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AN OVERVIEW ON DENGUE

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ABSTRACT
Dengue is most common viral disease spread through the bites of mosquito (family Flaviviridae). All over the world, cases are increasing day by day and present treatment is focussed on reduction of complications caused due to Dengue fever and reduces the symptoms. There are many factors influencing the death rates. Early diagnosis and rational treatment can decrease the mortality rate of dengue. Clinical Pharmacist plays a important role in suggesting rational treatment, monitor the treatment, drug and food interactions and help in decreasing the duration of stay in the hospital. Educating the public about dengue preventation methods helps in controlling dengue. Diet plays an important role in boosting the immune system and helps the immune system to defence against the viral pathogen. This paper mainly focuses on the viral structure, pathophysiology, epidemiology, diagnostic tests, treatment, diet, case management, various control strategies to prevent dengue and death rates due to dengue and role of the clinical pharmacist in dengue management.

Keywords: DENV, Viral proteins, Clinical Pharmacist

INTRODUCTION

Dengue is the most common arboviral disease of humans, spread worldwide through the Aedes mosquito bite (Flaviviridae family) and the serotypes include of the virus DV1, DV2, DV3, DV4 and a positive stranded RNA virus [1, 2]. Every year 100 new cases are estimated in 100 to 125 countries [1], however due to the misdiagnosis and failure in reporting the cases, actual number is not reported [1]. Clinical Pharmacist plays a vital role in dengue management and helps in fast recovery of patients. Dengue virus causes mild asymptomatic illness to severe fatal haemorrhagic fever/dengue shock syndrome (DHF/DSS). Dengue fever is classified into severe and uncomplicated dengue [2].

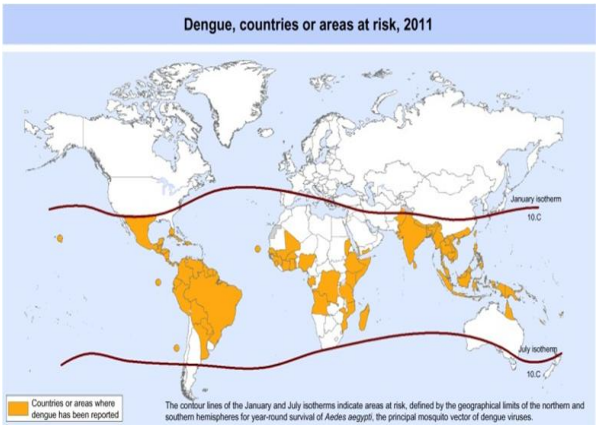
History

Dengue fever is called as "water poison" associated with flying insects by a Chinese medical encyclopedia in 1992 from the Jin Dynasty (265-42 AD). In 1780, the first clinically recognized dengue virus epidemic occurred simultaneously in Asia, Africa, North America [2]. Benjamin Rush coined the term "BREAK BONE FEVER" because dengue fever includes both myalgia and arthralgia [1]. The first clinical case was reported in Philadelphia 1789 of 1780 epidemic [2]. About 390 million dengue cases occur annually and of them only 96 million manifested clinically [3]. Before 1970, dengue epidemic is experienced by only 9 countries, and currently it is endemic in more than 100 countries, including subtropical and tropical countries [3]. In India first epidemic illness was recorded in Madras in the year 1970, virologic dengue fever was recorded in Calcutta (now Kolkata). 2.5 billion new people live in dengue risk areas and annually 100 million new cases are reported worldwide [2] .

Epidemiology

First dengue outbreak was reported in 1779 in Jakarta, Indonesia [4]. Since then more than 100 countries on the Asia-pacific regions, America, Middle east, and Africa have succumbed to this Infectious disease and case infections continue to rise world-wide [5]. In South America > 70 % cases are accounted in Brazil. According to WHO, the number of cases doubled in early 1990s and 96 million new cases were identified worldwide in 2010 [6]. South East Asia countries have 18 times increased rate of severe dengue compared to America. Western Pacific and South East Asia regions both combinedly attribute 75 % of the global dengue disease burden. The cases increased above 1000 in Australia in 2010. Between 1960 and 2010 African countries reported sporadic outbreaks. In 20th century, EUROPE was free of dengue but the global expansion of dengue finally affected this region. According to many experts hypothesis, dengue will increase in future according to geographical expansion, incidence and reports of WHO [6].

Figure 1. Prevalence of Dengue in different parts of the world. (as per WHO) [6]



Dengue mortality and its factors

Despite deaths due to dengue are 99 % avoidable, 20,000 deaths occurred in over more than 100 countries. Social Determinants of Health (SDH) and Biological factors are related to dengue deaths. SDH was categorized based on individual, social and environmental and health system dimensions [5]. Presence of comorbidities such as DM, HTN, Renal failure, pulmonary disorders and severe dengue are the cumulative risk factors for the hospitalised dengue deaths. Presence of comorbidities increases the risk of dengue deaths 11 times higher in hospitalised patients [7]. Individual dimension factors causing death includes Age, sex, occupation, immunological status, income, education and other factors [5].

About the virus

Dengue virus is a positive stranded RNA virus which belongs to Flaviviridae family and the gene flavivirus [8]. The serotype includes (DENV1, DENV2, DEN4), Infection with any one serotype give lifelong protection against it, but in secondary infection there are no chances of protection by a heterologous serotypes. There are no effective antiviral drugs and vaccines against dengue virus. Disease severity is enhanced by cross-reactive antibodies [9]. This virus is transmitted through the bites of mosquitoes *Aedes aegypti* and *Aedes albopichs* during the day time [10].

Structural proteins [11]

- **Capsid:** Helps in binding and stabilizes the viral RNA.
- ***Pre membrane:*** Prevents from premature fusion.
- ***Envelope:*** Helps recognise and binds to the host cell, uncoating of virus by enabling the fusion of viral endosomal membranes.

Non-structural proteins

- **NS1:** Viral RNA replication and viral defence
- **NS2A:** Viral replication and assembly
- **NS2B:** Cofactor for NS3 protein
- **NS3:** Serine protease will cleave viral polyprotein

Pathophysiology

The exact causes of dengue events are unclear. After mosquito bite, virus enters the host cell and first targets macrophages and dendritic cells with a incubation period of about 7 to 10 days [12]. Viremia may be present for 24 to 48 hr before the onset of the symptoms. Increased microvascular permissibility and shock syndrome is thought to be of secondary dengue virus [13]. In severe dengue infection antibody dependent enhancement plays a major role in pathogenesis. Destruction of platelets in the liver and spleen are seen. In patients with severe dengue antiplatelet antibodies will cause lysis of platelets in

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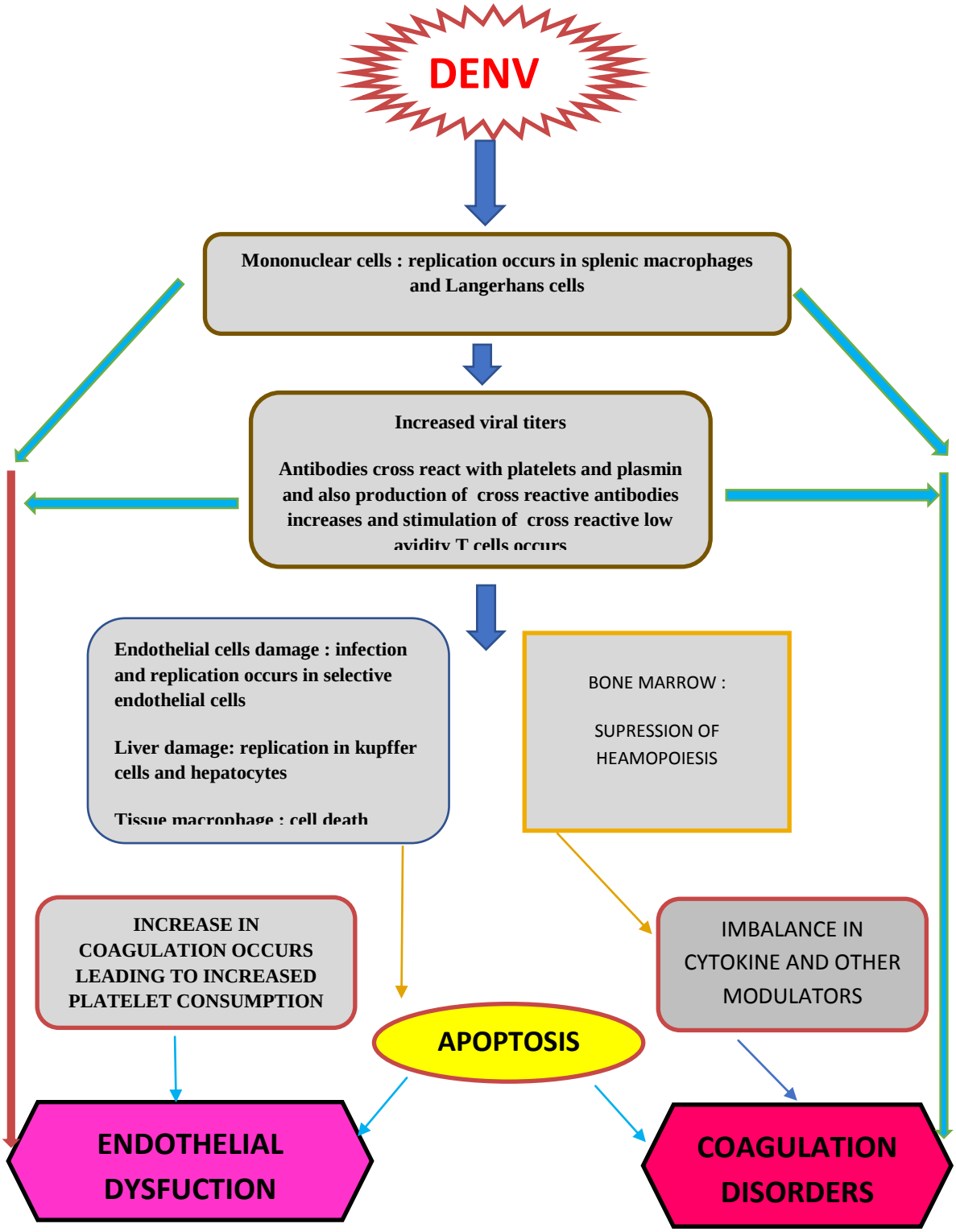
the presence of compliment which accounts for high risk of thrombocytopenia [12].

Figure 2. Pathophysiology of dengue causing endothelial dysfunction and development of coagulant disorders [14].



Clinical manifestations

Dengue is self-limiting and in rare cases it leads to death, The patient may recover within 10 days

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without any complications after the onset of illness. Symptoms may include retroorbital pain, myalgia, arthralgia, vomiting, weakness and maculopapular rashes may appear after fever [2, 15]. In about 5 % of cases, dengue haemorrhage fever (DHF) is seen. gum bleeding, epistaxis and thrombocytopenia, haemoconcentration >20 % difference from previous concentration are reported. Leakage of plasma shows the severity of the patient condition. Irritability, cold clammy skin, restlessness and flushed face are the signs of circulatory failure. Earlier about 24 to 36 hrs intense abdominal pain, weak pulse, and decrease in blood pressure is observed [9]. Clinical manifestations associated with encephalitis, myocarditis, cholecystitis, myelitis, acute motor weakness, seizures and acute colitis are seen [2]. Non severe dengue is divided into 2 sub-groups based on warning signs abdomen pain and tenderness; lethargy, mucosal bleeding, liver enlargement > 2cm and vomiting are seen. Whereas severe dengue is characterised by plasma bleeding and organ dysfunction [9]. Based on severity dengue fever is divided into 4 grades includes DHF grade I, DHF grade II – DHF DHF grade III and DHF grade IV – DSS [16].

Diagnosis

Early detection of dengue virus and clinical diagnosis are important factors to decrease the fatality rates in dengue. In case of suspected dengue cases immediately obtain CBC and it should be done from the day 3 of illness [17]. Tourna quit test is done for capillary fragility **[**9]. Increase in leucopoenia in suspicious dengue cases is seen. ELISA is also preferred for detecting NS1 protein and IgM antibodies and they are used for rapid diagnosis. NS1 has high sensitivity to early illness but it will be declined by 5th day [17]. Assay should be done on anti-DENV IgM antibody on 5th day of illness. Tests to be done to identify hematemesis, melena, hyper menorrhea, haemoglobinuria. Haematological data is helpful in detecting the onset of plasma leakage, thrombocytopenia and early leakage of plasma. Narrowing of pulse pressure (< 20 mmHg) in adults is seen. Patient should undergo LFT, BUN, Creatinine, Coagulation profile, cardiac enzymes test and amylase test should be done in case the patient is not responding to fluid resuscitation. Abdominal ultrasound and x-ray helps in identifying plasma leakage. Pleural effusion and ascites are seen in dengue DHF. Undifferentiated febrile illness can only be diagnosed through serological tests [16]**.**

Case management

The management of dengue cases mainly depends on the stage of illness and severity of the patient condition.

- Reduce the fever using paracetamol and tapid sponging, giving oral fluids and IV fluids
- Fluid resuscitation and fluid overload should be managed
- Comorbidities and high risk patients with obesity, low appetite, bleeding, pregnancy should manged carefully [16].
- Consider and treat BBH.
- Misdiagnosis of dengue should be avoided [2].
- Daily CBC must be followed [2]
- Supportive and symptomatic care should be given in dengue management [2-10].

Treatment

Pharmacological treatment

At present there is no treatment for dengue and treatment is aimed only to reduce the symptoms of the patient, complications and organ damage. Tetravalent vaccines simultaneously provide long-term protection against Dengue virus serotypes DV1, DV3, DV4 using flexible pentaglycyl linkers [2].

Drugs:

- **Chloroquine**: It is widely used as antimalarial agent and is given 600 mg from day 1 - day 3. Chloroquine inhibits the fusion between virus and host membrane.
- **Celegosivir**: It acts as placebo and is given 400 mg loading dose and 200 mg bid [18]. It is a cellular nucleosidase inhibitor and it shows antiviral activity against all fever serotypes of DENV. It is safe and well tolerated.
- **Balapiravir**: It is given 1500 mg or 3000 mg bid for 5 days, presumed to be an NS5 nucleoside inhibitor. It was developed by the scientist Roche [17].
- **HMG CO-A reductase**: (lovastatin) given 80 mg OD for 5 days. Statins have anti-inflammatory and endothelial stability

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property and are used as adjuvant therapy in sepsis, pneumonia and acute lung injury [19].

- Prednisolone is used to control inflammation and Acetaminophen is given to decrease the fever [17-19].

Fluid management:

Titrate the fluid based on the blood volume, laboratory data and clinical observations. Isotonic crystalloid solutions are used except in very young children (< 6 months of age), 0.45 % sodium chloride is preferred. In patients with massive plasma leakage, if they do not respond to minimum volume of crystalloids, then 10 % Dextrane-40 saline is recommended and isotonic colloids and albumin are given. Frequent assessment of volume and dehydration should be monitored. Fluid overload may occur after the resolution of leakage (12-24 hours), so reduction of rate over next 24 hours to 5 ml / kg / hr, 3 ml / kg / hr, < 3 ml / kg / hr by 18 hours, fluid should not be continued more than 60-72 hours unless the complications are seen [15]. In febrile condition, IV fluid administration should be avoided except in patients with vomiting and dehydration [12]. In severe critical phase DHF cases plasma do not have any role in the management of dengue. IV fluids must be stopped immediately in case of itching, rashes and sinus bradycardia [16].

Table: 1 Intravenous fluid infusion rates [15]

S.no	*Patient condition*	*Infusion rates*
1	Shock	Initial: 10 ml / kg / h isotonic crystalloid for 1-2 h, If no change is seen : Check Haematocrit, Acidosis, blood sugar, calcium, RBC and bleeding. If Haematocrit rise is seen : Give colloid 10 ml / kg / h is given If Haematocrit fall is seen: then blood transfusion must be initiated *In case no improvement in patient response then slowly reduce the infusion rates 7, 5, 3, 1.5 ml / h over 24 – 48 h.*
2	Non-shock	Initial: Haemoconcentration > 20 % : give 3 ml / kg / h (80 ml / hr for adults) Haemoconcentration < 20 %: give 1 – 2 ml / kg / h (20 - 40 ml / h for adults)
3	Prolonged shock	Initial: start with 20 ml / kg normal saline over 15 – 20 min or until BP comes to normal. ABCS* must be corrected. If no response is seen : Re-check the Haematocrit If haematocrit decreases: transfuse whole blood (10 ml / kg) or packed RBC (5 ml / kg) over 1 h

*ABCS: Acidosis, Bleeding , Calcium, Sugar. BP - Blood Pressure, RBC - Red Blood Cell

Prophylactic platelet transfusion:

Thrombocytopenia (< 10,000 cells / mm^3) is a condition where platelets decrease, so transfusion should be done. However, prophylactic transfusion is

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not beneficial in paediatric and adult dengue patients. This practice is cost effective and in some conditions it is very dangerous as it constitutes administration of blood products, fluid challenge and infections may also be seen. Adult dengue platelet study (ADEPT) classify the evidence of prophylactic platelet transfusion in dengue [19]. Platelet transfusion should be done only in case of severe bleeding and in patients with underlying HTN. In children there is no platelet prophylaxis transfusion even though the platelet count falls low [16].

Non pharmacological treatment:

Diet

- Breakfast: Juices (apple, orange, pomegranate mix), vegetables, boiled egg without yolk, paneer, soups (tomato, spinach, beetroot), coconut water are recommended.
- Lunch: Well cooked rice and pulses are preferred
- Dinner: green leafy vegetables, paneer, milk and curd are preferred. Micronutrients help in boosting the immune system and decrease the severity of the disease by improving the defencing power of the immune system [12].
- Vitamin D: vitamin D supplements help in boosting immunity and promoting innate adaptive immunity
- Vitamin A: It helps in immune functioning, decrease the severity of the disease and protects the epithelium tissue of eyes ,gut and lungs [21].
- Ayurvedic: Cardamom and ginger tea reduces fever. Consuming crushed papaya leaf extracts are beneficial [22].

Research on dengue:

RNA based studies are under progress which would inhibit the gene expression [17]. Research studies focussed on host cell receptor, viral proteins may lead to the discovery of novel anti DENV therapeutic agents which will help in treating the patients [3].

Control Methods of Dengue

- Educating about dengue and its vector control and their prevention methods are essential in controlling the dengue.
- Control of Aedes aegypti and suppressing its population by specific genetic modification, Para trans genesis, larvivores fish and crustaceans, natural potential repellents. Example: callistemon rigidus, erythrine, Asparagus racemosus.
- DHIM: Dengue Human Infection Model is to understand pathogenesis, effective dengue control measures and strategies for vaccine development [23]
- Removal of stagnant water from tanks and containers and maintaining a clean environment [24].
- Mosquito sprays, coils, vaporizers, mats, cleaning house, covering containers, use of fans, smoke to drive away mosquitos, screening window doors, covering body with cloths and use of mosquito repellent creams will helps in controlling the mosquitoes [25]

Role of Clinical Pharmacist in treatment of dengue

- Monitor the patient status regularly and emergency clinical manifestations should be immediately reported to the physician.
- Patient counselling and diet should be recommended according to patient status and immune condition.
- Improper diagnosis should be identified by clinical pharmacist.
- Pharmacist should give appropriate treatment recommendation to physician based on assessing the patient condition and haemodynamic status of the patient.
- Fluid resuscitation should be monitored carefully.
- Patient's complete demographic data, past medical history should be assessed
- Identify food, drug interactions and ADRS and therapeutic effect of the drugs.
- Special patient population must be treated with special attention as there is risk of developing complications

Conclusion:

Dengue is the most common viral disease spread through mosquito bite world-wide. There is no treatment for dengue at present and only symptomatic

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treatment is given to reduce the complications that may lead to fatal conditions. Control measures are to be taken by public health officials and society for preventing and spread of dengue. Cost effective diagnosis and treatment should be provided to the patients. Platelet transfusion should be done in case of emergency only. Clinical pharmacist can help in reducing the complications and mortality rate by closely monitoring the patient and also help in decreasing duration of the hospital stay by providing rational treatment.

Abbreviations:

DENV- Dengue virus

DHF- Dengue Haemorrhagic Fever

DSS - Dengue Shock Syndrome

SDH - Social Determinants of Health

DM- Diabetes Mellitus

HTN- Hypertension

CBC- Complete Blood Count

BBH- Bacterial Infections, Bleeding and Hepatitis

ADEPT- Adult Dengue Platelet Study

DHIM- Dengue Human Infection Mode

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