Contents lists available at ScienceDirect

Asian Pacific Journal of Tropical Medicine

journal homepage:www.elsevier.com/locate/apjtm

Document heading doi: 10.1016/S1995-7645(14)60016-X

Clinical implications and treatment of dengue

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ARTICLE INFO

Article history:
Received 10 September 2013
Received in revised form 15 November 2013
Accepted 15 January 2014
Available online 20 March 2014

Keywords:
Dengue
DHF
DSS
Aedes
Flavivirus

ABSTRACT

Dengue is a common pathogenic disease often proving fatal, more commonly affecting the tropics. Aedes mosquito is the vector for this disease, and outbreaks of dengue often cause mass damage to life. The current review is an effort to present an insight into the causes, etiology, symptoms, transmission, diagnosis, major organs affected, mitigation and line of treatment of this disease with special emphasis on drugs of natural origin. The disease has a potential to spread as an endemic, often claiming several lives and thus requires concerted efforts to work out better treatment options. Traditional medicine offers an alternative solution and could be explored as a safer treatment option. Development of a successful vaccine and immunization technique largely remains a challenge and a better antiviral approach needs to be worked out to complement the supportive therapy. No single synthetic molecule has found to be wholly effective enough to offer curative control and the line of treatment mostly utilizes a combination of fluid replacement and antipyretics-analgesics like molecules to provide symptomatic relief.

1. Introduction

Dengue (DEN) virus, a member of the genus *Flavivirus* (family Flaviviridae), is one of the most rapidly spreading mosquito-borne human pathogens in the tropics (Figure 1). DEN viruses are classified into four serotypes (DEN-1, DEN-2, DEN-3 and DEN-4), causing a spectrum of illnesses ranging from a flu-like disease dengue fever (DF) to dengue hemorrhagic fever (DHF), a fulminating illness which can progress to dengue shock syndrome (DSS) and death[1]. Today DF and DHF/DSS are considered the most important arthropod-borne viral diseases in terms of morbidity and mortality[2]. The incidence of dengue has grown dramatically around the world in recent decades. Over 2.5 billion people-over 40% of the world's population are now at risk from dengue. WHO currently estimates there may be 50-100 million dengue infections worldwide every year. Before 1970, only nine countries had experienced severe dengue epidemics. The disease is now endemic in more than 100 countries in Africa, the Americas, the Eastern Mediterranean, South-east Asia and the Western Pacific. South-east Asia and the Western Pacific regions are the most seriously affected. Since 2003, dengue cases have risen dramatically in Singapore. In 2004, there was a record 9 459 cases notified with eight deaths, with the highest incidence of disease in young adults aged 15-24 years. More than three quarters of all dengue cases in Singapore were hospitalized[3].

The African and Eastern Mediterranean regions have also recorded more outbreaks of the disease in the last ten years. In a recent publication, 22 countries in Africa have reported sporadic cases or outbreaks of dengue from 1960-2010[4]. In 2010, indigenous transmission of dengue was also reported in two countries of Europe. Urbanization, rapid movement of people and goods, favorable climatic conditions and lack of trained staff have all contributed to the global increase of dengue. The "official" number of dengue cases in India is 30 000 the actual number, according to the New York Times,

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is more than 1 000 times that. But the actual dengue cases in India are more than 37 million, according to experts[5].

Figure 1. Mosquito *A. aegypti*.

1.1. Structure

Dengue viruses are spherical, lipid-enveloped that contain a positive strand RNA genome of approximately 10 200 nucleotides coding for three structural proteins (capsid, membrane and envelope) and seven nonstructural proteins (NS1, NS2a, NS2b, NS3, NS4a, NS4b, NS5) (Figures 2 and 3). The envelope protein (E) plays a key role in several important processes including receptor binding, blood cell hemagglutination, induction of a protective immune response, membrane fusion and virion assembly[6]. This is a glycoprotein of approximately 55 kDa, with 3 distinct domains. Using X-ray crystallography, these domains have been characterized for DENV-2 and DENV-3. Domain I is located in the center, and domain Ⅱ contains an internal fusion loop which is involved in membrane fusion and dimerization of the E protein. Domain Ⅲ is an immunoglobulin-like domain thought to be involved in cell receptor binding. Domain Ⅱ is important, as it contains mostly flavivirus group and sub-group crossreactive epitopes. The M-protein, which is important in the formation and maturation of the viral particle, consists of seven antiparallel β-strands stabilized by three disulphide bonds[7].

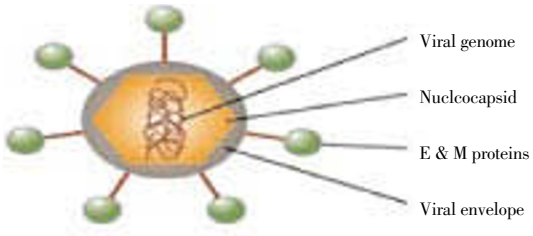

Figure 2. Structure of dengue virus.

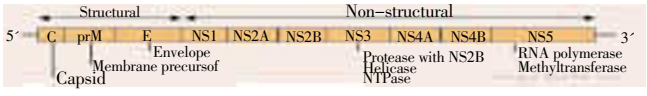

Figure 3. Dengue virus genome.

1.2. Transmission

All four serotypes of dengue virus have a similar natural history, including humans as the primary vertebrate host and *Aedes* mosquitoes of the subgenus *Stegomyia* [especially *Aedes aegypti* (*A. aegypti*), *Aedes albopictus* (*A. albopictus*) and *Aedes polynesiensis*] as the primary mosquito vectors[8]. In Africa, and the Indian subcontinent, dengue viruses also exist in enzootic and epizootic forest cycles with nonhuman primates as the vertebrate host[9,10]. Other vertebrate species are generally not susceptible to dengue viruses, with the exception of neonatal mice, challenged intracerebrally. After ingestion of a blood meal containing virus, there is infection of the epithelial cells lining the midgut. The virus then escapes from the midgut epithelium into the haemocele and infects the salivary gland. Finally, virus is secreted in the saliva, causing infection during probing. The genital tract is also infected and virus may enter the fully developed egg at the time of oviposition[11]. For transmission to occur, the female *A. aegypti* must bite an infected human during the viraemic phase of the illness which generally lasts 4 to 5 days but may last up to 12 days[12]. *A. aegypti* may be infected with 2 different viruses without affecting the yield of either virus[13]. The extrinsic incubation period refers to the time required from itself becomes infective. This period is about 8 to 12 days[14]. The feeding behaviour of the mosquito is characterized by easily interrupted feeding and repeated probing of one or several hosts[15].

Whilst the *A. aegypti* has a generally low susceptibility to oral infection with dengue virus, it remains the most important vector because of its highly domesticated habits[16].

The persistence of dengue virus therefore depends on the development of high viral titres in hosts to ensure transmission in mosquitoes. This vector/virus relationship may be a major factor in selecting and propagating pathogenic strains of dengue in the urban setting[17].

1.3. Signs and symptoms

In endemic areas, most patients with DF are either asymptomatic or present with mild febrile illness[18]. The illness ranges from asymptomatic infection, through undifferentiated fever and benign DF to severe haemorrhagic fever with or without shock syndrome (Figure 4)[19].

Others have more severe illness (5%), and in a small proportion it is life-threatening[20]. The incubation period ranges from 3-14 days, but most often it is 4-7 days[21]. Therefore, travellers returning from endemic areas are unlikely to have dengue if fever or other symptoms start more than 14 days after arriving home[22]. Children often experience symptoms similar to those of the common cold and gastroenteritis (vomiting and diarrhoea)[23] and generally have less severe symptoms than adults, but are more susceptible to the severe complications.

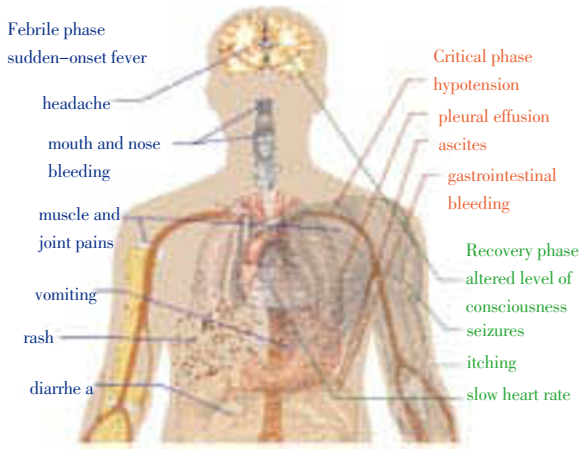

Figure 4. Schematic depiction of the symptoms of dengue fever.

1.4. Clinical course

The characteristic symptoms of dengue are sudden-onset fever, headache (typically located behind the eyes), muscle and joint pains and rashes. The alternative name for dengue, "break-bone fever", comes from the associated muscle and joint pains[24]. The course of infection is divided into three phases: febrile, critical and recovery. The febrile phase involves high fever, often over 40 ℃ (104 °F), and is associated with generalized pain and headache; this usually lasts for two to seven days[25]. At this stage, rashes occur in 50-80% of those with symptoms. It occurs in the first or second day of symptoms as flushed skin, or later in the course of illness (days 4-7), as measles-like rashes[11]. Some petechiae (small red spots that do not disappear when the skin is pressed, which are caused by broken capillaries) can appear at this point as well as mild bleeding from the mucous membranes of the mouth and nose. The fever itself is classically biphasic in nature, breaking and then returning for one or two days, although there is wide variation in how often this pattern actually happens[12,13].

In some people, the disease proceeds to a critical phase, which follows the resolution of the high fever and typically lasts for one to two days. During this phase, there may be significant fluid accumulation in the chest and abdominal cavity due to increased capillary permeability and leakage. This leads to depletion of fluid from the circulation and decreased blood supply to vital organs. During this phase, organ dysfunction and severe bleeding, typically from the gastrointestinal tract, may occur. Shock (DSS) and hemorrhage (DHF) occur in less than 5% of all cases of dengue, however those who have previously been infected with other serotypes of dengue virus ("secondary infection") are at an increased risk[26].

The recovery phase occurs next, with resorption of the leaked fluid into the bloodstream. This usually lasts for two to three days. The improvement is often striking, but there may be severe itching and a slow heart rate. Another rash may occur with either a maculopapular or a vasculitic appearance, which is followed by peeling of the skin. During this stage, a fluid overload state may occur; if it affects the brain, it may cause a reduced level of consciousness or seizures. A feeling of fatigue may last for weeks afterwards[8].

2. Dengue diagnosis

Three factors have been fundamental in dengue diagnosis:

2.1. Development of ELISAs for dengue-specific IgM detection

The diagnostic test employed most commonly is IgG and IgM antibodies assay by ELISA. This test is based on an increase in the IgG titre by a factor of four, is difficult in routine clinical care because a second blood sample is required at the convalescent stage[27]. Primary infections are characterized by an increase in dengue-specific IgM antibodies four to five days after the onset of fever and by an increase in IgG antibodies. Only after seven to ten days, IgM antibodies are detectable for three to six months, whereas IgG antibodies remain detectable for life. In secondary infections, the level of IgM antibodies is lower than in primary infections and the antibodies are sometimes absent, whereas levels of IgG antibodies rise rapidly in secondary infections, even during the acute phase. Thus, the presence of high titers of IgG early in the course of the disease is a criterion for secondary infection. The sensitivity of IgM ELISA ranges from 90%-97% as compared with the gold standard haemagglutination inhibition test. Some false positive reactions can be observed in less than 2% of cases and a low or negative IgM reaction in secondary infections[28]. A number of commercial kits are available in the market used for detection of anti-dengue antibodies[29-36].

2.2. Mosquito cell lines and monoclonal antibody development for viral isolation and identification

This method depends on the availability of host-cell cultures or mice that serve as an indicator of virus infection, ie. cytopathic effects in cell culture, sign of illness or death in mice. This is the most common method for virus isolation[37].

Several continuous mosquito cell lines have been known to be highly susceptible to dengue virus infection. The C6/36 clone of *A. albopictus* cells was chosen for virus isolation because it high sensitivity to dengue virus infection and ease of handling[38,39].

Mosquito cell cultures are a recent addition to dengue virus isolation methodologies. Three cell lines of comparable sensitivity are most frequently used. The C6/36 clone of *A. albopictus* cells is less sensitive than the mosquito inoculation method. Use of these cell lines has provided a

rapid, sensitive and economical method for dengue virus isolation. The sensitivity mosquito cell lines may vary with the strain of the virus. Even though cell cultures are less sensitive than the mosquito inoculation, large number of samples can be processed in a relatively short time[40]. Mammalian cell cultures have many of the same advantages as baby mice for isolation of dengue viruses, such as being expensive, slow and intensive[41].

2.3. Reverse transcriptase PCR

In recent years, reverse transcriptase-polymerase chain reaction (RT-PCR), has been developed for a number of RNA viruses, including dengue viruses. Unlike most other techniques which require screening of pools of mosquitoes to detect viruses, RT-PCR carries out the job with solitary specimen. The technique allows for the multifold biological amplification of viral nucleic acid and has been used to rapidly diagnose viral diseases[42-45]. The primary advantage of this molecular tool lies in the speed at which specimens can be screened for the presence of dengue viruses and also by its highly sensitive and specific detection. It is able to monitor the infection rate in mosquitoes, both adults and larvae, with a high degree of precision[46]. RT-PCR can also detect small quantities of virus-3. This method has also been employed for detecting and typing dengue virus RNA in the field caught *Aedes* mosquitoes, besides determining the infection rate in local *Aedes* mosquitoes[47].

These three methods cover the serological, virological, and molecular diagnosis of dengue[48].

3. Tissues/Organs affected by dengue

Several body organs are affected by dengue in many ways.

3.1. Liver

The spectrum of hepatic involvement in dengue varies from jaundice to elevation in liver enzymes[49]. Hepatomegaly and increased serum liver enzymes are the two most clinical evidence of the involvement of liver in dengue infection. It has been reported that among the two, hepatomegaly is more frequent in patients with DHF than in those with DF. Several studies document raised serum transaminase levels in dengue infection (higher in DHF/DSS than in DF), however these tend to return to normal in 14-21 days after infection[50]. The enzymes, aspartate aminotransferase (AST) and alanine aminotransferase (ALT), are believed to be highly sensitive indicator of liver damage. The studies conducted by Kuo and colleagues on nearly 240 dengue patients from the 1987-1988 outbreak in Taiwan showed elevated levels of AST and ALT in 93.3% and 82.2% of cases respectively[51]. Presence of fever, jaundice and hepatomegaly in endemic areas should arouse the suspicion of dengue hepatitis.

3.2. Heart

Dengue continues to cause significant global morbidity and mortality. Severe disease is characterized by cardiovascular compromise from capillary leakage. Cardiac involvement in dengue has also been reported but has not been adequately studied. Studies have reported patients with severe dengue had septal and right ventricular wall being predominantly affected leading to systolic and diastolic cardiac impairement[52]. During episodes of DHF, cardiac rhythm disorders such as atrioventricular blocks, atrial fibrillation, sinus node dysfunction and ectopic ventricular beats have been reported. Cases of complicated dengue viral infection with acute myocarditis involving young male adults have been reported. Two cases were studied of which one was fatal. The first case presented with typical signs of myocardial disease: chest pain and diaphoresis with myocardial depression. The second case deteriorated rapidly and demised within the first day of admission[53]. However, the incidence of cardiac complications in patients with dengue illness varies greatly[54,55].

Further studies carried out by Wali *et al* showed that 70% of 17 patients with DHF/DSS who underwent myocardial scintigraphic study suffered diffuse left ventricular hypo kinesis with a mean ejection fraction of 40%[55]. Whereas Kabra *et al* reported that 16.7% of 54 children with dengue illness had a decreased left ventricular ejection fraction of <50%[56].

These studies suggest that cardiac complications in dengue illness are not uncommon, but have been under-diagnosed as cases with cardiac complications are clinically mild and self-limited. Although severe cardiac impairment is not commonly reported in dengue infection, it can be life threatening.

3.3. Kidney

Dengue shock syndrome is the most severe form of dengue that can be fatal. Nonresponders to standard therapy need intensive care. A report on the clinical features, complications, and outcomes of DSS not responding to standard therapies and needing supportive care in a tertiary referral intensive care unit of a developing country indicated that nearly one-third died within 3 days of admission to ICU. Peritoneal dialysis increased the risk to 100%[57]. Acute renal failure is rare in dengue fever and it mainly presents as shock induced acute tubular necrosis. It has been observed as a complication of dengue fever in French Guiana and was found to occur in 0.3% of cases in a series of 6 154 patients with DHF. Acute renal failure and multiple organ failure can also be a manifestation of rhabdomyolysis. The role of immune complex in development of renal failure in dengue infection is still unclear. Wiwanitkit discovered that the diameter of dengue virus-immunoglobulin complex is much smaller than the diameter of glomerulus. Thus, he postulated

that immune complex can be entrapped only if a previous glomerular lesion causes narrowing of the glomerulus's diameter, and concluded that the immune complex does not play a significant role in pathogenesis of renal failure in dengue infection. Reports of renal failure because of haemolytic uraemic syndrome are rare[58].

3.4. Eye

Studies on ocular complication in dengue fever have been reported in literature. These ocular manifestations may be a result of inflammatory changes in vascular endothelium resulting in vascular leakage, haemorrhage and ischaemia. Ocular manifestations reported in DHF are subconjunctival hemorrhage, intraretinal haemorrhage, macular haemorrhage, vitreous hemorrhage, Roth spots, cotton wool spots, retinal oedema, disc oedema or choroidal effusion. A characteristic maculopathy has only rarely been reported and may be due to actual infection of macular tissue. This maculopathy may manifest itself reduced visual acuity, abnormal visual fields or electrophysiological studies. Good recovery is the norm but exceptions have been seen in patients with macular hemorrhages[59]. The spectrum of ophthalmologic manifestations would lead one to conclude that several pathophysiologic processes are involved. The first and most obvious pathogenesis would be the thrombocytopenic state, with its resultant bleeding tendency, which gives rise to increased incidence of hemorrhage. These hemorrhages manifest as retinal blot hemorrhages in the macula and retinal periphery. Most patients with dengue-related ophthalmic complications recover spontaneously without any treatment. Despite this, isolated reports of cases of dengue ophthalmic complications with poor visual acuity refractory to treatment have been reported[60].

3.5. Blood

In severe condition of dengue, the fibrinolytic system has also been found to get greatly disturbed. Such fibrinolytic abnormalities suggest a stressed haemostatic system that may ultimately result in overt disseminated intravascular coagulation[61].

Thrombocytopenia is common in DF and always found in dengue hemorrhagic fever/ dengue shock syndrome[62]. However, the pathogenesis of thrombocytopenia is unknown and it is believed that dengue- virus-induces bone marrow suppression leading to depressed platelet synthesis and thrombocytopenia[63].

Another study reported that dengue-2 virus can bind to human platelets in the presence of virus-specific antibodies, and proposed that the immune-mediated clearance of platelets was involved in the pathogenesis of thrombocytopenia in DHF/DS[64]. The titre of IgM anti-platelet antibodies is higher in DHF/DSS than in DF patients. The presence of these auto antibodies not only induces platelet lysis via complement activation, but also inhibits ADP-induced platelet aggregation[65]. The production of anti-platelet autoantibodies whose affinities are enhanced in secondary infection not only explains the immune-mediated destruction of platelets, but also raises an important issue of the long-term safety of a dengue vaccine.

3.6. Brain

Encephalopathy in DHF is an atypical manifestation and may occur because of various reasons such as intracranial haemorrhage, cerebral oedema, hyponatremia, cerebral anoxia, fulminant hepatic failure with portosystemic encephalopathy, renal failure or release of toxic products. The signs and symptoms of neurological involvement appear in various forms, including depressed sensitivity, convulsions, neck rigidity, pyramidal signs, headache, papilloedema, myoclonus and behavioural disorders. Post-infectious sequelae are mainly amnesia, dementia, manic psychosis, Reye's syndrome and meningo encephalitis. Pathophysiology may include the following factors: direct tissue lesion caused by the virus because of its neurotropicity, capillary haemorrhage, disseminated intravascular coagulation and metabolic disorders[66].

In a study, it was reported that dengue virus was observed in the cerebrospinal fluid (CSF) in five of six patients presenting with encephalitis, indicating that the virus may cross the blood-brain barrier and directly invade the brain. In another study, samples of 150 individuals suspect of an infection disease and with fatal outcomes were investigated for evidence of the presence of DENV. The sampling was made up of 150 CSF, 120 tissue samples, and 109 blood specimens. Out of 150 studied patients, 84 were dengue positive. Evidence of the presence of DENV was found in 41 CSF, showing the following neurologic diagnosis: 46.3% encephalitis, 34.1% meningoencephalitis, and 19.5% meningitis, giving a frequency of 48.8% of the 84 dengue-positive cases. The major clinical manifestations observed on these individuals were fever, headache, mental irritability, breathless, vomiting, muscle pain, tiredness, abdominal pain, somnolence, restlessness, dizziness, cough, seizure, coma, and neck stiffness[67,68].

3.7. Pancreas

Acute pancreatitis is a rare complication of dengue fever. Pancreas may be affected due to direct viral invasion or hypotension in dengue hemorrhagic fever. Case studies of dengue lead to an emphasis on the possibility of dengue related pancreatitis in patients with abdominal pain and fever. This will help the patient to receive adequate monitoring and supportive care directed at the management of dengue along with the management of acute pancreatitis. The exact pathogenesis in the development of acute

abdomen from infection with dengue virus is unknown. However, it might be due to virus invasion of the gallbladder wall, appendicular wall or pancreas, which causes oedematous change. Recently a case study was reported wherein acute pancreatitis as the complication of DHF was studied. Although rare, this complication can cause more severe fatal condition, and difficulties in treatment. Acute pancreatitis is an uncommon but life-threatening complication of dengue fever[69]. Early diagnosis and quick management of dengue related complications is necessary to improve the patient's condition and survival[70].

3.8. Effect on Endothelial cells

The endothelium is the primary fluid barrier of the vasculature and ultimately the effects of dengue virus infection that bring about capillary leakage impact endothelial cell barrier functions. Infection of endothelium by dengue virus alters capillary permeability, permits virus replication and induces responses that recruit immune cells to the endothelium[71]. In a postmortem study, Jessie *et al* reported dengue virus antigen in sinusoidal ECs in the liver as well as macrophages, lymphoid cells in the spleen, the vascular endothelium of the lung, monocytes within the blood, and kidney tubules[72]. Salgado *et al*. also demonstrated the presence of viral antigen in endothelial cells within the heart and small myocardial vessels of a patient post-mortem[73]. Leakage of the vascular endothelium is a central component of dengue virus disease and studies discussed here suggest that the dengue infected endothelium may contribute to pathogenic immune responses and immune targeting of the endothelium.

3.9. Pregnant patients

Dengue in pregnancy must be carefully differentiated from preeclampsia. An overlap of signs and symptoms, including thrombocytopenia, capillary leak, impaired liver function, ascites and decreased urine output may make this clinically challenging. Pregnant women with dengue fever respond well to the usual therapy of fluids, rest and antipyretics. An awareness of the clinical and laboratory manifestations of dengue in pregnancy should allow its early recognition and the institution of appropriate treatment. If the mother acquires infection in the peripartum period, newborns should be evaluated for dengue with serial platelet counts and serological studies[74,75]. Dengue fever in pregnancy most often is treated conservatively. Complications like pre-eclampsia, pre-term labour, increased risk of caesarean section and fetal transmission have been noted. Platelet count may fall rapidly but no active intervention required unless patient is in labour or has bleeding disorder[76].

4. Treatment against dengue

Treatment of dengue may involve following four parameters which may or may not be successful.

4.1. Vaccination

The development of a dengue vaccine has unique challenges. The four dengue serotypes circulate globally and infection with one dengue serotype confers life-long protection against re-infection with the same serotype, but only short-term protection against the other 3 serotypes. Moreover, dengue is unique in that sequential infections with different serotypes increase the risk of developing severe and potentially lethal disease[77]. There is limited understanding of how the virus interacts with the immune system and how certain types of pre-existing immunity can exacerbate disease. Therefore, a safe and effective dengue vaccine must be tetravalent and induce strong and long-lived protection against all 4 serotypes simultaneously in order to avoid the risk of sensitizing the vaccine recipient to severe disease[78]. There are a number of dengue vaccine candidates in different stages of development. The more advanced consist of tetravalent mixtures of live attenuated viruses representing each serotype. Different attenuation mechanisms have been used to develop three of the leading candidates:

a) Chimerization with yellow fever 17D vaccine strain, developed by Sanofi Pasteur.

b) Combinations of defined mutations/deletions and chimeras, developed by NIH.

c) Chimerization with dengue 2 PDK53 virus, attenuated by cell culture passage, developed by Inviragen.

But several disadvantages are associated with all live attenuated vaccine:

1)Single inoculation is not sufficient to induce protection to all 4 serotypes, probably due to viral interference among the live components of the vaccine.

2)Booster doses are not effective when administered less than 6 months apart.

Therefore, live attenuated vaccines require three immunizations over an extended dosing schedule of 12 months to elicit balanced neutralizing antibody responses to all 4 serotypes. As a result, there is a risk that an incomplete response induced by the initial immunizations will enhance disease if infection occurs during the window between the first and the last immunization.

4.2. Medication /Treatment

Dengue fever is usually a self-limited illness. There is no specific antiviral treatment currently available for dengue fever. Supportive care with analgesics, fluid replacement and bed rest is usually sufficient[79].

No medication has been found to be useful in treatment

dengue and its association disorder or complication. However, Acetaminophen may be used to treat fever and relieve other symptoms. Aspirin, nonsteroidal anti-inflammatory drugs (NSAIDs) and corticosteroids should be avoided. Management of severe dengue requires careful attention to fluid management and proactive treatment of hemorrhage. Single-dose methylprednisolone showed no mortality benefit in the treatment of dengue shock syndrome in a prospective, randomized, double-blind, placebo-controlled trial[80].

The Novartis Institute for Tropical Diseases (NITD) in Singapore is carrying out research to find inhibitors of dengue viral target proteins to reduce the viral load during active infection[81].

Some measures can be taken as a supportive care in dengue fever. They can be classified in to two categories:

4.2.1. For suspected dengue

1) Patients with moderate dehydration caused by high fever and vomiting are recommended oral rehydration therapy.

2) Should have their platelet count and hematocrit measured daily from the third day of illness until 1-2 days after defervescence.

3) Patients with clinical signs of dehydration and a rising hematocrit level or falling platelet count should have intravascular volume deficits replaced under close observation[82].

4.2.2. For severe dengue

1)Severe dengue requires careful attention to fluid management and proactive treatment of hemorrhage. Admission to an intensive care unit is indicated for patients with dengue shock syndrome.

2)Patients may need a central intravenous line for volume replacement and an arterial line for accurate blood pressure monitoring and frequent blood tests[83].

3)Intravascular volume deficits should be corrected with isotonic fluids such as Ringer lactate solution.

4)Boluses of 10-20 mL/kg should be given over 20 minutes and may be repeated.

5)If this fails to correct the deficit, the hematocrit value should be determined. If it is rising, limited clinical information suggests that a plasma expander may be administered. Starch, dextran 40, or albumin 5% at a dose of 10-20 mL/kg may be used. One study has suggested that starch may be preferable because of hypersensitivity reactions to dextran[84].

4.3. Natural treatment options for dengue fever

Natural drugs possess activity against *A. aegypti* by their antiviral mechanism, larvicidal and mosquitocidal action and mosquito repellants property. Some of the important natural cures are enumerated below.

1) *Eupatorium perfoliatum* (Boneset): Bonoset is a commonly available plant which plays an important role in management of dengue fever. It is best consumed in the form of a tea[85].

2) *Boesenbergia rotunda* (Temu kunci): A paste made with the roots is often used for treatment. The use of the herb reduces muscular pain and nausea which causes great distress in people who suffer from this condition[86].

3) *Kaempferia parviflora*: Leaves and stem are used as herbal remedy against virus. Studies have shown that DEN 2 particles are directly inactivated by some bioactive compound in Kaempferia parviflora[87].

4) *Carica papaya*: Juice of the leaves is utilized for increasing the platelet count[88].

5) *Solanum villosum*: Berry extract is reported to possess larvicidal activity against *Stegomyia aegepti*[89].

6) *Combretum collinum*: Extract of shoot bark possess larvicidal against *A. aegypti*[90].

7) *Azadirecta indica* and *Pongamia glabra*: Herbal formulation named PON-NEEM imparts larvicidal, ovicidal, oviposition deterrant activity against *A. aegypti* and *A. albopictus*[91].

8) *Nyctanthes arbortistis*, *Catharanthus roseus*, *Eupatorium odoratum*: Leaf extract exert larvicidal activity against *A. aegypti*[92].

9) *Citrus limetta*: Extract from peels exert larvicidal activity against *A. aegypti*[93].

10) *Acalypha alnifolia*: Leaf extract exert larvicidal activity against *A. aegypti*, *Aedes stephensi* (*A. stephensi*)[94].

11) *Delonix elata*: Leaf and seed extracts are reported to exert larvicidal and ovicidal activities against *A. aegypti* and *A. stephensi*[95].

4.4. General prevention

The only way to prevent dengue virus acquisition is to avoid being bitten by a vector mosquito. Although this can be accomplished by avoiding travel to areas where dengue is endemic, that is not an ideal strategy because it would require a person to avoid most tropical and subtropical regions of the world, many of which are popular travel and work destinations[96]. Other measures are as follows:

a) Apply N,N-diethyl-3-methylbenzamide-containing mosquito repellant;

b) Wear protective clothing, preferably impregnated with permethrin insecticide;

c) Remain in well-screened or air-conditioned places;

d) The use of mosquito netting is of limited benefit, as *Aedes* are day-biting mosquitoes;

e) Eliminate the mosquito vector using indoor sprays[97,98].

5. Conclusion

The authors aimed at presenting an overview on dengue, a common pathogenic disease. An exhaustive, cumulative and in-depth literature review has been used to present

the details of the etiology, transmission and treatment models with special emphasis on drugs of natural origin. The pathophysiological changes on several major body organs have been dealt in great detail. The myths regarding the disease need to be avoided and the safe bet as always remains: prevention is better than cure!

Conflict of interest statement

We declare that we have no conflict of interest.

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