or abnormally low levels[89].

DIAGNOSIS

Dengue virus infection is diagnosed by confirmation of anti-DV IgM antibody or by NS-1 antigen in the serum of infected person using ELISA kits and other commercial kits[90]. Five basic serologic tests regularly used for diagnosis of dengue infection are Hemagglutination-inhibition (HI), neutralization test (NT), complement fixation (CF), immunoglobulin M (IgM) capture enzyme-linked immunosorbent assay (MAC-ELISA), and indirect immunoglobulin G ELISA[124, 125,126]. Molecular method which includes the use of PCR is also used for diagnosis[127]. Also isolation of dengue virus in tissue culture cells and its sequencing is performed[128]. Rooted diagnosis of dengue can be done by various tests like counting of platelets, Hematocrit Test, Detecting specific antibodies[129]. The favoured microbiological assays include the isolation of virus in cell cultures serological recognition of viral antigens (such as NS1) or particular antibodies and nucleic acid expression by polymerase chain reaction (PCR) [12]. However early disease is sometimes confused with other viral disease[22]. The diagnosis should be examined in anyone who develops a fever within two weeks of being in the tropics or subtropics[130]. Virus isolation and nucleic acid recognition are more correct and precise in comparison to antigen detection, but on the other hand these tests are not broadly accessible due to higher cost [11] . In worse case such as internal hemorrhage, whole blood transfusion can be done[130]

TREATMENT

As dengue is an infection caused by virus sotreatment can be undertaken using the uncomplicated perception for getting relieve from pathogen and hence restraining the difficulties [131]. Generally in simple dengue oral fluid is administered and hospitalization is not required whereas in severe cases fluid replacement is must along with hospitalization and proper care[132]. Intravenous fluid substitution with the help of either colloids or crystalloids must be considered to avoid shock[133]. It is important to maintain the electrolyte status of the body to prevent the low or excessive administration of fluids [134]. It is observed that there are high chances of developing shock due to the continuous increase in hematocrit with a subsequent decrease of platelet count therefore detecting the hematocrit and platelet count must be performed for at least one day after the intravenous fluid administration is discontinued in order to block fluid intoxication in the recovery phase which is likely to occur due to fluid relocation[135]. A particular antiviral drug is not on hand till now whereas in plants medicine, various sulfated polysaccharides obtained from seaweeds have been studied which are proven to have high antiviral activity against dengue virus[133]. Some of the drugs including Ribavirin and glycyrrhizin and 6-azauridine are proved to have cytostatic and suppressing effects on the dengue virus[134]. An adenosine analog 'NITD008' is another capable drug at present being considered for the treatment of dengue[135]. Discovery of viral proteins may help in the development of successful drugs against dengue virus [136] .

DENGUE VACCINE

Researchers are now working on the development of tetravalent vaccine for all serotypes of dengue virus because it is reported that a lifelong protection can be achieved for the homologous virus with the help of antibodies produced during the time period of infection but only short-lived protection is available from the other three serotypes[137]. There are five types of vaccines which are in progress; these are classified as inactivated vaccines, subunit vaccines, chimeric live attenuated vaccines, live attenuated vaccines and nucleic acid-based vaccines[138,139] . These vaccines are required several times to attain immunity against dengue virus[140]. Different antibody responses, such as antibody dependent cell mediated cytotoxicity and complement fixation, might also associate with antibody mediated protection in opposition to DENVs[141, 142]. Various examples of dengue vaccines includes DENVax[143] and a Vaccine developed by Sanfoi Pasture [144].Dengvaxia is the first vaccine to be developed which provide resistance against all four serotypes of dengue[145,146]. However Dengvaxia is not approved by the government of India because more clinical trials are thought to be necessary in India[147,148].

CONCLUSION

The current review reveals the concurrent infection of dengue as there has been increase in the number of infection cases. Dengue infection can prove to be lethal if not treated well on time. Considering this an early diagnosis is important. Awareness of this infection is necessary among common people. There is the possibility of treatment if diagnosis is done on time. Development of new diagnostic tests is also required. A vaccine has been developed known as Dengvaxia which was first approved by US government. Along with all above public engagement programs for prevention and

control of this mosquito transmitted infections are warrant.

AUTHORS CONTRIBUTION STATEMENT

Mrs.Hardeep kaur conceptualized and collected the data with regard to the topic. Ms.Reema Sharma designed the manuscript. Manuscript writing was done by both. Required changes were done by Mrs.Hardeep kaur. Both of them discussed and contributed to the final manuscript.

CONFLICT OF INTEREST

Conflict of interest declared none.

REFERENCES

1. Holmes E, Twiddy S. The origin, emergence and evolutionary genetics of dengue virus. Infect Genet Evol. 2003;3(1):19–28. DOI: 10.1016/s1567-1348(03)00004-2
2. Halstead SB. Pathogenesis of dengue: challenges to molecular biology. Science (80-). 1988;239(4839):476–81. DOI: 10.1126/science.239.4839.476
3. Kurane I. Dengue hemorrhagic fever with special emphasis on immunopathogenesis. Comp Immunol Microbiol Infect Dis. 2007;30(5–6):329–40. DOI: 10.1016/j.cimid.2007.05.010
4. Gubler DJ. Cities spawn epidemic dengue viruses. Nat Med. 2004;10(2):129–30. DOI: 10.1038/nm0204-129
5. Tran A, Raffy M. On the dynamics of dengue epidemics from large-scale information. Theor Popul Biol. 2006;69(1):3–12. DOI: 10.1016/j.tpb.2005.06.008
6. Kularatne SAM. Dengue fever. BMJ. 2015;h4661. DOI: 10.1136/bmj.h4661
7. Guzman MG, Gubler DJ, Izquierdo A, Martinez E, Halstead SB. Dengue infection. Nat Rev Dis Prim. 2016;2(1). DOI: 10.1038/nrdp.2016.56
8. Shepard DS, Undurraga EA, Betancourt-Cravioto M, Guzmán MG, Halstead SB, Harris E. Approaches to Refining Estimates of Global Burden and Economics of Dengue. PLoS Negl Trop Dis. 2014;8(11):e3306. DOI: 10.1371/journal.pntd.0003306
9. Gubler DJ. Dengue viruses: their evolution, history and emergence as a global public health problem.. Dengue and dengue hemorrhagic fever. CABI; p. 1–29. DOI: 10.1079/9781845939649.0001
10. Gubler DJ. Dengue and Dengue Hemorrhagic Fever. Clin Microbiol Rev. 1998;11(3):480–96. DOI: 10.1128/cmr.11.3.480
11. World Health Organization, Special Programme for Research, Training in Tropical Diseases, World Health Organization. Department of Control of Neglected Tropical Diseases, World Health Organization. Epidemic PA. Dengue: guidelines for diagnosis, treatment, prevention and control. World Health Organization; 2009.
12. Guzman MG, Halstead SB, Artsob H, Buchy P, Farrar J, Gubler DJ. Dengue: a continuing global threat. Nat Rev Microbiol. 2010;8(S12):S7–16. DOI: 10.1038/nrmicro2460
13. Bhatt S, Gething PW, Brady OJ, Messina JP, Farlow AW, Moyes CL. The global distribution and burden of dengue. Nature. 2013;496(7446):504–7. DOI; 10.1038/nature12060
14. Brady OJ, Gething PW, Bhatt S, Messina JP, Brownstein JS, Hoen AG. Refining the Global Spatial Limits of Dengue Virus Transmission by Evidence-Based Consensus. PLoS Negl Trop Dis. 2012;6(8):e1760. DOI; 10.1371/journal.pntd.0001760
15. Zhang H, Zhou YP, Peng HJ, Zhang XH, Zhou FY, Liu ZH. Predictive Symptoms and Signs of Severe Dengue Disease for Patients with Dengue Fever: A Meta-Analysis. Biomed Res Int. 2014;2014:1–10. DOI: 10.1155/2014/359308
16. Stanaway JD, Shepard DS, Undurraga EA, Halasa YA, Coffeng LE, Brady OJ. The global burden of dengue: an analysis from the Global Burden of Disease Study 2013. Lancet Infect Dis. 2016;16(6):712–23. DOI: 10.1016/s1473-3099(16)00026-8
17. East S. World's first dengue fever vaccine launched in the Philippines. CNN; 2016.
18. Organization WH. Prevention and control of dengue and dengue haemorrhagic fever. WHO Regional Office. South-East Asia; 1999. Available from: https://apps.who.int/iris/bitstream/handle/10665/205653/B0109.pdf
19. Guzmán MG, Kourí G. Dengue diagnosis, advances and challenges. Int J Infect Dis. 2004;8(2):69–80. DOI: 10.1016/j.ijid.2003.03.003
20. Organization WH. Global strategy for dengue prevention and control. Available from: https://apps.who.int/iris/bitstream/handle/10665/75303/9789241504034_eng.pdf
21. Ranjit S, Kissoon N. Dengue hemorrhagic fever and shock syndromes*. Pediatr Crit Care Med. 2011;12(1):90–100. DOI: 10.1097/pcc.0b013e3181e911a7
22. Ooi EE, Gubler DJ, Ooi EE, Vasudevan SG FJ. Surveillance for dengue. Dengue and dengue hemorrhagic fever. Oxfordshire. CAB International; 2014. 78-89 p.
23. Organization WH. Dengue haemorrhagic fever: diagnosis, treatment, prevention and control. Available from: https://apps.who.int/iris/bitstream/handle/10665/41988/9241542098_rus.pdf
24. SB. H. The XXth century dengue pandemic: need for surveillance and research. Rapp trimest Stat sanit mond. 1992;45:292. Available from: https://apps.who.int/iris/bitstream/handle/10665/53007/WHSQ_1992_45_2-3_p292-298_eng.pd
25. Graham RR, Juffrie M, Tan R, Hayes CG, Laksono I, Ma'Roef C, Porter KR, Halstead SB. A prospective seroepidemiologic study on dengue in children four to nine years of age in Yogyakarta, Indonesia I. studies in 1995-1996. The American journal of tropical medicine and hygiene. 1999 Sep 1;61(3):412-9.Available from: https://www.ajtmh.org/content/journals/10.4269/ajtmh.1999.61.412
26. Messina JP, Brady OJ, Scott TW, Zou C, Pigott DM, Duda KA. Global spread of dengue virus types: mapping the 70 year history. Trends Microbiol. 2014;22(3):138–46. DOI: 10.1016/j.tim.2013.12.011
27. Gubler DJ. Dengue, Urbanization and Globalization:

The Unholy Trinity of the 21st Century. Trop Med Health. 2011;39(4SUPPLEMENT):S3–11. DOI: 10.2149/tmh.2011-s05

28. Karamchandani P V. Dengue group of fevers in india. Lancet. 1946;247(6386):92–3. DOI: 10.1016/s0140-6736(46)91229-9
29. Carey DE, Rodrigues FM, Reuben R, Myers RM. Studies on Dengue in Vellore, South India. Am J Trop Med Hyg. 1966;15(4):580–7. DOI: 10.4269/ajtmh.1966.15.580
30. Ramakrishnan SP, Gelfand HM, Bose PN, Sehgal PN MR. The Epidemic Of Acute Haemorrhagic Fever, Calcutta, 1963: Epidemiological Inquiry. Indian J Med Res. 1964;52:633–50. Available from: https://europepmc.org/abstract/med/14195504
31. Sarkar JK, Pavri KM, Chatterjee SN, Chakravarty SK AC. Virological and Serological Studies of Cases of Haemorrhagic Fever in Calcutta. Material Collected by the Calcutta School of Tropical Medicine. Indian J Med Res. 1964;52:684. Available from: https://www.ncbi.nlm.nih.gov/pubmed/14195508
32. Chaudhuri RN, Saha TK CA. Dengue-like fever in Calcutta: Further preliminary observations. Bull Calcutta Sch Trop Med. 1965;13:2. Available from: https://www.ncbi.nlm.nih.gov/pubmed/14281058
33. Gupta N, Srivastava S, Jain A CU. Dengue in India. Indian J Med Res. 2012;36(3):373. Available from: http://repository.ias.ac.in/95851/1/dengue.pdf
34. Krishnamurthy K, KASTUR T CG. Clinical and pathological studies of an outbreak of dengue-like illness in Visakhapatnam. Indian J Med Res. 1965;53(8):800–12. Available from: https://www.cabdirect.org/cabdirect/abstract/19662701249
35. Balaya S, Paul SD, D'lima LV PK. Investigations on an outbreak of dengue in Delhi in 1967. Indian J Med Res. 1969;57(4):767–4. Available from: https://www.cabdirect.org/cabdirect/abstract/19702701096
36. Chaturvedi UC, Mathur A, Kapoor AK, Mehrotra NK MR. Virological study of an epidemic of febrile illness with haemorrhagic manifestations at Kanpur, India, during 1968. Bull World Heal Organ. 1970;43(2):289. Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2427646/
37. Chaturvedi UC, Kapoor AK, Mathur A, Chandra D, Khan AM MR. A clinical and epidemiological study of an epidemic of febrile illness with haemorrhagic manifestations which occurred at Kanpur, India, in 1968. Bull World Health Organ. 1970;43(2):281. Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2427638/
38. Chaturvedi UC, Mathur A, Kapoor AK, Tandon HO MR. Clinicovirological study of the recurrence of dengue epidemic with haemorrhagic manifestations at Kanpur during 1969. Indian J Med Res. 1972;60(3):329–3. Available from: https://www.cabdirect.org/cabdirect/abstract/19732700916
39. Chaturvedi UC, Mathur A MR. Experimentally produced cardiac injury following dengue virus infection. Indian J Pathol Bacteriol. 1974;17(4):218. Available from: https://www.ncbi.nlm.nih.gov/pubmed/4457475
40. Dar L, Broor S, Sengupta S, Xess I SP. The first major outbreak of dengue hemorrhagic fever in Delhi, India. Emerg Infect Dis. 1999;5(4):589. Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2627747/
41. Agarwal R, Kapoor S, Nagar R, Misra A, Tandon R, Mathur A, Misra AK, Srivastava KL CU. A clinical study of the patients with dengue hemorrhagic fever during the epidemic of 1996 at Lucknow, India. Southeast Asian J Trop Med public Heal . 1999;30(4):735–40. Available from: https://europepmc.org/abstract/med/10928368
42. Parida MM, Dash PK, Upadhyay C, Saxena P JA. Serological & virological investigation of an outbreak of. Indian J Med Res. 2002;116:248–54. Available from: https://www.researchgate.net/publication/10708163_Serological_virological_investigation_of_an_outbreak_of_dengue_fever_in_Gwalior_India
43. Dar L, Gupta E, Narang P, Broor S. Cocirculation of Dengue Serotypes, Delhi, India, 2003. Emerg Infect Dis. 2012;12(2):352–3. DOI: 10.3201/eid1202.050767
44. Gupta E, Dar L, Kapoor G, Broor S. No Title. Virol J. 2006;3(1):92. DOI: 10.1186/1743-422x-3-92
45. Dash Pk, Sharma S, Srivastava A, Santhosh Sr, Parida Mm, Neeraja M. Emergence of dengue virus type 4 (genotype I) in India. Epidemiol Infect. 2010;139(6):857–61. DOI: 10.1017/s0950268810001706
46. Cecilia D, Kakade MB, Bhagat AB, Vallentyne J, Singh A, Patil JA. Detection of dengue-4 virus in pune, western india after an absence of 30 years - its association with two severe cases. Virol J. 2011;8(1). DOI: 10.1186/1743-422x-8-46
47. Bharaj P, Chahar HS, Pandey A, Diddi K, Dar L, Guleria R. Concurrent infections by all four dengue virus serotypes during an outbreak of dengue in 2006 in Delhi, India. Virol J . 2008;5(1):1. DOI: 10.1186/1743-422x-5-1
48. Lambrechts L, Scott TW, Gubler DJ. Consequences of the expanding global distribution of Aedes albopictus for dengue virus transmission. PLoS neglected tropical diseases. 2010 May 25;4(5):e646.Available from: https://journals.plos.org/plosntds/article?id=10.1371/journal.pntd.0000646
49. Rezza G. Aedes albopictus and the reemergence of Dengue. BMC Public Health. 2012;12(1). DOI: 10.1186/1471-2458-12-72
50. Sim S, Ramirez JL, Dimopoulos G. Dengue Virus Infection of the Aedes aegypti Salivary Gland and Chemosensory Apparatus Induces Genes that Modulate Infection and Blood-Feeding Behavior. PLoS Pathog. 2012;8(3):e1002631. DOI: 10.1371/journal.ppat.1002631
51. Southwood TR, Murdie G, Yasuno M, Tonn RJ RP. Studies on the life budget of Aedes aegypti in Wat Samphaya, Bangkok, Thailand. Bull World Health Organ. 1972;46(2):211. Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2480713/
52. Racloz V, Ramsey R, Tong S, Hu W. Surveillance of Dengue Fever Virus: A Review of Epidemiological Models and Early Warning Systems. PLoS Negl Trop Dis. 2012;6(5):e1648. DOI: 10.1371/journal.pntd.0001648
53. Wang E, Ni H, Xu R, Barrett ADT, Watowich SJ, Gubler DJ. Evolutionary Relationships of Endemic/Epidemic and Sylvatic Dengue Viruses. J Virol. 2000;74(7):3227–34.

DOI: 10.1128/jvi.74.7.3227-3234.2000
54. Watts DM, Whitmire RE, Burke DS, Nisalak A, Harrison BA. Effect of Temperature on the Vector Efficiency of Aedes aegypti for Dengue 2 Virus. Am J Trop Med Hyg. 1987;36(1):143–52. DOI: 10.4269/ajtmh.1987.36.143
55. Schneider BS, Soong L, Zeidner NS, Higgs S. Aedes aegyptiSalivary Gland Extracts Modulate Anti-Viral and TH1/TH2 Cytokine Responses to Sindbis Virus Infection. Viral Immunol . 2004;17(4):565–73. DOI: 10.1089/vim.2004.17.565
56. Kabra SK, Jain Y, Singhal T, Ratageri VH. Dengue hemorrhagic fever: Clinical manifestations and management. Indian J Pediatr. 1999;66(1):93–101. DOI: 10.1007/bf02752362
57. Siler JF, Hall MW HA. Dengue: its history, epidemiology, mechanism of transmission, etiology, clinical manifestations, immunity, and prevention. J Sci. 1926;29:1–2. Available from: https://www.cabdirect.org/cabdirect/abstract/19261000360
58. Gubler DJ, Rosen L. A Simple Technique for Demonstrating Transmission of Dengue Virus by Mosquitoes without the Use of Vertebrate Hosts *. Am J Trop Med Hyg. 1976;25(1):146–50. DOI: 10.4269/ajtmh.1976.25.146
59. Tsai CY, Lee K, Lee CH, Yang KD, Liu JW. Comparisons of dengue illness classified based on the 1997 and 2009 World Health Organization dengue classification schemes. Journal of Microbiology, Immunology and Infection. 2013 Aug 1;46(4):271-81.Available from: https://www.sciencedirect.com/science/article/pii/S1684118212001491
60. MD. S. Seroprevalence and its Molecular Characterization of Dengue viruses at Kanpur. Available from: https://shodhgangotri.inflibnet.ac.in/handle/123456789/4730
61. Wilder-Smith A, Chen LH, Massad E, Wilson ME. Threat of Dengue to Blood Safety in Dengue-Endemic Countries. Emerg Infect Dis. 2009;15(1):8–11. DOI: 10.3201/eid1501.071097
62. Stramer SL, Hollinger FB, Katz LM, Kleinman S, Metzel PS, Gregory KR. Emerging infectious disease agents and their potential threat to transfusion safety. Transfusion. 2009;49:1S–29S. DOI: 10.1111/j.1537-2995.2009.02279.x
63. Modis Y, Ogata S, Clements D, Harrison SC. Variable Surface Epitopes in the Crystal Structure of Dengue Virus Type 3 Envelope Glycoprotein. J Virol. 2004;79(2):1223–31. DOI: 10.1128/jvi.79.2.1223-1231.2005
64. de Alwis R, Beltramello M, Messer WB, Sukupolvi-Petty S, Wahala WMPB, Kraus A. In-Depth Analysis of the Antibody Response of Individuals Exposed to Primary Dengue Virus Infection. PLoS Negl Trop Dis. 2011;5(6):e1188. DOI: 10.1371/journal.pntd.0001188
65. Messer WB, de Alwis R, Yount BL, Royal SR, Huynh JP, Smith SA. Dengue virus envelope protein domain I/II hinge determines long-lived serotype-specific dengue immunity. Proc Natl Acad Sci. 2014;111(5):1939–44. DOI: 10.1073/pnas.1317350111
66. de Alwis R, Smith SA, Olivarez NP, Messer WB, Huynh JP, Wahala WMPB. Identification of human neutralizing antibodies that bind to complex epitopes on dengue virions. Proc Natl Acad Sci. 2012;109(19):7439–44. DOI: 10.1073/pnas.1200566109
67. Fibriansah G, Ibarra KD, Ng T-S, Smith SA, Tan JL, Lim X-N. Cryo-EM structure of an antibody that neutralizes dengue virus type 2 by locking E protein dimers. Science (80-). 2015;349(6243):88–91. DOI: 10.1126/science.aaa8651
68. Watanabe S, Chan KWK, Wang J, Rivino L, Lok S-M, Vasudevan SG. Dengue Virus Infection with Highly Neutralizing Levels of Cross-Reactive Antibodies Causes Acute Lethal Small Intestinal Pathology without a High Level of Viremia in Mice. J Virol. 2015;89(11):5847–61. DOI: 10.1128/jvi.00216-15
69. Dejnirattisai W, Jumnainsong A, Onsirisakul N, Fitton P, Vasanawathana S, Limpitikul W. Cross-Reacting Antibodies Enhance Dengue Virus Infection in Humans. Science (80-). 2010;328(5979):745–8. DOI: 10.1126/science.1185181
70. Murphy BR, Whitehead SS. Immune Response to Dengue Virus and Prospects for a Vaccine. Annu Rev Immunol. 2011;29(1):587–619. DOI: 10.1146/annurev-immunol-031210-101315
71. Kuhn RJ, Zhang W, Rossmann MG, Pletnev S V, Corver J, Lenches E. Structure of Dengue Virus. Protein Data Bank, Rutgers University; 2002. DOI: 10.2210/pdb1k4r/pdb
72. Perera R, Khaliq M, Kuhn RJ. Closing the door on flaviviruses: Entry as a target for antiviral drug design. Antiviral Res. 2008;80(1):11–22. DOI: 10.1016/j.antiviral.2008.05.004
73. Muller DA, Young PR. The flavivirus NS1 protein: Molecular and structural biology, immunology, role in pathogenesis and application as a diagnostic biomarker. Antiviral Res. 2013;98(2):192–208. DOI: 10.1016/j.antiviral.2013.03.008
74. Akey DL, Brown WC, Dutta S, Konwerski J, Jose J, Jurkiw TJ. Flavivirus NS1 Structures Reveal Surfaces for Associations with Membranes and the Immune System. Science (80-). 2014;343(6173):881–5. DOI: 10.1126/science.1247749
75. Scaturro P, Cortese M, Chatel-Chaix L, Fischl W, Bartenschlager R. Dengue virus non-structural protein 1 modulates infectious particle production via interaction with the structural proteins. PLoS pathogens. 2015 Nov 12;11(11):e1005277.Available from: https://journals.plos.org/plospathogens/article?id=10.1371/journal.ppat.1005277
76. Mackenzie JM, Jones Mk, Young Pr. Immunolocalization of the Dengue Virus Nonstructural Glycoprotein NS1 Suggests a Role in Viral RNA Replication. Virology. 1996;220(1):232–40. DOI: 10.1006/viro.1996.0307
77. Libraty DH, Young PR, Pickering D, Endy TP, Kalayanarooj S, Green S, et al. High Circulating Levels of the Dengue Virus Nonstructural Protein NS1 Early in Dengue Illness Correlate with the Development of Dengue Hemorrhagic Fever. J Infect Dis. 2002;186(8):1165–8. DOI: 10.1086/343813
78. Beatty PR, Puerta-Guardo H, Killingbeck SS, Glasner DR, Hopkins K, Harris E. Dengue virus NS1 triggers endothelial permeability and vascular leak that is prevented by NS1 vaccination. Sci Transl Med 2015;7(304):304ra141-304ra141. DOI: 10.1126/scitranslmed.aaa3787

79. Modhiran N, Watterson D, Muller DA, Panetta AK, Sester DP, Liu L. Dengue virus NS1 protein activates cells via Toll-like receptor 4 and disrupts endothelial cell monolayer integrity. Sci Transl Med. 2015;7(304):304ra142-304ra142. DOI: 10.1126/scitranslmed.aaa3863
80. Durbin AP, Whitehead SS. Next-Generation Dengue Vaccines: Novel Strategies Currently Under Development. Viruses. 2011;3(10):1800–14. DOI: 10.3390/v3101800
81. Bhamarapravati N. Hemostatic Defects in Dengue Hemorrhagic Fever. Clin Infect Dis. 1989;11(Supplement_4):S826–9. DOI: 10.1093/clinids/11.supplement_4.s826
82. N. B. Pathology of dengue infections. Dengue and dengue hemorrhagic fever. New York,: CAB International; 1997. 117-32 p.
83. Bhamarapravati N, Tuchinda P, Boonyapaknavik V. Pathology of Thailand haemorrhagic fever: a study of 100 autopsy cases. Ann Trop Med Parasitol. 1967;61(4):500–10. DOI: 10.1080/00034983.1967.11686519
84. Rigau-Pérez JG, Clark GG, Gubler DJ, Reiter P, Sanders EJ, Vance Vorndam A. Dengue and dengue haemorrhagic fever. Lancet. 1998;352(9132):971–7. DOI: 10.1016/s0140-6736(97)12483-7
85. Kalayanarooj S, Vaughn DW, Nimmannitya S, Green S, Suntayakorn S, Kunentrasai N. Early Clinical and Laboratory Indicators of Acute Dengue Illness. J Infect Dis. 1997;176(2):313–21. DOI: 10.1086/514047
86. Phuong CXT, Nhan NT, Wills B, Kneen R, Ha NTT, Mai TTT. Evaluation of the World Health Organization standard tourniquet test and a modified tourniquet test in the diagnosis of dengue infection in Viet Nam. Trop Med Int Heal. 2002;7(2):125–32. DOI: 10.1046/j.1365-3156.2002.00841.x
87. Balmaseda A, Pérez Ma, Harris Eva, Rocha J, Idiaquez W, Cuadra R. Assessment Of The World Health Organization Scheme For Classification Of Dengue Severity In Nicaragua. Am J Trop Med Hyg. 2005;73(6):1059–62. DOI: 10.4269/ajtmh.2005.73.1059
88. Srikiatkhachorn A, Krautrachue A, Ratanaprakarn W, Wongtapradit L, Nithipanya N, Kalayanarooj S. Natural History of Plasma Leakage in Dengue Hemorrhagic Fever. Pediatr Infect Dis J. 2007;26(4):283–90. DOI: 10.1097/01.inf.0000258612.26743.10
89. Martinez-Torres E, Polanco-Anaya AC P-SE. Why and how children with dengue die. Rev Cuba de. 2008;
90. Boonnak K, Slike BM, Burgess TH, Mason RM, Wu S-J, Sun P. Role of Dendritic Cells in Antibody-Dependent Enhancement of Dengue Virus Infection. J Virol. 2008;82(8):3939–51. DOI: 10.1128/jvi.02484-07
91. Carvalho de Macedo F, Nicol AF, Cooper LD, Yearsley M, Cordovil Pires AR, Nuovo GJ. Histologic, Viral, and Molecular Correlates of Dengue Fever Infection of the Liver Using Highly Sensitive Immunohistochemistry. Diagnostic Mol Pathol. 2006;15(4):223–8. DOI: 10.1097/01.pdm.0000213462.60645.cd
92. Durbin AP, Vargas MJ, Wanionek K, Hammond SN, Gordon A, Rocha C. Phenotyping of peripheral blood mononuclear cells during acute dengue illness demonstrates infection and increased activation of monocytes in severe cases compared to classic dengue fever. Virology. 2008;376(2):429–35. DOI: 10.1016/j.virol.2008.03.028
93. Ho L, Shaio M, Chang D, Liao C, Lai J. Infection of Human Dendritic Cells by Dengue Virus Activates and Primes T Cells Towards Th0-Like Phenotype Producing Both Th1 and Th2 Cytokines. Immunol Invest. 2004;33(4):423–37. DOI: 10.1081/imm-200038680
94. Ho L-J, Wang J-J, Shaio M-F, Kao C-L, Chang D-M, Han S-W. Infection of Human Dendritic Cells by Dengue Virus Causes Cell Maturation and Cytokine Production. J Immunol. 2001;166(3):1499–506. DOI: 10.4049/jimmunol.166.3.1499
95. Huerre MR, Lan NT, Marianneau P, Hue NB, Khun H, Hung NT, Khen NT, Drouet MT, Huong VT, Buisson Y D V. Liver histopathology and biological correlates in five cases of fatal dengue fever in Vietnamese children. Virchows Arch. 2001;438(2):107–15. Available from: https://link.springer.com/article/10.1007/s004280000329
96. Jessie K, Fong MY, Devi S, Lam SK, Wong KT. Localization of Dengue Virus in Naturally Infected Human Tissues, by Immunohistochemistry and In Situ Hybridization. J Infect Dis. 2004;189(8):1411–8. DOI: 10.1086/383043
97. Kou Z, Quinn M, Chen H, Rodrigo WWSI, Rose RC, Schlesinger JJ. Monocytes, but not T or B cells, are the principal target cells for dengue virus (DV) infection among human peripheral blood mononuclear cells. J Med Virol. 2007;80(1):134–46. DOI: 10.1002/jmv.21051
98. Kwan W-H, Helt A-M, Maranon C, Barbaroux J-B, Hosmalin A, Harris E. Dendritic Cell Precursors Are Permissive to Dengue Virus and Human Immunodeficiency Virus Infection. J Virol. 2005;79(12):7291–9. DOI: 10.1128/jvi.79.12.7291-7299.2005
99. Libraty DH, Pichyangkul S, Ajariyakhajorn C, Endy TP, Ennis FA. Human Dendritic Cells Are Activated by Dengue Virus Infection: Enhancement by Gamma Interferon and Implications for Disease Pathogenesis. J Virol. 2001;75(8):3501–8. DOI: 10.1128/jvi.75.8.3501-3508.2001
100. Huy NT, Van Giang T, Thuy DH, Kikuchi M, Hien TT, Zamora J, Hirayama K. Factors associated with dengue shock syndrome: a systematic review and meta-analysis. PLoS neglected tropical diseases. 2013 Sep 26;7(9):e2412.Available from: https://journals.plos.org/plosntds/article?id=10.1371/journal.pntd.0002412
101. Whitehorn J, Farrar J. Dengue. Br Med Bull. 2010;95(1):161–73. DOI: 10.1093/bmb/ldq019
102. Heilman JM, De Wolff J, Beards GM, Basden BJ. Dengue fever: a Wikipedia clinical review. Open medicine. 2014;8(4):e105.Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4242787/
103. Organization WH. Strategies for the prevention of blindness in national programmes: a primary health care approach. World Health Organization; 1997.
104. Swaminathan S, Khanna N. Experimental Dengue Vaccines. Molecular Vaccines. Springer Vienna; 2013. p. 135–51. DOI: 10.1007/978-3-7091-1419-3_7
105. Ahmed FU, Mahmood CB, Sharma JD, Hoque SM, Zaman R HM. Dengue and Dengue Haemorrhagic Fever in children during the 2000 outbreak in Chittagong, Bangladesh. Dengue Bull. 2001;25:33–9. Available from:

https://apps.who.int/iris/bitstream/handle/10665/163693/dbv25p33.pdf
106. Narayanan M, Aravind MA, Thilothammal N, Prema R, Sargunam CR RN. Dengue fever epidemic in Chennai-a study of clinical profile and outcome. Indian Paediatr. 2002;39(11):1027–33. Available from: https://www.indianpediatrics.net/nov2002/nov-1027-1033.htm
107. Radakovic-Fijan S, Graninger W, Mller C, Hnigsmann H, Tanew A. Dengue hemorrhagic fever in a British travel guide. J Am Acad Dermatol. 2002;46(3):430–3. DOI: 10.1067/mjd.2002.111904
108. Gibbons R V. Dengue: an escalating problem. BMJ. 2002;324(7353):1563–6. DOI: 10.1136/bmj.324.7353.1563
109. Thomas EA, John M, Bhatia A. Cutaneous manifestations of dengue viral infection in Punjab (north India). Int J Dermatol. 2007;46(7):715–9. DOI: 10.1111/j.1365-4632.2007.03298.x
110. Chadwick D, Arch B, Wilder-Smith A, Paton N. Distinguishing dengue fever from other infections on the basis of simple clinical and laboratory features: Application of logistic regression analysis. J Clin Virol. 2006;35(2):147–53. DOI: 10.1016/j.jcv.2005.06.002
111. Kabra SK, Juneja R, Jain Y, Singhal T, Dar L, Kothari SS BS. Myocardial dysfunction in children with dengue haemorrhagic fever. Natl Med J India. 1998;11:59–61. Available from: https://www.researchgate.net/profile/Shobha_Broor/publication/13659383_Myocardial_dysfunction_in_children_with_dengue_haemorrhagic_fever/links/0fcfd5140203f55cf9000000.pdf
112. Sabin AB. Research on Dengue during World War II 1. Am J Trop Med Hyg. 1952;1(1):30–50. DOI: /10.4269/ajtmh.1952.1.30
113. Dietz V, Gubler DJ, Ortiz S, Kuno G, Casta-Velez A, Sather GE, Gomez I VE. The 1986 dengue and dengue hemorrhagic fever epidemic in Puerto Rico: epidemiologic and clinical observations. Puerto Rico Heal Sci journal. 1996;15(3):201–10. Available from: https://europepmc.org/abstract/med/8994286
114. Halstead SB, Lan NT, Myint TT, Shwe TN, Nisalak A, Kalyanarooj S. Dengue Hemorrhagic Fever in Infants: Research Opportunities Ignored. Emerg Infect Dis. 2002;8(12):1474–9. DOI: 10.3201/eid0812.020170
115. Gubler DJ, Eram S, Lubis I, Gunarso S, Suharyono W. Epidemic Dengue 3 in Central Java, Associated with Low Viremia in Man *. Am J Trop Med Hyg. 1981;30(5):1094–9. DOI: 10.4269/ajtmh.1981.30.1094
116. SP S. Demam berdarah dengue pada anak di Jakarta. University of Indonesia, Jakarta.; 2018.
117. Sumarmo HW, Jahja E, Gubler DJ, Suharyono W SK. Clinical observations on virologically confirmed fatal dengue infections in Jakarta, Indonesia. Bull World Health Organ. 1983;61(4):693. Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2536140/
118. F. I. Dengue and hemorrhagic fever J Porterfield, Exotic Viral Infections. London: Kass Handbook of Infectious Diseases, Chapman and Hall Medical Editions,; 1995.
119. Chiu Y-C, Chiu K-W, Kee K-M, Wu K-L, Kuo C-H, Changchien C-S. Endoscopic Findings And Management Of Dengue Patients With Upper Gastrointestinal Bleeding. Am J Trop Med Hyg. 2005;73(2):441–4. DOI: 10.4269/ajtmh.2005.73.441
120. La Russa VF, Innis BL. 11 Mechanisms of dengue virus-induced bone marrow suppression. Baillieres Clin Haematol. 1995;8(1):249–70. DOI: 10.1016/s0950-3536(05)80240-9
121. Rosenfeld SJ, Young NS. Viruses and bone marrow failure. Blood Rev. 1991;5(2):71–7. DOI: 10.1016/0268-960x(91)90037-d
122. Phanichyakarn P, Pongpanich B, Israngkura PB, Dhanamitta S, Valyasevi A KC. Studies on Dengue hemorrhagic fever. III. Serum complement (C3) and platelet studies. J Med Assoc Thailand. 1977;60(7):301–6. Available from: https://www.cabdirect.org/cabdirect/abstract/19782900542
123. Richards AL, Bagus R, Baso SM, Graham RR, Punjabi N, Corwin AL. The First Reported Outbreak of Dengue Hemorrhagic Fever in Irian Jaya, Indonesia. Am J Trop Med Hyg. 1997;57(1):49–55. DOI: 10.4269/ajtmh.1997.57.49
124. Chakravarty A, Kumar A MS. Detection of dengue infection by combining the use of an NS1 antigen based assay with antibody detection. Southeast Asian J Trop Med Public Health. 2011;42(2):297. Available from: http://www.tm.mahidol.ac.th/seameo/2011-42-2/08-4806.pdf
125. Gubler DJ SG. Laboratory diagnosis of dengue and dengue hemorrhagic fever. Simp Int sobre Febre Amarela e Dengue. 1988;15:291–322. Available from: https://www.researchgate.net/publication/292814286_Laboratory_diagnosis_of_dengue_and_dengue_hemorrhagic_fever_In_da_Cunha_F_Fonseca_ed_Simposio_Internacional_sobre_Febre_Amarela_e_Dengue/amp
126. Guzmán MG KG. Advances in dengue diagnosis. Clin Diagn Lab Immunol. 1996;3(6):621. Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC170421/
127. Gubler D. J., G.Vorndam V. KG. Laboratory diagnosis of dengue virus infections. in Dengue and dengue hemorrhagic fever. London, United Kingdom: CAB International,; 1997. 313-334 p.
128. Mishra B, Sharma M, Pujhari SK, Ratho RK, Gopal DVRS, Kumar CVMN. Utility of multiplex reverse transcriptase-polymerase chain reaction for diagnosis and serotypic characterization of dengue and chikungunya viruses in clinical samples. Diagn Microbiol Infect Dis. 2011;71(2):118–25. DOI: 10.1016/j.diagmicrobio.2011.06.020
129. Kadhiravan T, Saxena A, Singh A, Broor S, Sharma SK, Mitra DK. Association of Intracellular TH1-TH2 Balance in CD4+ T-cells and MIP-1α in CD8+ T-cells with Disease Severity in Adults with Dengue. Immune Netw. 2010;10(5):164. DOI: 10.4110/in.2010.10.5.164
130. Simmons CP, Farrar JJ, van Vinh Chau N, Wills B. Dengue. New England Journal of Medicine. 2012 Apr 12;366(15):1423-32. Available from: http://clinicalevidence.pbworks.com/w/file/fetch/52723769/DENGUE%202012.pdf
131. Simmons CP, Farrar JJ, van Vinh Chau N, Wills B. Dengue. N Engl J Med. 2012;366(15):1423–32. DOI: 10.1056/nejmra1110265
132. Khetarpal N, Khanna I. Dengue Fever: Causes, Complications, and Vaccine Strategies. J Immunol Res. 2016;2016:1–14. DOI: 10.1155/2016/6803098

133. Soni A, Chugh K, Sachdev A, Gupta D. Management of dengue fever in ICU. Indian J Pediatr. 2001;68(11):1051–5. DOI: 10.1007/bf02722356
134. Nhan NT, Phuong CXT, Kneen R, Wills B, Van My N, Phuong NTQ. Acute Management of Dengue Shock Syndrome: A Randomized Double-Blind Comparison of 4 Intravenous Fluid Regimens in the First Hour. Clin Infect Dis. 2001;32(2):204–13. DOI: 10.1086/318479
135. Damonte E, Matulewicz M, Cerezo A. Sulfated Seaweed Polysaccharides as Antiviral Agents. Curr Med Chem. 2004;11(18):2399–419. DOI: 10.2174/0929867043364504
136. Crance JM, Scaramozzino N, Jouan A, Garin D. Interferon, ribavirin, 6-azauridine and glycyrrhizin: antiviral compounds active against pathogenic flaviviruses. Antiviral Res. 2003;58(1):73–9. DOI: 10.1016/s0166-3542(02)00185-7
137. Yin Z, Chen Y-L, Schul W, Wang Q-Y, Gu F, Duraiswamy J. An adenosine nucleoside inhibitor of dengue virus. Proc Natl Acad Sci. 2009;106(48):20435–9. DOI: 10.1073/pnas.0907010106
138. Noble CG, Chen Y-L, Dong H, Gu F, Lim SP, Schul W. Strategies for development of dengue virus inhibitors. Antiviral Res. 2010;85(3):450–62. DOI: 10.1016/j.antiviral.2009.12.011
139. Murrell S, Wu S-C, Butler M. Review of dengue virus and the development of a vaccine. Biotechnol Adv. 2011;29(2):239–47. DOI: 10.1016/j.biotechadv.2010.11.008
140. Sin Leo Y, Wilder-Smith A, Archuleta S, Shek LP, Chong CY, Nam Leong H. Immunogenicity and safety of recombinant tetravalent dengue vaccine (CYD-TDV) in individuals aged 2–45 years. Hum Vaccin Immunother. 2012;8(9):1259–71. DOI: 10.4161/hv.21224
141. Mahoney R, Chocarro L, Southern J, Francis DP, Vose J, Margolis H. Dengue Vaccines Regulatory Pathways: A Report on Two Meetings with Regulators of Developing Countries. PLoS Med. 2011;8(2):e1000418. DOI: 10.1371/journal.pmed.1000418
142. Guirakhoo F, Kitchener S, Morrison D, Forrat R, McCarthy K, Nichols R. Live Attenuated Chimeric Yellow Fever Dengue Type 2 (ChimeriVax^{TM}-DEN2) Vaccine: Phase I Clinical Trial for Safety and Immunogenicity: Effect of Yellow Fever Pre-immunity in Induction of Cross Neutralizing Antibody Responses to All. Hum Vaccin. 2006;2(2):60–7. DOI: 10.4161/hv.2.2.2555
143. Laoprasopwattana K, Libraty DH, Endy TP, Nisalak A, Chunsuttiwat S, Ennis FA. Antibody-Dependent Cellular Cytotoxicity Mediated by Plasma Obtained before Secondary Dengue Virus Infections: Potential Involvement in Early Control of Viral Replication. J Infect Dis. 2007;195(8):1108–16. DOI: 10.1086/512860
144. García G, Arango M, Pérez AB, Fonte L, Sierra B, Rodríguez-Roche R. Antibodies from patients with dengue viral infection mediate cellular cytotoxicity. J Clin Virol. 2006;37(1):53–7. DOI: 10.1016/j.jcv.2006.04.010
145. Hombach J. Vaccines against dengue: a review of current candidate vaccines at advanced development stages. Rev Panam Salud Pública. 2007;21(4):254–60. DOI: 10.1590/s1020-49892007000300011
146. Sanfoi. Dengue Vaccine Succeeds in Reducing Disease. Study Shows‖ By AlbertinaTorsoli Apr. 2014;2:27.
147. Beck S. Moving beyond the linear model of expertise? IPCC and the test of adaptation. Reg Environ Chang. 2010;11(2):297–306. DOI: 10.1007/s10113-010-0136-2
148. Mutheneni SR, Morse AP, Caminade C, Upadhyayula SM. Dengue burden in India: recent trends and importance of climatic parameters. Emerg Microbes Infect. 2017;6(1):1–10. DOI: 10.1038/emi.2017.57
149. Sanofi awaits govt approval to launch dengue vaccine in India. India S. 2019 [cited 2019 Jun 11]. Available from: http://www.newindianexpress.com/nation/2016/oct/06/sanofi-awaits-govt-approval-to-launch-dengue-vaccine-in-india-1525666.html?pm=210 (accessed 22 October 2016).
150. Mohan DS, Singh K PY. Atypical skin manifestations of dengue fever. Indian J Child Health. 2018;5(6):450–2. Available from: https://atharvapub.net/index.php/IJCH/article/view/1009