Invited Review Article

Dengue Fever Update

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Abstract

Dengue fever is being caused by Flaviviridae family and has four serotypes. The vector is mosquito Aedes aegypti and Aedes albopictus. Dengue fever also known as bone break fever. Primary infection with any one of the four dengue virus serotypes typically causing dengue fever (DF), which is a severe but self limited acute febrile illness, some primary infections and more of secondary infections with two different serotype results in very severe, debilitating and life-threatening DHF/DSS, which is characterized by increased vascular permeability and haemorrhagic manifestations. In rare cases of DHF/DSS, neurologic abnormalities, including encephalitis, may also occur. There are some evidence of other atypical manifestations of dengue fever as well such as a calculus cholecystitis, appendicitis, pneumonitis and myocarditis. Variations in virus strains within and between the four serotypes may influence disease severity. Secondary infections are more likely to result in severe disease and dengue haemorrhagic fever.

Keywords: Dengue fever, dengue haemorrhagic fever, vector, serotype
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Introduction

Dengue fever, first identified in the 1950s, caused by dengue virus contributes to significant morbidity and mortality in most of the tropical and sub-tropical countries across the universe[1]. The dengue virus, single stranded RNA virus belongs to the serological group of the family *Flaviviridae*, genus *Flavivirus*, comprising off our antigenically closely related serotypes known as DEN-1, DEN-2, DEN-3 and DEN-4[2]. Few other viruses like West Nile virus, Yellow fever (YFV), Japanese encephalitis, and St. Louis encephalitis viruses, all single stranded RNA viruses also belong to the same family[3]. The transmission of dengue has increased in recent years, more prevalent in urban and semi-urban areas, declaring it a major public health concern globally. Some of the reasons for this rise include population growth, uncontrolled urbanization, spread of the mosquito vectors, and movement of the virus from one place to another along with the rapid transit of people all around the globe[4].

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Epidemiology

The principal vector of dengue fever is *Aedes aegypti* mosquito, with its unique characteristics has proved to be an efficient vector for several reasons: high susceptibility to dengue virus; preferential feeding on human blood; thriving in close proximity to humans; daytime feeder; its bite is almost imperceptible; a very restless mosquito, very little movement interrupts feeding, in short period of one blood meal many people may be bitten by this mosquito. Unlike most mosquitoes, *Aedes aegypti*

feeds on more than one blood meal during a gonotropic cycle, that is, before the eggs are laid[5].

Aedes aegypti mostly found near or inside human habitats, often rest in dark rooms (e.g., inside bathrooms and under beds) and breed in small water pools that collect inside or outside of the house in discarded human waste. Early morning and the late afternoon are the most preferred feeding times of *Aedes aegypti*. However the risk of exposure for travelers is highest in rural and urban areas especially those belonging to low socioeconomic group, because effective mosquito control programmes are not existing in those parts of the world[6].

Aedes aegypti is the primary urban vector not only for dengue but also for transmission of yellow fever, often abundantly found in the peri-domestic environment, especially in areas where plentiful vegetation is found. However, in addition to humans, it feeds freely on animals and birds, and so can exist far from human habitation. *Aedes albopictusis* also responsible for spreading dengue virus, generally regarded as a secondary and less important vector of dengue virus. Nevertheless, dengue epidemics have been recorded in places where *Aedes albopictusis* the only vector, and in recent years, the species has proved highly effective in urban transmission of another African sylvatic virus, chikungunya virus[7-8].

In many areas, dengue epidemics occur during the warm, humid, rainy seasons, which favor abundant mosquito growth and therefore lead to spread of dengue fever[9].

Aedes aegypti strongly affected by ecological and human drivers, particularly water-bearing containers, but is also influenced by climate, including variability in temperature, moisture and solar radiation. *Aedes aegypti* and *Aedes albopictus* both have shown great compliance to environmental changes by human habitation, dengue has spread with the increasing sprawl of unregulated housing areas in many tropical cities[10].

Both vectors are well adapted to an urban environment: they lay eggs in tires, cans, water jars, near human dwellings. The female mosquito transmits dengue virus more quickly and easily because of their predilection for human blood and habit of multiple, interrupted feedings. In many areas where dengue fever is endemic, policies for mosquito control are completely not existing or if they are there than too far from being successful in controlling the vector and disease[6].

Due to demographic and societal changes, uncontrolled urbanization, globalization, and dissemination of DEN-transmitting mosquitoes, the frequency of DEN epidemics has increased. That's why Dengue haemorrhagic fever (DHF) and dengue shock syndrome (DSS) has spread more widely. Currently, DEN is a major public health problem throughout the world, up till now DEN-specific therapies and vaccines are unavailable[11].

Primary infection with any one of the four-dengue virus serotypes typically leads to dengue fever (DF), which is a debilitating but self limited acute febrile illness. However, some primary infections and a larger percentage of secondary infections with a different serotype result in the severe, life-threatening DHF/DSS, which is characterized by increased vascular permeability and haemorrhagic manifestations. Despite its name, bleeding manifestations are usually minor while major hemorrhages are unusual. In rare cases of DHF/DSS, neurologic abnormalities, including encephalitis, may also occur. Variations in virus strains within and between the four serotypes may influence disease severity. Secondary infections are more likely to result in severe disease and dengue haemorrhagic fever[12].

Several reports have indicated that DENV-2 and DENV-3 may cause more severe disease than the other serotypes[13]. Recovery from infection by one type gives rise to lifelong immunity against that particular serotype. However, cross protective immunity to the other serotypes after recovery is only partial and temporary. Subsequent infections by other serotypes increase the risk of developing severe dengue. There has also been a resurgence of the other major mosquito-borne *flavivirus*, *yellow fever*, and Japanese encephalitis and West Nile virus other than dengue virus[14]. Classic dengue is more

commonly seen among older children, adolescents, and adults[15].

Global burden of dengue

The incidence of dengue has increased dramatically all around the world in recent decades. An estimated 2.5 billion people are at risk for dengue infection in subtropical and tropical regions of the world[16]. According to WHO, currently there may be 50-100 million dengue infections reported worldwide every year. Before 1970, only nine countries had experienced severe dengue epidemics. Dengue is now being endemic in more than 100 countries in Africa, the Americas, the Eastern Mediterranean, South-east Asia and the Western Pacific. The American, South-east Asia and the Western Pacific regions are the most seriously affected. Recently the number of reported cases has continued to increase. In 2013, 2.35 million cases of dengue were reported in America alone, with 37,687 severe cases. The threat of a possible outbreak of dengue fever still exists in Europe while local transmission of dengue was reported for the first time in France and Croatia in 2010 and imported cases were detected in three other European countries. In 2012, during an outbreak of dengue in Madeira Islands of Portugal reported over 2000 cases and imported cases were detected in 10 other countries in Europe apart from mainland Portugal. In 2013, cases have occurred in Florida (United States of America) and Yunnan province of China. Dengue also continues to affect several South American countries Honduras, Costa Rica and Mexico. In Asia, Singapore has reported an increase in cases after a lapse of several years and outbreaks have also been reported in Laos. In 2014, trends indicate increases in the number of cases in the Cook Islands, Malaysia, Fiji and Vanuatu, with Dengue Type 3 (DEN-3) affecting the Pacific Island countries after a lapse of over 10 years. An estimated 500,000 people with severe dengue require hospitalization each year, a large proportion of whom are children. About 2.5% of those affected die[17].

Dengue in Pakistan

The first confirmed dengue haemorrhagic fever outbreak in Pakistan occurred in1994. During 2005-2006, there was an unprecedented ascent in epidemic DHF activity in the country, with a large number of cases being reported from Karachi. More than 3,640 patients with signs and symptoms suggestive of dengue fever were admitted to several referral hospitals in the country, and 40 were reported dead. It was appalling to note that 37 of these deaths occurred in Sindh province. Majority of the cases were from the east, center and north of Karachi. It was evident that co-circulation of DEN-2 and DEN-3 was responsible for the 2006 out-break. In previous studies, significant independent association of male gender with DHF has been observed. A higher mortality rate was however seen in females. A shift in the age distribution of affected individuals has also been noted; children being affected less in later studies[18].

However, knowledge about dengue fever among general population was found to be 38.5% in Pakistan[19].

Clinical features

Almost 80% of all dengue infections are asymptomatic. Severe arthralgia and myalgia are the well known characteristics of dengue fever known as 'break-bone fever'. Fever and other symptoms rarely last more than seven days, but convalescence can be prolonged and debilitating[7].

The clinical features of dengue also varies with the age of the patient and, in addition to clinically apparent infections, can be classified into five presentations: nonspecific febrile illness, classic dengue fever(DF), dengue haemorrhagic fever(DHF), dengue haemorrhagic fever with dengue shock syndrome(DSS), and other unusual syndromes such as encephalopathy and fulminant liver failure.

Incubation period of dengue is 4-7 days (range 3-14). Clinical presentation characterized by fever (febrile painful period of DF lasts for 5-7 days and may leave the patient feeling tired for several days),

dengue virus disappears from the blood after an average of 5 days, closely correlated with the disappearance of fever, myalgias, body aches and pains, joint pain, backache, headaches, retro orbital pain, nausea and vomiting, skin rash arising on the 3rd or 4th day, lymphadenopathy, positive tourniquet test, petechiae, and haemorrhagic manifestations such as epistaxis and bleeding from mucosal surfaces. Lab investigations more frequently reveals thrombocytopenia (<10/mL), leukopenia, haemoconcentration (haematocrit increased by at least one fifth or decreased by same amount after I/V hydration, hypoalbuminemia, hypoprotenatremia[20,21].

The symptomatic phase of the disease is divided into three phases, i.e. febrile phase, critical phase, and recovery phase. In most of the patients, febrile phase is followed by the recovery phase and entire illness may pass off as a simple febrile episode. Some of the patients have prolonged periods of thrombocytopenia while others may have a prolonged febrile phase. The critical phase can start at any time from 3-7 days since the onset of the fever. The most important feature of the critical phase is increased capillary permeability which leads to the extravasation of fluid[22].

Vast majority of the cases resolved without specific treatment but their recognition is important because the risk of severe disease is several times higher in secondary infection than the primary infection itself[23].

A high proportion of patients with DHF had abdominal symptoms: diarrhoea (32%), vomiting (68%) and abdominal pain (18.7%). In some cases abdominal pain simulated an acute surgical abdomen. Fewer adults developed pleural effusions or ascites (adults 10.2%, children 81.4%) or shock (adults 14%, children 30%)[24].

Skin lesions are very common presenting features of dengue fever and often can be diagnostic. The characteristic combination of fever, rash and headache are called the "dengue triad". The types of skin lesions associated with dengue fever are generally not well-known to doctors and there seems to be confusion regarding the skin lesions. General practitioners and other non-dermatologists require a clear understanding of the various types of skin lesions seen in cases of dengue fever[25].

The characteristic exanthem of DF is estimated to occur in 50-82% of patients with DF. In DF, the initial rash is a transient flushing erythema of face that typically occurs shortly before or within the first 24-48 hours of the onset of symptoms because of capillary dilatation. The second rash usually occurs 3-6 days after the onset of fever and it is characterized by asymptomatic maculopapular or morbilliform eruption. In some cases, individual lesions may coalesce and are then seen as generalized confluent erythema with petechiae and rounded islands of sparing-"white islands in a sea of red" and is thought to be due to an immune response to the virus. The rash is usually asymptomatic but sometimes associated with pruritus in minority of patients. In some cases, recovery phase is also marked by cutaneous changes in the form of a purpuric eruption on the hands, forearms, feet and legs, and in the mouth. Mucosal involvement is estimated to occur in 15% to 30% of patients with dengue more commonly in patients with DHF than with DF. Mucosal manifestations are mostly conjunctival and scleral injection, small vesicles on the soft palate, erythema and crusting of lips and tongue[26].

Haemorrhagic manifestations on the skin such as petechiae, purpura, or ecchymosis with positive tourniquet test are commonly seen in DHF and DSS but rarely in DF. Tourniquet test is performed by inflating a blood pressure cuff on the upper aspect of arm to a point midway between systolic and diastolic pressures for 5 minutes. The test is considered positive when >20 petechiae/2.5 cm^2 are observed. Hemorrhagic manifestations usually appear 4-5 days after the onset of fever[26].

Uncommon clinical features

Less frequently occurring symptoms include epistaxis, bleeding gums, gastrointestinal haemorrhage, haematuria and intracranial haemorrhage.

Pulmonary manifestations such as pneumonitis, pleural effusion, haemoptysis and pulmonary haemorrhage are rarely seen in DHF. Haemoptysis has been reported in 1.4% of dengue infection[27].

However, various other clinical presentations and complications are now being increasingly recognized. These include acute myocarditis, acute hepatitis, hepatic failure and dengue encephalitis, There are also reports describing apparent illnesses resembling acute surgical emergencies occurring during DF, such as acute pancreatitis, acute acalculous cholecystitis and, acute appendicitis[28].

Dengue virus results in a wide spectrum of ophthalmic manifestations as well, ranging from nonspecific symptoms to symptomatic retinal haemorrhages and from non immunological to immunological manifestations like uveitis. Ocular manifestations reported to be associated with dengue infection are mostly associated with posterior segment manifestations like macular edema, vascular occlusions, chorioretinits, and vasculitis with related retinal bleeding, or cotton wool spots. Anterior segment manifestation has mostly been reported in the form of subconjunctival haemorrhage, which is related to thrombocytopenia. Anterior uveitis has been rarely described in the acute dengue infection[29].

Clinical and experimental observations also showed that liver involvement occurs during dengue infections. Patients may present with right hypochondrium pain, hepatomegaly, alterations in the aminotransferase levels, even jaundice and acute hepatitis. Liver involvement being more pronounced in the more severe forms of infection. It is evident that dengue viral antigens have been found within hepatocytes, and the virusis capable of replicating in both hepatocytes and Kupffer cells. However there are limitations in the investigation of liver involvement in dengue infection[30].

It has been observed that the greatest alterations in aminotransferase levels found in females with haemorrrhagic fever. In hepatitis, the levels of these enzymes reach a maximum on the ninth day after the onset of symptoms, and they gradually return to normal levels within three weeks. However, liver is not the main target organ for this disease. In most cases, hepatic involvement prolongs the clinical course of this self-limiting viral infection, but it does not constitute a sign of worse prognosis[31].

Dengue fever may also be associated with acalculous cholecystitis. The diagnosis of acute acalculous cholecystitis was made according to clinical features and sonographic findings. The clinical manifestations were fever, right upper quadrant tenderness and a positive Murphy's sign. Sonographic findings were a thickened gallbladder wall (defined as wall thickness>3.5 mm), a positive sonographic Murphy's sign (defined as maximum tenderness of the sonographically localized gallbladder), pericholecystic fluid collection, and no stone(s) in the gallbladder. Patients had no recent history of burns, trauma, vasculitis, or recent surgery[32].

Nervous system involvement has been identified with the serotypes 2 and 3. Neurologic manifestations occur in 4% to 5% of patients, and the manifestations include encephalopathy, encephalitis, Guillain-Barre syndrome (GBS), myelitis, meningitis, acute disseminated encephalomyelitis (ADEM), facial and ulnar mononeuropathy and stroke, both ischemic and haemorrhagic etc[33].

Usually recent infections with *Campylobacter jejuni*, Cytomegalovirus, Epstein-Barr virus and mycoplasma pneumonia are specifically related to GBS. It has also been reported that Gullian-Barre syndrome (GBS) is occurring as a course of dengue fever[34]. Marked neurological symptoms were also noted in fatal case of dengue fever[35]. There are few case reports of vertical transmission of dengue fever from mother to baby as well[36].

One case had severe haemorrhage following cesarean section and one had abruptio placenta. The consequences for the fetuses were as follows: IUD (intrauterine death), acute fetal distress and mother to fetal transmission, bleeding from different sites (GIT, CNS, skin) has also been reported in

vertical transmission, premature birth, even death from massive left intra-cerebral haemorrhage with midline shift[37].

There are some case reports showing dengue fever mimicking like acute appendicitis and acute surgical abdomen as well[38]. Clinical manifestations in severe dengue and yellow fever and chickungunya are similar. All are arboviral diseases. Viruses causing dengue and yellow fever are closely related (both are flaviruses, transmitted by the same group of vectors)[39].

Dengue and malaria coexistence

Dual infections are not very uncommon. Coexisting malaria and dengue infection would be common in areas where both illnesses are endemic. Dual infections with two infectious agents can result in an illness having overlapping symptoms, resulting in situation where both diagnosis and treatment of a patient may become difficult for a physician. Differentiating malaria from dengue, based on purely clinical grounds is difficult. The patients with combined infection had prolonged fever of more than 7 days, myalgias, bleeding manifestations, rash and anemia. Malaria produces almost similar symptoms like dengue like fever, headache, malaise, abdominal discomfort; vomiting and other flu like symptoms, but rash is not the characteristic feature of malaria. Compared with those with malaria, patients with dengue are more likely to develop abrupt onset of fever, with severe headache, myalgias and arthralgias (severe pain gives it the name of break bone fever), and rashes. Complicated falciparum malaria can produce altered level of consciousness, renal failure, hypotensive shock, pulmonary edema, abdominal pain with diarrhea, hepatosplenomegaly, spontaneous bleeding and coagulopathy, hyper-pyrexia and unarousable coma.

In Pakistan co infection was found to be 23.21%[40-41].

Dengue and chikungunya virus coinfection

Dengue and chikungunya are both arboviral infections transmitted by *Aedes aegypti* and *Aedes albopictus*. Chikungunya is a self-limiting and non-fatal acute illness whereas dengue has shown severe complications. Symptoms of both diseases resemble each other. In those areas where both viruses exist together in the environment, coinfection with dengue and chikungunya can be presented commonly[39,42].

Diagnostic tools and investigations

With all the characteristic signs and symptoms and lab investigations we can confirm dengue by different serological tests. haemagglutination-inhibition (HI), Complement fixation (CF), neutralizing test (NT), Immunoglobulin M (IgM) capture enzyme linked immunosorbent assay (MAC-ELISA), and indirect immunoglobulin GELISA[43].

First of all IgM antibody appears in blood. Anti-dengue IgG appears in low titer at the end of the first week of illness, and increases slowly. While, during secondary infection antibody titers rise extremely rapidly and antibody reacts broadly with many flaviviruses. High levels of IgG are detectable even in the acute phase and they rise dramatically in next two weeks. Some anti-dengue IgM false negative reactions are also observed in secondary infections. According to Pan American Health Organization (PAHO) guidelines, by day five of illness, 80% of cases have detectable IgM antibody, and by day six to ten, 93-99% of cases have detectable GM that may persist for over 90 days. Anti-dengue IgM detection using ELISA represents one of the most important advances. Specifically, MAC-ELISA (IgM antibody capture ELISA) diagnosisis based on detecting dengue-specific IgM antibodies in the test serum by capturing them using anti-human IgM antibody previously bound on a solid phase. Almost, 10% false negative and 1.7% false positive reactions have been observed. Different formats such as capture ELISA, capture ultra micro ELISA, dot-ELISA, AuBioDOTIgM capture and dipstick have been developed. Serum, blood on filter paper, and more recently saliva are useful for IgM detection if samples are taken within the appropriate time frame (after five days of onset of fever)[44].

Management

Case-fatality rates are usually 2.5%, can exceed up to 20% but can be reduced to <1% with rapid diagnosis and proper treatment of the patients[45]. The most important step is implementing timely, appropriate clinical management, which involves early clinical and laboratory diagnosis, intravenous rehydration, staff training and hospital reorganization. For this disease which apparently behave to be a complex disease in its manifestations, its management is relatively simple, inexpensive and highly effective in saving lives provided correct and timely interventions are instituted as stated earlier. The key is early recognition and understanding of the clinical problems during the different phases, leading to a rational approach to case management and a good clinical outcome. This is especially so for the treatment of plasma leakage with oral or intravenous rehydration. Serological assays to detect specific immunoglobulin M (IgM) or immunoglobulin G (IgG) antibodies to dengue virus are widely available, and WHO has taken a leading role in coordinating the production of standardized panels for comparison. These assays can provide an alternative to virus isolation or polymerase chain reaction to support the diagnosis of dengue fever[46].

Prevention and control of dengue fever

Five factors are keys to the epidemiology of vector-borne diseases: the ecology and behaviour of the host, the ecology and behavior of the vectors, and the degree of immunity in the population. A holistic view of this complexity is the key to assessing the likelihood of transmission in Europe[7].

An appropriate community intervention is clearly needed to reduce the burden of vector. Reduction of mosquito breeding in household water vessels through larvicides, predatory crustaceans,or elimination of discarded containers, and control of adult mosquitoes by spraying with insecticide, require a continuous effort by the community. Implementing these measures could be expensive for community. Use of window curtains treated with insecticide alone or in combination with treated jar covers can substantially reduce the dengue vector population and potentially reduce disease transmission[47].

An effective, safe, affordable vaccine against dengue virus is not an immediate prospect. Since preexisting heterotypic antibodies within the host increase the risk for DHF and DSS, an effective vaccine will have to offer a greater than100% protection against all 4 serotypes of the virus. Attenuated vaccine viruses have been evaluated, and a tetravalent formulation of such viruses is currently being tested in repeated trials. Another approach is construction of recombinant vaccines with construction of chimeric viruses by insertion of specific genes of dengue virus into a vaccine candidate virus. Through genetic manipulation, these recombinants may be able to replicate faster, be more immunogenic, and be safer than traditional attenuated strains[6].

Other programs continue towards further development of tetravalent vaccines. Hawaii Biotech are in Phase 1 trials of amonovalent Dengue-1 vaccine. With successful results, this vaccine will next progress to tetravalent trials. Another chimeric dengue vaccine has been developed by CDC on an attenuated Dengue-2 backbone used in the same way as Acambis/Sanofi vaccines have used the 17D Yellow Fever vaccine backbone. The CDC vaccine has been licensed to in viragen for clinical trials towards a tetravalent vaccine due to begin shortly. The clinical trial program is becoming typical of dengue vaccine development with initial trials in dengue-free countries, in this case USA, before Inviragen moves to Singapore for later phase clinical trials in an endemic area[48]. Aventis Pasteur aim for it to be on the market in 2015[48]. However, current developments are promising and six tetravalent candidate vaccines are in Phase I-III trials. Optimistically, a licensed vaccine can be anticipated in the next 5-7 years[49].

Conflict of interest

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