Review Article

Dengue Fever its Diagnosis, Treatment, Prevention and Control

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Abstract

Background: Dengue virus has emerged as a major public health problem worldwide in the recent decades. The incidence of this infection has increased in tropics and subtropics including Pakistan. It is one the most common and perhaps the most dangerous viral disease transmitted by mosquitoes. Current epidemic of dengue fever of 2011 in Pakistan has highlighted the lack of direction and neglect of this devastating disease. Now it is of fundamental importance to implement public health measures and also to improve management of Dengue Hemorrhagic Fever and Dengue shock syndrome in our hospitals.

Objectives: The objectives of this review article are to;

1. Describe the epidemiology, virology, risk factors, clinical features, diagnosis and management of dengue fever.
2. Determine the complications of dengue fever.
3. Find out different modalities for prevention and control of dengue fever.
4. Provide awareness to the public about this disease and to dispel undue fears.

Conclusion: Fever is the symptom present in almost all patients .Bleeding leads to serious complications in dengue fever. No effective vaccine or antiviral agents are available to treat dengue infection at the moment. **Prognosis and Control:** Attempts to control dengue vector (mosquitoes) and effective vaccine remain the important preventive measures.

Key Words: Dengue virus, Dengue fever, Dengue Hemorrhagic Fever , Dengue shock syndrome, GIT manifestations, Retro orbital pain, Internal bleeding.

INTRODUCTION

Dengue fever (DF) is an acute febrile viral disease frequently presenting with headaches, bone, joint and muscular pains, rash and leucopenia. It is also known as break bone fever [1]. Dengue hemorrhagic fever (DHF) is characterized by four major clinical manifestations: high grade fever, hemorrhagic phenomena, often with hepatomegaly and, in severe cases, signs of circulatory failure. Such patients may develop hypovolaemic shock resulting from plasma leakage .This is called dengue shock syndrome (DSS) and can be fatal[2]. DHF is now a significant public health problem in most of the countries in the tropical areas of the South-East Asia and Western Pacific Regions. The disease is among the ten leading causes of hospitalization and death in children in at least eight tropical Asian countries[3].

EPIDEMIOLOGY

Dengue or dengue-like epidemics were reported throughout the nineteenth and early twentieth centuries in the Americas, southern Europe, North Africa, the eastern Mediterranean, Asia and Australia, and on various islands in the Indian Ocean, and central Pacific. Annually, it is estimated that there are 20 million cases of dengue infection, resulting in around 24000 deaths. It established seasonal and cyclical epidemic patterns, with large outbreaks occurring at 2-3 years intervals mostly in children[3]. Epidemiologically important new introductions of DHF/DSS were reported in China, Maldives, India, New Caledonia, Sri Lanka and Tahiti. The experiences in India and Sri Lanka are particularly interesting, because virological surveillance documented the endemic transmission of all four dengue serotypes accompanied by DF cases. DHF/DSS prior to the above-mentioned outbreaks[3]. All four dengue serotypes are present in these two Regions, and increasing international travel serves to introduce new virus strains and serotypes rapidly into susceptible populations. DHF/DSS is gradually becoming endemic

in several countries of the Americas, following the trend observed in Asia[3].

DENGUE IN THE AFRICAN AND EASTERN MEDITERRANEAN REGIONS INCLUDING PAKISTAN

Dengue disease has been prevalent and its virus reported in the African and Eastern Mediterranean Regions including Pakistan, Saudi Arabia, Senegal, Seychelles, Sierra Leone, Somalia, Sudan and the United Republic of Tanzania since 1967. The first case of Dengue fever in Pakistan was reported in the southern port city of Karachi in 1994[3]. Another study reported ten confirmed cases of dengue with four deaths from the north eastern city of Pakistan in 2003.[4] The province of Punjab, particularly its capital, Lahore have seen a growing number of cases since 2007. This year in the form of epidemic more than 4,000 cases of dengue fever have been reported, a significant increase over previous years. As the world temperatures rise the epidemic is moving north[5].

RISK FACTORS OF DENGUE EPIDEMIC IN PAKISTAN

Risk factors in Pakistan could include passenger traffic and trade with India and increased traffic from India. Pakistan is being used as a conduit in its trade with Afghanistan. (This route of infection is highly suspected because a recent study done by Agha Khan University[6]. Shows the prevalence of Dengue virus serotype 3 in recent infections compared to dengue serotype 2 usually isolated in the past). This serotype is the same which have been isolated in Dehli, India in the past. So it is no wonder that Lahore is the epicenter of this infection. Although it is understandable that it is difficult to prevent its spread to other cities but simple measures like fumigation of all transport coming out of epidemic zone has been tried in the past in epidemics world wide with variable success[7.] In view of its deadly nature a long term planning is needed to contain this disease because although in the more colder parts of the country it is likely to remain a seasonal threat but in the warmer south and east once the reservoir of the infection is established it can become a perennial nightmare. Although the lifespan of an adult *Aedes-aegypti* is between two to four weeks depending on conditions, *Aedes-aegypti's* eggs can be viable for over a year in a dry state, which allow the mosquito to re-emerge after a cold winter or dry spell [8.]

VIROLOGY

Dengue viruses belong to family flaviviridae of the genus flavivirus. The Dengue virus has four closely related but distinct serotypes, DEN1 to DEN4; within which are several genotypes. The virion is composed of 3 structural proteins known as core, membrane and envelope and 7 non-structural (NS1, NS2a, NS2b, NS3, NS4, NS4b, and NS5) proteins [9.] As the infection with one dengue virus provides life long immunity. There is no cross protective immunity to the other dengue viruses, therefore all dengue virus types may infect a person in an endemic area. Aedes-aegypti (A. aegypti) is a vector which infects the human host, who in turn serves as source of viral amplification. The A.aegypti is a small highly domesticated, black and white tropical insect that prefers to feed on humans during the daytime. There are two peaks of biting activity; early morning for 2 to 3 hours and in the afternoon for several hours before dark. It breads in artificial containers in and around homes. Females A.aegypti feeds on several persons and may transmit dengue virus to many persons in short course of time[8,9.]

TRANSMISSION [10]

- Dengue viruses are transmitted to vulnerable human host through the bites of infective female Aedes-aegypti mosquitoes.
- They generally acquire the virus while feeding on the blood of an infected person.
- After incubation for 8-10 days, an infected mosquito is able to transmit the virus by biting susceptible individual for the rest of its life. Infected female mosquitoes may also transmit the virus to their offspring by trans-ovarian (via eggs) transmission.
- Humans are the main amplifying host of the virus.
- The virus circulates in the blood of infected humans for 2-7 days during which they have fever.
- Female Aedes-aegypti mosquitoes may acquire the virus by feeding on infected person during this period10.
- There are several other possible routes of transmission without mosquito vector such as muco-cutaneous transmission by blood of infected patient with dengue, needle stick injuries, bone marrow transplant, blood transfusion, intra-partum and vertical transmission[9].

CLINICAL FEATURES & DIAGNOSIS

Characteristics of Dengue Fever & Dengue Hemorrhagic Fever

Dengue Fever

- It is a severe, flu-like illness that affects infants, young children and adults, but seldom causes death.
- The clinical features of dengue fever vary according to the age of the patient.
- Infants and young children may have a non-specific febrile illness with rash.
- Older children and adults may have either a mild febrile syndrome or the classical incapacitating disease with abrupt onset and high fever, severe headache, pain behind the eyes, muscle and joint pains, and rash[10.]

Dengue Hemorrhagic Fever

- It is a potentially deadly complication that is characterized by high grade fever, hemorrhagic phenomena, often with enlargement of the liver and in severe cases, circulatory failure.
- The illness commonly begins with a sudden rise in temperature accompanied by facial flush and other non-specific constitutional symptoms of dengue fever.
- The fever usually continues for two to seven days and can be as high as 40-41 C, possibly with febrile convulsions and hemorrhagic phenomena [10.]

IN MODERATE DHF CASES

All signs and symptoms abate after the fever subsides. In severe cases, the patient's condition may suddenly deteriorate after a few days of fever when the temperature drops, followed by signs of circulatory failure, and the patient may rapidly go into a critical state of shock and die within 12-24 hours, or quickly recover following appropriate volume replacement therapy[10.]

LABORATORY DIAGNOSIS

Essential Laboratory Tests [3]

In assessing a patient's condition, the following tests are recommended:

- Haematocrit
- Serum electrolytes and blood gas studies
- Platelet count, prothrombin time, partial thromboplastin time and thrombin time
- Liver function tests–serum aspartate aminotransferase, serum alanine
- Aminotransferases
- Renal Function tests
- Serological tests- dengue antibodies
- Serum Cholesterol & Albumen
- Chest X-Ray PA view
- Abdominal Ultrasound
- Virological Studies

Table-1

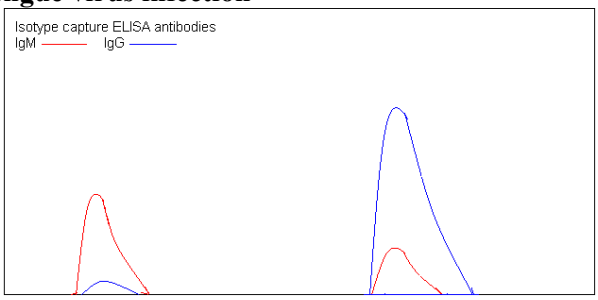
Results and Clinical Interpretation[3]

Possible results and their clinical interpretation include.

Result s	Clinical Interpretation
IgM Positive Only	Primary Dengue infection
IgM and IgG Positive	Late primary or early secondary infection
IgG Positive	Previous Dengue infection or secondary infection
IgM and IgG Negative	No Dengue Viral infection at present. Repeat the test 5 days if it is still suspected.

Figure-1

Primary and Secondary immunological response in dengue virus infection[3]



(A) Primary Response (B) Secondary Response

MANAGEMENT

Indications for Hospitalization[3]

Hospitalization for bolus I/V fluid is necessary, where significant dehydration (>10% of normal body weight has occurred. Sign & Symptoms include.

- Tachycardia
- Increased capillary refill time (>2s).
- Cool, mottled or pale skin.
- Diminished peripheral pulses
- Changes in mental status
- Oliguria
- Sudden rise in haematocrit

- Narrowing of pulse pressure (<20mmHg)
- Hypotension [3]

Table-2
Guidelines for the Families of Affected Persons [10]

Age	Dose (Table 250mg)	M/dose
< 1 year	¼ Tablet	60
1-4 years	½ Table	60-120
5 and above	1 Tablet	240

MANAGEMENT OF DENGUE FEVER
- Keep body temperature below 39 Centigrade
- Give the patient paracetamol (not more than four times in 24 hours) according to the dose prescribed below**.**
- Do not give the patient Aspirin or Ibuprofen.
- Give large amounts of fluids (water, soups, milk and juices) along with the patient's normal diet [10.]

Immediately Consult the Physician if any of the Following Manifestations appear [10]
- Red spots or points on the skin.
- Bleeding from the nose or gums.
- Frequent vomiting; vomiting with blood; black stools.
- Sleepiness; constant crying; abdominal pain; excessive thirst (dry mouth).
- Pale; cold or clammy skin; or difficulty in breathing.[3,10,11].

MANAGEMENT OF DENGUE HEMORRHAGIC FEVER & DENGUE SHOCK SYNDROME
Dengue hemorrhagic fever & dengue shock syndrome is a medical emergency. The immediate administration of intravenous fluid to expand plasma volume is essential.

Immediate Replacement of Plasma Loss
Fluids used for rapid volume expansion include the following:
- Physiological saline
- Ringer's lactate or Ringer's acetate
- 5% glucose solution diluted 1 : 2 or 1 : 1 in physiological saline
- Plasma, plasma substitutes (e.g., dextran 40) or 5 % albumin (50g/l)

Continues Replacement of Further Plasma Loss
Plasma loss may continue for 24-28 hours, requiring continued fluid administration. Determination of central venous pressure may be necessary in the management of refractory shock. The administration of intravenous fluid should be discontinued when the haematocrit level drops to approximately 40%, with stable vital signs.
- Correction of electrolyte and metabolic disturbances in hyponatraemia and metabolic acidosis
- Sedative therapy is needed in some cases to restrain an agitated child. A single dose of chloral hydrate (12.5-50mg/kg), orally or rectally, is recommended.
- Oxygen therapy should be given to all patients in shock.
- Blood transfusion is only indicated in cases with significant clinical bleeding. Fresh frozen plasma or concentrated platelets may be indicated in cases where coagulopathy causes massive bleedings.
- Monitoring of patients in shock with frequent recording of the vital signs and determination of the haematocrit are important in evaluating the results of treatment[3].

Complications of the Dengue Fever
Liver failure, myocarditis, acute renal failure, hemolytic uremic syndrome, acute transverse myelitis, encephalopathy, disseminated intravascular coagulation, acute respiratory distress syndrome, abdominal compartment syndrome, neurological symptoms, refractory shock, acute disseminated encephalomyelitis [12.]

Criteria for Discharging Patients [3]
This criteria should be met before patients recovering from DHF/DSS are discharged.
- Absence of fever for at least 24 hours without the use of antipyretics
- Return of appetite
- Visible clinical improvement
- Good urine output and Stable haematocrit
- No respiratory distress from pleural effusion
- Platelet count of more than 50,000 permm^3
- At least 2 days after recovery from shock[3]

Prevention & Control Measures
- Presently, the only method of controlling or preventing Dengue Fever & Dengue Hemorrhagic Fever is to combat the vector mosquitoes.

- Aedes aegypti breeds primarily in man-made containers like earthenware jars, metal drums and concrete cisterns used for domestic water storage, as well as discarded plastic food containers, used automobile tyres and other items that collect rainwater.

Vector Control

- It is implemented using environmental management and chemical methods.
- Proper solid waste disposal and improved water storage practices, including covering containers to prevent access by egg laying female mosquitoes, are encouraged through community-based programs.
- The application of appropriate insecticides to larval habitats, particularly those used by the households, such as water storage vessels can prevent mosquito breeding for several weeks therefore these insecticides must be used periodically.
- The use of family size insecticide treated nets (ITNs) is also recommended.
- General insecticide spraying targeting mosquito breeding habitats need to be carried out to kill adults using portable or truck-mounted machines.

Prevention of Mosquito Bites

- Dengue mosquitoes bite during day time. Mosquito repellants should be used to prevent mosquito bites.
- Wear full-sleeve cloths, socks and long dresses to cover the limbs.
- Care should be taken in using repellents on very young children or the elderly.
- Use mosquito coils and electric vapor mats during the daytime to prevent mosquito bites.
- Use insecticide treated nets (ITNs) to protect young children, pregnant women, old people, in addition to others who may rest during the day.
- Curtains (cloth or bamboo) can also be treated with insecticide and hung at windows or doorways, to repel or kill mosquitoes.

Prevent Multiplication of Mosquitoes (Vector Control)

Mosquitoes which spread Dengue live and breed in stagnant water in and around houses, and places where solid waste is dumped.

- Drain out the water from desert/window air coolers when not in use, in addition to tanks, barrels, drums, and buckets.
- Remove all objects containing water such as plant saucers from the house.
- All stored water containers should be kept covered at all times.
- Collect and destroy discarded containers in which water collects, such as bottles, plastic bags, tins, tires,etc.
- Efficient disposal of all solid waste/garbage[10].
- The most effective way to control the mosquitoes is the reduction of larva by eliminating or cleaning of water holding containers as stated above that serve as the larval habitat for A.aegypti. Public involvement is necessary to implement mosquito control program .It can be achieved by public education and law enforcement[13].

VACCINE

An effective tetravalent vaccine remains a significant challenge. Two live attenuated dengue virus vaccines, attenuated by passing several times in non-human cells, have been developed. Trial of a tetravalent vaccine showed significant sero-conversion rates (89%) against all 4 serotypes of DV after the third dose. However, two doses of this vaccine confer 80-90% protection in children [14.] Other vaccine, prepared by Walter Reed Army Institute of Research, produced similar sero-conversion rates in adult volunteers [15.] Several risk factors are associated with live attenuated RNA vaccine such as reversal to a virulent phenotype, and short life.

CONCLUSION

Dengue viral infections are a major and emerging global public health problem. The recent epidemic of this disease in Pakistan has caused harassment in all the communities of our country. Fever is the symptom present in almost all patients. Bleeding leads to serious complications in dengue fever. No effective vaccine or antiviral agents are available for prevention and treatment of dengue infections at the moment. Since these infections are on the continuous rise, so it is of paramount importance to describe and categorize the common manifestations of these infections and dispel undue public fears, employ laboratory tests for its diagnosis and utilize all possible resources and adopt all appropriate measures for the management and

prevention of this disease. Health education of the public can play key role in the containment and control of this dangerous disease.

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