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An endemic challenge of Dengue – A crucial review.

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Abstract

Dengue fever is a serious threat to global health issues; it leads us to a public health challenge with an economic saddle. Approximately 100 countries are endemic for dengue fever and 40% of the world's population or about 2.5 billion people in the tropical and sub-tropics have an increased risk. It is also known break bone fever, is a self-limited, systematic viral infection transmitted from mosquitoes to humans.. Symptoms include fever, headache, muscle and joint pains, and with a characteristic skin rashes that is similar to measles. In a small proportion of cases, the disease develops into the life-threatening dengue hemorrhagic fever, resulting in bleeding, low levels of blood platelets and blood plasma leakage, or into dengue shock syndrome. To the core of this review are ought to discuss about the symptoms, mechanism of the virus in the host, penetration towards our body, characteristic antibody responses, life cycle, various phases involved in the cycle, efficient vector control strategies, pathogenesis, Diagnosis, ongoing therapies, and its management and prevention.

Keywords: *Aedes aegypti*, Systematic viral infection, DENV-1, DENV-2, DENV- 3, and DENV-4, symptoms, Nonstructural (NS) enzyme.

Introduction

Dengue is the most important arthropod-borne viral infection of human. Dengue fever is spread through the *Aedes aegypti* mosquito are the causative fever. More than 50 million of low-grade fever infections with 400,000 cases of dengue hemorrhagic fever were reported annually, which has caused many deaths of children in several countries in the Asian countries. Dengue viruses belong to the flaviviridae family. Dengue virus has four serotypes, which is based on the type of antibodies produced in the human body after infection, such as DENV-1, DENV-2, DENV- 3, and DENV-4.

The initial symptom of the diseases appears in about 5 to 7 days after the infected mosquito bites the healthy persons. Dengue can infect multiple times because the virus has four different serotypes. Although each infection confers lifelong immunity to the particular serotype, a subsequent infection with a different serotype increases the risk of astringent, much deadlier form known as dengue hemorrhagic fever (DHF). Subsequent symptoms of dengue fever include high fever, rash, and a severe headache (dengue triad). Patients diagnosed with dengue in endemic areas such as South East Asia generally have secondary infection, whereas patients in non-endemic areas are usually diagnosed with primary infection. Characteristic antibody responses to the disease enable serological diagnosis and differentiation between primary and secondary dengue.Table.1 shows the phases in Dengue.

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Table 2. Febrile, critical and recovery phases in dengue		
1	Febrile phase	Dehydration; high fever may cause neurological disturbances and febrile seizures in young children
2	Critical phase	Shock from plasma leakage; severe haemorrhage; Organ impairment
3	Recovery phase	Hypervolaemia (only if intravenous fluid therapy fluid therapy has been excessive and / or has extended into this period

Morphology and pathogenesis

Nonstructural (NS) enzyme such as NS3 protease with NS2B cofactor, NS3 helicase / nucleoside triphospatase (NTPase) / RNA 5 'triphospatase (RTPase), NS5 methyltransferase (Mtase), and NS5 RNA-dependent RNA polymerase (RdRp) were known to have an important role in the replication of dengue virus. Currently, NS3 and NS5 of dengue virus enzyme are the most understood mechanism, making these enzymes as an ideal target for antiviral manufacture of dengue virus.

Transmission

The virus

Fig.1. shows the Dengue virus genome structure with the structural and nonstructural genes. Dengue virus (DEN) is a small single-stranded RNA virus includes four distinct serotypes (DEN 1 to 4). These closely related serotypes of the dengue virus belong to the Genus - Flavivirus, Family - Flaviviridae. The mature dengue virus is spherical shape with a diameter of 50nm containing multiple copies of the three structural proteins, a host-derived membrane bi-layer and a single copy of a positive-sense, single-stranded RNA genome.

Host and viral proteases has capsid C, prM, membrane M, protein and envelope, E and seven nonstructural proteins (NS) cleave the genome. Distinct genotypes or lineages (viruses highly related in nucleotide sequence) have been identified within each serotype with the extensive genetic variability of the dengue serotype. A leading theme in dengue viral evolution is viruses that are "fit" for both human and vector can withstand. Among them, "Asian" genotypes of DEN-2 and DEN-3 are frequently associated with severe disease accompanying secondary dengue infections. Intra-host viral diversity (quasispecies) has also been described in individual hosts.

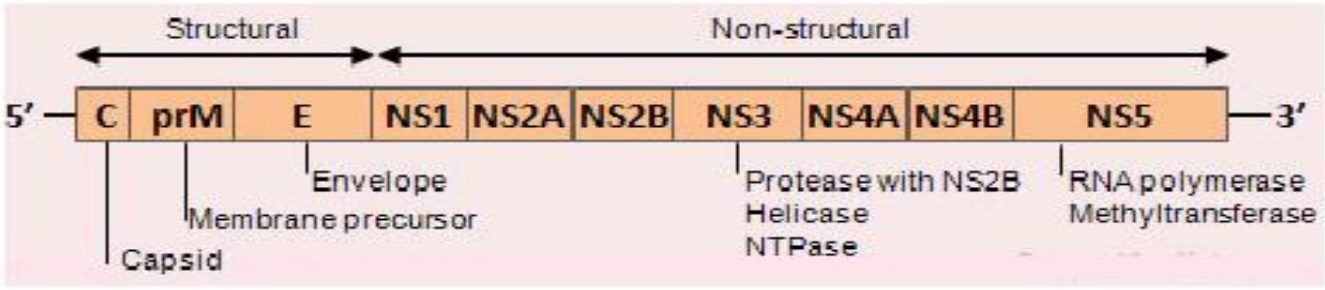
The vectors

Aedes aegypti mosquitoes, which are most active during the day, are usually found near human dwellings. Elevated temperatures significantly shorten the incubation periods for the dengue virus in mosquitoes. *A. aegypti* cannot withstand temperatures below 48 F, and will die after less than an hour of 32 F. It is currently limited to a range below 35N latitude. The various serotypes of the dengue virus are transmitting to humans through the bites of infected *Aedes* mosquitoes, principally *Ae. aegypti*.

Also, because of lower temperatures, *Ae. aegypti* is relatively above 1000 m. The immature stages are found in water-filled habitats, mostly in artificial containers closely associated with human dwellings and often indoors. Studies recommend that most female *Ae. aegypti* may spend their lifetime in or around the houses where they emerge as adults.

The host

Fig.1. Dengue virus genome structure with the structural and nonstructural genes source from (NCBI GenBank)



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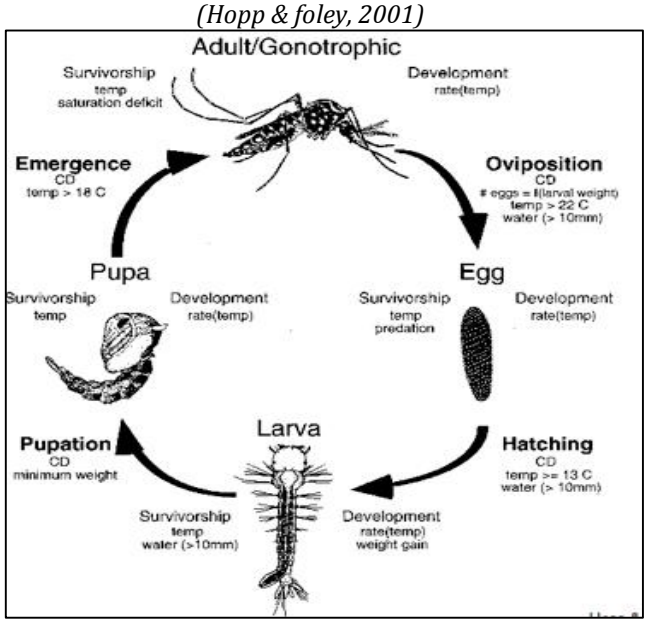
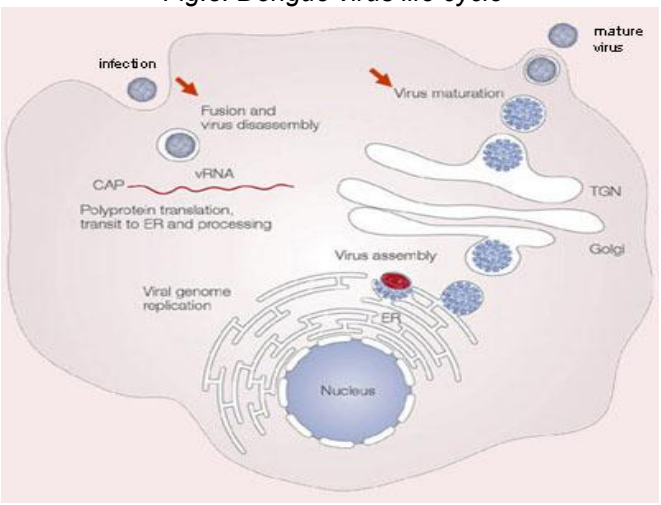
The main target of the virus is human. Female mosquitoes ingest dengue virus circulating in the blood of humans during feeding. The virus then infects the mosquito mid-gut and subsequently spreads systemically over a period of 8 -12 days. After this extrinsic incubation period, the virus can be transmitted to other humans during subsequent probing or feeding. The extrinsic incubation period are influenced in part by environmental conditions, especially ambient temperature. Thereafter the mosquito remains infective for the rest of its life. *Ae. aegypti* is one of the most efficient vectors for arboviruses because it is highly anthropophilic, frequently bites several times before completing oogenesis, and thrives in close proximity to humans.Fig.2.represents the life cycle of dengue virus.

Fig.2 Life cycle of Aedes mosquito (Hopp & foley, 2001)



Serotypes can construct a wide spectrum of illness; although most infections are asymptomatic, subclinical primary infection is thought to be induce lifelong shielding immunity to the infecting serotype. Individuals suffering an infection are protected from clinical illness with a different serotype within 2-3 months of the primary sickness but with no long-term cross-protective immunity. Individual risk factors determine the severity of disease and include secondary infection, age,

Fig.3. Dengue virus life cycle



ethnicity and possibly chronic diseases (bronchial asthma, sickle cell anaemia and diabetes mellitus). Young children in particular may be less able than adults to compensate for capillary leakage may and are consequently at greater risk of dengue distress.

The increased number of infected cells is predicted to result in a higher viral burden and induction of a robust host immune response that includes inflammatory cytokines and mediators, some of which may contribute to capillary leakage. During a secondary infection, cross-reactive memory T cells are also rapidly activated, proliferate, express cytokines and die by apoptosis in a manner that generally correlates with overall disease severity. Host genetic determinants might influence the clinical outcome of infection though most studies have been unable to adequately address this issue. Studies in the American region show the rates of severe dengue to be lower in individuals of African ancestry than those in other ethnic groups.

The dengue virus enters via the skin while an infected mosquito is taking a blood meal. During the acute phase of illness, the virus is present in the blood and its clearance from this compartment generally coincides with defervescence. Humoral and cellular immune responses are considered to contribute to virus clearance via the generation of neutralizing antibodies and the activation of CD4+ and CD8+ T lymphocytes.

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In addition, innate host defence may limit infection by the virus. After infection, serotype specific and cross-reactive antibodies and CD4+ and CD8+ T cells remain measurable for years. Plasma leakage, haemo concentration and abnormality in homeostasis characterize severe dengue. The mechanisms leading to severe illness are not well defined but the immune response, the genetic background of the individual and the virus characteristics may all contribute to severe dengue.

Recent data suggest that endothelial cell activation could mediate plasma leakage. Plasma leakages are thought to be associated with functional rather than destructive effects on endothelial cells. Activation of infected monocytes and T cells, the complement system and the production of mediators, monokines, cytokines and soluble receptors may also be involved in endothelial cell dysfunction.

Thrombocytopenia may be associated with alterations in megakaryocytopoieses by the infection of human haematopoietic cells and impaired progenitor cell growth, resulting in platelet dysfunction (platelet activation and aggregation), increased destruction or consumption (peripheral sequestration and consumption). Haemorrhage may be a consequence of the thrombocytopenia and associated platelet dysfunction or disseminated intravascular coagulation.

Symptoms

The fever rises rapidly to as high as 104 F and may be accompanied by bradycardia. The petechiae rash appears 3-4 days after the onset of fever, and usually appears on the trunk first, before spreading peripherally. Symptoms usually persist for 7 days, hence one of the common names for the disease: seven-day fever. Dengue does not produce long-term complications.

Symptoms of dengue include:

- fever
- headache
- pain behind the eyes
- joint and muscle pain
- rash
- nausea/vomiting
- mild bleeding, such as nose or gum bleeding or easy bruising

Anyone with dengue who experiences the subsequent admonition signs should go to a doctor or crisis room instantaneously:

- Severe abdominal pain or persistent vomiting
- Red spots or patches on the skin
- Bleeding from nose or gums
- Vomiting blood
- Black, tarry stools (faeces, excrement)
- Drowsiness or irritability
- Pale, cold, or clammy skin
- Difficulty breathing

People who have had dengue before may get severe dengue if they are infected again. Some phase is to promote the life cycle of the virus.

Febrile phase

Patients typically develop high-grade fever suddenly. This acute hot phase usually lasts 2–7 days and is often accompanied by facial flushing, skin erythematic, generalized body ache, myalgia, arthralgia and headache Some patients may have sore throat, injected pharynx and conjunctival injection. Anorexia, nausea and vomiting are common. It can be difficult to distinguish dengue clinically from non-dengue febrile diseases in the early crimson phase. A positive tourniquet test in this phase increases the chance of dengue Mild haemorrhagic manifestations like petechiae and mucosal membrane bleeding (e.g. nose and gums)

Critical phase

Around the time of defervescence, when the temperature drops to 37.5–38^{o}C or less and remains below this level, usually on days 3-7 of illness, an increase in capillary permeability in parallel with rising haematocrit levels may occur (*6,7*). This marks the beginning of the critical phase. The period of clinically significant plasma leakage usually lasts 24-48 hours. Progressive leukopenia followed by a rapid decrease in platelet count usually precedes plasma leakage. At this point patients without an increase in capillary permeability will improve, while those with increased duct permeability may become

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worse because of lost plasma volume. The degree of plasma leakage varies.

Recovery phase

If the patient survives the 24-48 hrs critical phase, a gradual reabsorption of extravascular compartment fluid takes place in the following 48-72 hours. General well-being improves, appetite returns, gastrointestinal symptoms abate, haemodynamic status stabilizes and diuresis ensues. Some patients may have a rash of "isles of white in the sea of red". Some may experience widespread pruritus. Bradycardia and electrocardiographic changes are common during this stage. The haematocrit stabilizes or may be lower due to the dilution effect of reabsorbed fluid. White blood cell count usually starts to rise soon after defervescence but the recovery of platelet count is typically later than that of white blood cell count. Table 1 represents the requirement of fluid basedon body weight.

Treatment

1. Ongoing Prevention
2. Response to Sporadic Cases
3. Outbreak Response

Table 2. Requirement of fluid based on body weight

S.No	Body weight (kgs)	Volume of fluid to be given in 24 hrs	Rate of fluid (ml/Hour)			
			R*1	R*2	R*3	R*4
1	10	1500	30	60	100	200
2	15	2000	45	60	150	300
3	20	2500	60	90	200	400
4	25	2800	75	120	250	500
5	30	3200	90	150	300	600
6	35	3500	105	180	350	700
7	40	3800	120	210	400	800
8	45	4000	135	240	450	900
9	50	4200	150	270	500	1000
10	55	4400	165	300	550	1100
11	60	4600	180	360	600	1200

Dengue fever treatment

- See a doctor / general practitioner (GP) immediately.
- Apply insect repellent. If you have dengue fever, mosquitoes that bite you may pass dengue on to other people.
- Drink plenty of liquids and take paracetamol for fever and pain. Do not take aspirin because it can affect blood clotting.

Dengue haemorrhagic fever treatment

All patients with dengue haemorrhagic fever need to be hospitalised for fluid therapy and monitoring. Doctors and health professionals can refer to Dengue haemorrhagic fever: diagnosis, treatment, prevention and control (2nd Edn. Geneva: World Health Organization, 1997) for detailed information on dengue symptoms and treatment. Aspirin and nonsteroidal anti-inflammatory drugs (e.g. ibuprofen, diclofenac) and corticosteroids should be avoided. During dengue platelet, count in the blood goes down. Since medicines as aspirin reduce platelet count, they should be avoided.

Fluids required for intravenous therapy

Fluids Recommended

Table 4. The maintenance fluid should be calculated using the Holliday and Segar formula

Body weight(Kgs)	Maintenance volume (ml) administered over 24 hrs
<10	100/Kg
10-20	1000+50 for each Kg in excess of 10
>20	1500+20 for each Kg in excess of 20

Crystalloid

(a) 5% dextrose in isotonic normal saline solution (5% D/NSS)

(b) 5% dextrose in half-strength normal saline solution (5% D/1/2/NSS)

(c) 5% dextrose in lactated Ringer's solution (5% D/RL)

(d) 5% dextrose in acetated Ringer's solution (5% D/RA)

Colloidal: Dextran 40: Plasma

In order to ensure adequate fluid replacement and avoid over-fluid infusion, the rate of intravenous fluid should be adjusted throughout the 24 to 48 hour period of plasma leakage by periodic haematocrit it determinations and frequent assessment of vital signs.

The volume of fluid replacement should be just sufficient to maintain effective circulation during the period of plasma leakage

Excessive fluid replacement and continuation for a longer period after cessation of leakage will cause respiratory distress from massive pleural effusion, ascites, and pulmonary congestion/Edema. This can be

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dangerous. The required regimen of fluid should be calculated on the basisof bodyweight and charted on a 1-3 hourly basis, or even more frequently in the case of shock. The regimen of the flow of fluid and the time of infusion are dependent on the severity of DHF. The schedule given below is recommended as a guideline. It is calculated for moderate dehydration of about 6% deficit (plus maintenance) (Table. 3).

Table 3. Guidelines for treatment of dengue fever/dengue haemorrhagic fever in small hospitals

Ml/lb Body weight/day	Weight on admission		Ml/lb Body weight/day
	Lbs	Kgs	
100	<15	<7	220
75	16-25	7-11	165
60	26-40	12-18	130
40	>40	>18	90

In older children who weigh more than 40 kgs, the volume needed for 24 hrs should be calculated as twice that required for maintenance (using the Holliday and Segar formula). The maintenance fluid should be calculated as follows (Table.4).

For a child weighing 40 kgs, the maintenance is 1500 + (20x20) = 1900 ml. This means that the child requires 3800 ml IV fluid during 24 hours. For intravenous fluid therapy of patients with DHF, *four regimens* of flow of fluid are suggested: 3ml/kg/hr; 6ml/kg/hr; 10ml/kg/hr, and 20ml/kg/hr. For ready reference, the calculation of fluid requirements, based on bodyweight and rate of flow of fluid volume for the four regimens are given in Table 2.

The fluid volumes mentioned are approximations.

Normally change should not be drastic. Do not jump from R-2 to R-4 since this can overload the patient with fluids. Similarly, reduce the volume of fluid from R-4 to R-3, from R-3 to R2, and from R-2 to R-1 in a stepwise manner.

It is advised to procure only a bottle of 500 ml initially, and order more as and when required. The decision about the speed of IV fluid should be reviewed every 1-3 hours. The frequency of monitoring should be determined on the basis of the condition of the patient.

Important instructions for treatment of DHF

- ✓ Cases of DHF should be observed every hour.
- ✓ Serial platelet and haematocrit determinations drop in platelets and rise in haematocrits are essential for early diagnosis of DHF.
- ✓ Timely intravenous therapy – isotonic crystalloid solution – can prevent shock and/or lessen its severity.
- ✓ If the patient's condition becomes worse despite giving 20ml/kg/hr for one hour, replace crystalloid solution with colloid solution such as dextran or plasma. As soon as improvement occurs, replace with crystalloid.
- ✓ If growth occurs, reduce the speed from 20 ml to 10 ml, then to 6 ml, and finally to 3 ml/kg.
- ✓ If haematocrit falls, give blood transfusion 10 ml/kg and then give crystalloid IV fluids at the rate of 10ml/kg/hr.
- ✓ In case of severe bleeding, give fresh blood transfusion about 20 ml/kg for two hours. Then give crystalloid at 10 ml/kg/hr for a short time (30-60 minutes) and later reduce the speed.
- ✓ In case of shock, give oxygen.
- ✓ For correction of acidosis (sign: deep breathing), use sodium bicarbonate7.

For more details on management of DFH/DSS cases, the physician is advised to consult other appropriate references on their treatment.

Drugs

Nisar Ahmad et al. (2011) has been investigate the potential of *Carica papaya* leaves extracts beside dengue fever treatment Before the extract administration the blood samples from patient were analyzed. Platelets count (PLT) $176\times10^3/\mu L$, white Blood cells 8.10×10^3 µL and neutrophils decreased from, 84.0% to $55\times10^3/\mu L$ and 46%, and then where blood are rechecked after the administration of leaves extract then it is observed that the PLT count increased from 55×103/µL to

168×103/µL WBC from 3.7×103/µL and NEUT from 46.% to 78.4%.

Syarifuddin Idrus et al. (2012) where been watched that the designing cyclopentapeptide inghibitor as potential antiviral drug for dengue virus NS5 methyltransferase. Shivendra Kumar et al.(2012), where they review that some of the herbal inhibitors for dengue virus , Klawikkan et al.(2011), where studied that Thailand has many traditional medicinal plants that have been reported on strong antiviral activity and some of them have already been used to treat people who were infected with viruses. Therefore, the aim of this study is to investigate the *in vitro* anti-dengue activity from Thai medicinal plants. In this present study, ten medicinal plants were collected from Siri Ruckhachati Natural Park, Salaya campus, Mahidol University. These plants were extracted with dichloromethane ethanol and subsequently tested for their anti-dengue type II activities in Vero cell by MTT method. The results showed that the ethanol extracts of *Rhizophora apiculata* Blume, *Flagellaria indica* Linn. and *Cladogynos orientalis Zipp.* at a concentration of 12.5 µg/ml exhibited inhibitory activity on DENV-2 with 56.14%, 45.52% and 34.85%, respectively. Moreover, *Houttuynia cordata* Thunb. Exhibited inhibitory activity against DENV-2 with 35.99% at a concentration of 1.56 µg/ml.

Annual report

Surveillance system and efficient management of cases, the case fatality rate because of dengue has declined from 3.3 %1996 to less than 1% in 2009. Dengue Mortality Reduction Rate: 50 per cent by 2010 and sustaining at that level until 2012.

Discussion and contribution

A comprehensive review heads us towards the empowering threatening disease to our knowledge, the upcoming endemic economic global issue to be solved either by therapies, and research oriented methods and a better knowledge towards its prevention and management. We also state the research to this particular area to be accelerated and must cover a wide research to beat up the health issues and which illustrates the importance for a serious proposal towards a wide research. Moreover, our ancient way could head us towards a particular site specific strategy. Plants could serve as a better option to these types of Diseases.

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