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EPEDIOMOLOGY, MANAGEMENT AND CONTROL OF DENGUE VIRUS INFECTIONS: A REVIEW

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Abstract

This study was conducted at Department of Zoology, University of Gujrat, Pakistan in 2017. The data regarding epediomology, management and control of dengue virus infections was obtained and compiled through a thorough review of various published research articles of international reputed journals and relevant books. Dengue viral infections are one of the most important mosquito borne diseases in the world. They may be asymptomatic or may give rise to undifferentiated fever, dengue fever, dengue hemorrhagic fever (DHF), or dengue shock syndrome. Annually, 100 million cases of dengue fever and half a million cases of DHF occur worldwide. Ninety percent of DHF subjects are children less than 15 years of age. At present, dengue is endemic in 112 countries in the world. No vaccine is available for preventing this disease. Dengue viruses are members of the Flaviviridae, transmitted principally in a cycle involving humans and mosquito vectors.

Keywords: DHF, Dengue Hemorrhagic Fever; DSS, Dengue Shock Syndrome, Flavivirus; Vector-borne virus, Arbovirus

INTRODUCTION

Dengue is an acute febrile disease caused by the mosquito-borne dengue viruses (DENVs), consisting of four serotypes (DENV 1 to 4), that are members of the Flaviviridae family, genus flavi-virus [1]. All four DENV serotypes have emerged from sylvatic strains in the forests of South-East Asia [2].DENV is presently the most common cause of arbo-viral disease globally, and all four serotypes of DENV can be found worldwide. More than 100 countries are endemic, primarily affecting 2.5 billion inhabitants in the tropical and subtropical regions as well as 120 million travelers to these regions every year [3].The four DENV serotypes can cause a wide range of diseases in humans even though DENV infections may also be asymptomatic. The diseases range in severity from undifferentiated acute febrile illness,

classical dengue fever (DF), to the life-threatening conditions DHF/DSS [4]. DF is sometimes referred to as 'break bone fever' due to its incapacitating symptoms with severe muscle and joint pain [8] or 'seven-day fever' since the symptoms usually persist for 7 days. Early symptoms of DF and DHF are indistinguishable, but DHF is associated with hemorrhagic manifestations,plasma leakage resulting from an increased vascular permeability, and thrombocytopenia (<100,000 platelets/mm3).DSS is distinguished from DHF by the presence of cardiovascular compromise, which occurs when plasma leakage into the interstitial spaces results in shock. DSS is a fatal condition with mortality rates as high as 20% but can also be less than 1% in places with sufficient resources and clinical experience. Common clinical warning signs for DSS include a rapidly rising haematocrit, intense abdominal pain, persistent vomiting, and narrowed or absent blood pressure [4]. The contribution of climatic change is controversial, and it is not known to what extent this enhances the spread of mosquitoes, and indirectly the DENVs [3, 6, 7]geographical distribution underlining why mosquito density is an important parameter for predicting DENV epidemics [8]. The female mosquitoes lay their eggs in artificial water containers such as tires, cans, and jars. Due to water requirements for breeding, mosquito densities peak during wet season, with the direct consequence of rising numbers of dengue cases. The A. aegypti mosquito is well adapted to an urban environment and is a highly competitive vector due to its anthropophilic nature. Thus, the female mosquito can infect multiple persons in order to complete a single blood meal. Protective clothing and mosquito- repellent sprays are essential to avoid DENV transmission since the Aedes mosquitoes are active during the day, minimizing the use of bed nets. In general, *A.aegypti* is less susceptible to infection by DENV than *A. albopictus*, which could act as a selection mechanism for more virulent strains of DENV.

HISTORY OF EPIDEMICS AND THE EMERGENCE OF DHF/DSS

Dengue fever has been recognized clinically for over 200 years. During the 18th and 19th centuries the disease occurred in intermittent pandemics affecting Asia and the Americas, occurring at intervals of up to several decades [9, 10]. Spread was slow, generally by ships carrying breeding populations of *A. aegypti* and susceptible human hosts. In many areas, dengue was recognized only among expatriate settlers or colonial military forces, and the disease escaped attention in the indigenous populations under poor medical surveillance. This pattern changed dramatically during and after World War II. Dengue viruses were spread by viremic military personnel to staging areas in the Pacific. Multiple dengue serotypes were geographically shuttled by viremic troops and refugees, and the vector was spread by vehicles, water storage containers, and tires carrying along the ova and larvae of*A. aegypti*. The dissemination of virus and vector was enhanced after the war by rapid population growth andurbanization. Asian cities were characterized by poor sanitation, the necessity for domestic water storage, and crowded living conditions, creating conditions favoring breeding of*A. aegypti*.Superimposed on these phenomena was the rapid rise in air travel, providing the means for movement of viremic human beings within the region and beyond. These factors led to the establishment of hyper-endemic dengue infection in Southeast Asia, a pattern of annual outbreaks caused by all four dengue serotypes, and an increasing frequency ofsequential infections ofchildren [11]. It is in this setting that DHF/DSS emerged in 1954 in the Philippines. Over the next 20 years, outbreaks occurred that involved many parts of Asia and the Pacific, with a mean annual incidence of about 30,000 cases. In the 1970s and 1980s, the incidence of DHF rose dramatically, to over 250,000 cases per year. DHF is now the third orfourth leading cause of hospitalization of children in some areas [12].

ECOLOGIC BASIS FOR THE EMERGENCE OF DENGUE

Underlying the emergence of DHF in the Western Hemi- sphere are changes in human and mosquito ecologies that affect the rate and geographic range of virus transmission. The principal vector*, A. aegypti*, has made extraordinary evolutionary adjustments to coexist with

human beings. This mosquito originated (and still exists) in Africa as a forest species feeding principally on rodents and other wild animals and adapted to lay eggs and undergo larval development in forest tree holes containing rainwater. However, a subspecies *A. aegypti aegypti*, evolved in Africa to become a highly domesticated animal, following humankind on its journeys and migrations to the corners of the globe, breeding in the artificial containers used for storing clean water, resting between blood meals in human habitations away from predators and harsh weather, flying rarely more than 50 yards from these convenient locations, and adopting wary biting habits around its observant and dexterous human prey. Interestingly, *A. aegypti* is not a very efficient vector of dengue viruses, and has both a low susceptibility to oral infection and low rate of trans-ovarial infection [13]. Thus, virus titers in the blood of human hosts must exceed 105-107 virus particles per ml for infection and transmission to be sustained. The vector may thus serve as an important selection mechanism or biological filter for maintaining virus virulence at a high level, since only virus strains that replicate efficiently in humans and produce high viremias are transmissible by this mosquito.

TRANSMISSION CYCLE

Dengue is caused by four anti-genically distinct single-strand positive-polarity RNA viruses, designated dengue types 1-4, belonging to the family Flaviviridae [14]. Virus transmission in its simplest form involves the ingestion of viremic blood by mosquitoes and passage to a second susceptible human host. An extrinsic incubation period of 8-10 days is required after feeding on a viremic human for viral replication and internal dissemination in the mosquito before virus appears in the saliva and transmission on re-feeding can occur. As the blood meal stimulates oviposition by the female mosquito, which undergoes at least one, and often more, reproductive cycles during the extrinsic incubation period, there is an opportunity for virus to enter the egg and be passed to the next generation of mosquitoes.

DISEASE

The uncomplicated disease, classical dengue fever, is a biphasic illness beginning abruptly 3-8 days after the bite of an infected mosquito, characterized by fever, headache, severe malaise, lumbosacral aching, and generalized muscle, joint, or bone pain. Improvement after several days is followed by the reappearance of fever and development of a measles-like-rash, generalized lymphadenopathy, and, some- times, minor hemorrhagic phenomena [15].The case-fatality rate of DHF/ DSS is up to 20%if untreated, but with supportive treatment consisting of fluid and electrolyte management and oxygen, less than 1% of such cases prove to be lethal.

PATHOGENESIS OF DENGUE FEVER /DHF

Dengue may be caused by any of the dengue viral serotypes. Generally, infection with one serotype confers future protective immunity against that particular serotype but not against other serotypes. After the bite of an infected mosquito, the dengue virus enters the body and replicates within cells of the mono- nuclear phagocyte lineage (macrophages, monocytes, and B cells). Additionally, infection of mast cells, dendritic cells, and endothelial cells are known to occur [16, 17, 18].The incubation period of dengue infections is 7–10 days. A viremic phase follows where the patient becomes febrile and infective. Thereafter, the patient may either recover or progress to the leakage phase, leading to DHF and/or dengue shock syndrome. Peak plasma viraemia correlates with the severity of dengue infections [19]. Differences in antibody, cytokine, and T-cell responses are seen among patients with uncomplicated dengue fever or DHF/ dengue shock syndrome.

CHARACTERISTICS OF THE DENGUE VIRUS

The dengue virus is a single stranded RNA virus belonging to the Flaviviridae family [20]. There are four serotypes (DEN 1–4), classified according to biological and immunological criteria. The viral genome is approximately 11 kb in length [20]. The mature virion consists of three structural (core, membrane associated, and envelope) and seven non-structural (NS1, NS2a, NS2b, NS3, NS4a, NS4b, and NS5) proteins. The envelope protein is involved in the main biological functions of the virus. It binds to receptors on host cells, allowing the virus to be transported through it. In addition, the envelope protein is associated with haem-agglutination of erythrocytes, induction of neutralizing antibodies and protective immune responses [21]. Non-structural proteins (NS1–NS5) expressed as both membrane associated and secreted forms have also been implicated in the pathogenesis of severe disease. Unlike other viral glycoproteins, NS1 does not form a part of the virion but gets expressed on the surface of infected cells. Preliminary evidence suggests its involvement in viral RNA replication [22]. Plasma levels of secreted NS1 (sNS1) correlate with viral titers, being higher in patients with DHF compared with dengue fever [23]. Moreover, elevated free sNS1 levels within 72 hours of onset of illness identify patients at risk of developing DHF. Very high levels of NS1 protein are detected in acute phase samples from patients with secondary dengue infections but not primary infections. This suggests that NS1 may contribute to formation of circulating immune complexes, which are thought to have an important role in the pathogenesis of severe dengue infections [22].

MOSQUITO VECTORS IN DENGUE INFECTIONS

Mosquitoes belonging to the genus Aedes (*Aedes aegypti, Aedes albopictus*, and *Aedes polynesiensis)* play an important part in transmission of dengue. The primary and most important vector is *A. aegypti*, but *A. albopictus* and *A. polynesiensis* may act as vectors depending on the geographic location [23]. For instance, *A. albopictus* has been found to sometimes transmit dengue in Thailand, Samui Island, India, Singapore, and Mexico. Aedes aegypti, a container breeding, day biting mosquito is found in tropical and subtropical areas [24]. They rest indoors, mainly in living rooms and bedrooms. This maximizes man-vector contact and minimizes contact with insecticides sprayed outdoors, hence contributing to difficulty in controlling this vector [25]. Aedes aegypti can breed in polluted water or small collections of water such as flower vases or coconut shells [26]. Eggs can survive for long periods, as they are capable of withstanding desiccation. Improper disposal of garbage or inadequate wastewater drainage facilitates, both consequences of unplanned urbanization, may be responsible for high mosquito densities in endemic areas. Significant increases in the mosquito larval populations are seen during the rainy season. This may be a reason why epidemics of dengue tend to coincide with the rainy season [24]. Furthermore, ambient temperature and relative humidity affect viral propagation in mosquitoes; rates being highest in climates resembling the rainy season [27]. Environmental temperatures also affect the time to acute viraemia in female mosquitoes, being shorter with rises in temperature [28]. After biting an infected human, dengue viruses enter an adult female mosquito. The virus first replicates in the midgut, reaches the haemocoel and haemolymph, and then gains access to different tissues of the insect. After viral replication in the salivary glands, the infected mosquito can transmit the virus to another human. Ultrastructural studies show viral particles within the nervous system, salivary glands, foregut, midgut, fat body, epidermal cells, ovary and internal body wall lining cells of the mosquito. In contrast, they are absent from muscle, the hindgut, and malphigian tubules.

CLINICAL MANIFESTATIONS OF DENGUE INFECTIONS

Dengue infections may be asymptomatic or give rise to undifferentiated fever, dengue fever, DHF, or dengue shock syndrome.

Undifferentiated Fever
This usually follows a primary infection but may also occur during a secondary infection. Clinically it is indistinguishable from other viral infections.

Dengue Fever
Dengue fever may occur either during primary or secondary infections. The onset is sudden with high fever, severe headache (especially in the retro-orbital area), arthralgia, myalgia, anorexia, abdominal discomfort, and sometimes a macular papular rash. The fever may be biphasic and tends to last for 2–7 days [29, 30]. Flushing, a characteristic feature is commonly observed on the face, neck, and chest. Coryza may also be a prominent symptom especially in infants [31]. Younger children tend to present with coryza, diarrhea, rash and seizure, and less commonly with vomiting, headache, and abdominal pain [32]. Although, haemorrhagic manifestations are uncommon in dengue fever, petechiae / pupura, gastrointestinal bleeding, epistaxis, and gingival bleeding have been observed in some individuals [29, 33]. A positive tourniquet test has been reported in many individuals with dengue fever possibly due to reduced capillary fragility [34, 35]. Recovery from dengue fever is usually uneventful, but may be prolonged especially in adults [23]**.**

Dengue Haemorrhagic Fever
DHF usually follows secondary dengue infections, but may sometimes follow primary infections, especially in infants. Insuch infants, maternally acquired dengue antibodies are presumed to enhance primary infections [36, 37]. DHF is characterized by high fever, haemorrhagic phenomena, and features of circulatory failure [38, 39]. DHF is divided into three phases— namely: febrile, leakage, and convalescent phases.

Febrile Phase
The febrile phase begins with sudden onset fever accompanied by generalized constitutional symptoms and facial flush. The fever is high grade, intermittent, and associated with rigors [31]. Epi-gastric discomfort, myalgia, vomiting, and abdominal pain are common and patients are usually quite miserable. Sore throats and febrile convulsions may be seen, especially among young children. Tender hepatomegaly is observed in almost all patients and splenomegaly may be seen in some. A macular papular rash similar to that seen in dengue fever is also seen in many patients [40, 41, 42]. The fever lasts for 2–7 days and is followed by a fall in temperature to normal or subnormal levels. At this point, the patient may recover or progress to the phase of plasma leakage. Those who remain ill despite their temperature subsiding are more likely to progress to DHF. Clinical deterioration usually occurs during defervescence (often between days 3 and 4) [43, 44].

Plasma Leakage Phase
Tachycardia and hypotension characterize the onset of plasma leakage. When plasma leakage is severe patients may develop other signs of circulatory disturbance such as prolonged capillary refill time, narrow pulse pressures, and shock. Inadequate treatment of such patients often leads to profound shock. During the phase of plasma leakage (first 24–48 hours after onset of DHF), pleural effusions and ascites are common. Pleural effusions are usually seen on the right side; a right decubitus chest radiograph is best for detecting small effusions [45]. Abdominal ultrasound scans may demonstrate ascites or a thickened gall bladder wall.54. Pericardial effusions may also occur. This latter complication is uncommon, but is associated with high morbidity and mortality. In DHF, bleeding may occur from any site and does not correlate with the platelet counts. Haemorrhagic manifestations usually occur once the fever has settled [41]. Minor degrees of bleeding may manifest as gum bleeding and petechiae. The commonest site of haemorrhage is the gastrointestinal tract, which manifests as haematemesis or melaena, followed by epistaxis [39, 42, 46]. Vaginal bleeding is commonly reported in females [47].

Convalescent Phase

Convalescence in DHF is usually short and uneventful [23]. The return of appetite is a good indicator of recovery from shock. Bradycardia is also seen in this period. If present, a confluent petechial rash with erythema and islands of pallor (usually known as a recovery rash) is characteristic of dengue infections. During the convalescent stage, many patients also complain of severe itching especially on the palms and soles.

Dengue Shock Syndrome

Dengue shock syndrome is associated with very high mortality (around 9.3%, increasing to 47% in instances of profound shock) [48]. Severe plasma leakage leading to dengue shock syndrome is associated with cold blotchy skin, circumoral cyanosis, and circulatory disturbances. Acute abdominal pain and persisting vomiting are early warning signs of impeding shock [43]. Sudden hypotension may indicate the onset of profound shock [49]. Prolonged shock is often accompanied by metabolic acidosis, which may precipitatedisseminated intravascular coagulation or enhance ongoing disseminated intravascular coagulation, which in turn could lead to massive haemorrhage. Dengue shock syndrome may be accompanied by encephalopathy due to metabolic or electrolyte disturbances.

COMPLICATIONS OF DHF

Severe dengue infections may give rise to many complications such as liver failure, disseminated intravascular coagulation, encephalopathy, myocarditis, acute renal failure, and haemolytic uraemic syndrome [23]. Although these complications are generally rare, in recent years they have been reported with increased frequency [50].

Liver Failure

Since hepatocytes and Kupffer cells support viral replication, liver involvement is common in all forms of dengue infection [51]. Its severity varies with the overall severity of the dengue infection. Levels of aspartate transaminase and alanine transaminase are significantly higher, and globulins significantly lower among patients with the more severe grades of DHF [50, 52]. Infection with DEN-3 or DEN-4 serotypes produce greater liver involvement (liver enzymes higher compared with infection with the other two serotypes) [53]. Fulminant liver failure can occur due to hepatitis or focal necrosis of the liver causing hepatic encephalopathy and even death [54]. Liver failure usually presents with convulsions or a change in the level of consciousness. Jaundice may be present. Neurological examination may show hyper-reflexia or an extensor plantar response. Electrolyte abnormalities and hypoglycemia may accompany liver enzyme abnormalities.

Encephalopathy

Encephalopathy has been reported in 0.5% of patients with DHF, and has a mortality rate of 22% [55]. Many factors contribute towards development of encephalopathy including: hepatic dysfunction, electrolyte imbalances, cerebral oedema (caused by vascular changes leading to fluid extravasation), hypo-perfusion (due to circulatory disturbances), and dengue encephalitis [56]. The dengue virus has been isolated from the cerebrospinal fluid of some patients having features of encephalitis [56]. Furthermore, in mice, breakdown of the blood-brain barrier and direct viral infection of the brain has been shown to occur. There is suggestion that histamine might have a critical role in this process [57]. Other neurological manifestations such as altered consciousness, seizures, spasticity of limbs, hemiplegia, and a positive Kernig's sign have also been reported in 5.4% of patients with dengue [50].

Myocarditis

Acute reversible myocarditis has been reported in patients with dengue infections. ST segment and T wave changes in the electrocardiogram together with low ejection fractions and global hypokinesia on radionuclide ventriculography have been found. No myocardial necrosis was detected in any of the patients [58]. In another study, 16.7% of children had left ventricular dysfunction when assessed by two dimensional and color Doppler echocardiography [59]. The left ventricular failure may contribute to hypotension seen in DHF/dengue shock syndrome and may have implications in fluid management as fluid overload may worsen the condition [58, 59].

EPIDEMIOLOGY

During the 19th century, dengue was considered a sporadic disease, causing epidemics at long intervals. However, dramatic changes in this pattern have occurred and currently, dengue ranks as the most important mosquito borne viral disease in the world. In the past 50 years, its incidence has increased 30-fold with significant outbreaks occurring in five of six World Health Organization (WHO) regions. At present, dengue is endemic in 112 countries in the world [60]. Around 2.5 to 3 billion people, living mainly in urban areas of tropical and subtropical regions, are estimated to be at risk of acquiring dengue viral infections [23]. Estimates suggest that annually 100 million cases of dengue fever and half a million cases of dengue haemorrhagic fever (DHF) occur in the world with a case fatality in Asian countries of 0.5%–3.5%. Of those with DHF, 90% are children less than 15 years of age [23]. DHF first emerged as a public health problem in 1954, when the first epidemic occurred in Manila. This gradually spread to other countries in the region. Major epidemics occurred in other regions of the world in the 1980s and 1990s and were caused by all four dengue viral serotypes [61]. While the predominant serotype in the 1980s and the early 1990s was DEN-2, in recent years it has changed to the DEN-3 serotype [47]. In 1998, a pandemic of dengue viral infections occurred, where 1.2 million cases of dengue fever and DHF were reported from 56 countries worldwide. The world population was exposed to a new subtype of the DEN-3 virus (subtype 3) which originated in the Indian subcontinent and later spread to involve other continents [62]. Exposure of a non-immune population to this new subtype of DEN-3 may have been the cause of this pandemic. A situation of comparable magnitude was also seen in 2001–02.

Epidemiological Trends in South East Asia

The first epidemic of DHF in South East Asia occurred in 1954 in Manila, Philippines. Following this, epidemics have occurred in nearly all countries in this region, and currently are a major public health problem in seven of them. The incidence of DHF has increased dramatically in recent years with approximately five times more cases reported since 1980 than in the previous 30 years [23]. Although serological surveys conducted in Indonesia showed that DEN-1 and DEN-2 were the prevalent serotypes until the late 1980s, the DEN-3 serotype has been the predominant serotype in the recent out- breaks [63]. In fact, DEN-3 has been associated with severe dengue epidemics and it has been suggested that the DEN-3 virus may have certain characteristics that make it more virulent. Although DEN–4 has been isolated in almost all epidemics, it is primarily detected in secondary dengue infections [64]. DHFis a leading cause ofhospitalization in children in South East Asia. While this rate has now fallen in Thailand (95–103 cases/100 000 population in 1997) [60], some countries such as Vietnam, still experience very high attack rates [65]. Although case fatality rates in most countries in South East Asia have declined and are now less than 1%, those in some countries still exceed 4%, mainly due to late admission to hospital, when the disease is at an advanced state [66]. In the newly industrialized countries such as Singapore and Malaysia, successful vector control programmes led to a gradual decline in the incidence of dengue, but even here a resurgence has been seen since 1994 [66].

Epidemiological Trends in South Asia

Although small outbreaks of DHF occurred South Asia between 1964 and 1966 [67], the first major epidemic of DHF occurred in Sri Lanka in 1989. Since then regular epidemics have occurred in Sri Lanka, resulting in increasing numbers of cases each year. The DEN-3 subtype III was identified as the cause of the first and subsequent epidemics in Sri Lanka along with the DEN-2 serotype [62, 68]. Dengue infections were first reported in India in 1991 (6291 cases of dengue fever), and the first epidemic of DHF occurred in Delhi in 1996 [69]. The epidemiological pattern of DHF in South Asia is now similar to that in the South East Asian region.

Epidemiological Trends in Far East

In the Far East, epidemics of dengue fever / DHF have been further apart and less severe when compared with those in the South East Asian and South Asian regions. China has been the country most affected. The first epidemic of dengue fever occurred in China in 1978, and was followed by an epidemic of DHF in Hainan Island in 1985–86 (caused by the DEN-2 serotype) [70]. The case fatality rate was 0.25%, which is low compared with that in other regions [71]. At present, Japan is free of epidemics of dengue fever / DHF, and has previously only been reported before World War II [72]. Many cases of dengue are still reported from countries such as Australia, Fiji, and New Caledonia. The largest epidemic in recent times occurred in Fiji in 1998.

Epidemiologicaltrends in America

The first major epidemic of dengue fever occurred in Cuba in 1977–78 (caused by the DEN-1 serotype), followed by the first epidemic of DHF in 1981. This DHF epidemic was also the first in the American region, was caused by DEN-2, with secondary dengue infections accounting for 98%–99% of the cases. After this outbreak a very effective and successful control programme was launched in Cuba resulting in it being free from any dengue viral activity for 16 years (the period 1982–96) [73]. In 1989 an epidemic of DHF occurred in Venezuela [74] followed by a further epidemic in Cuba in 1997 (16 years after the first epidemic in this country) both caused by the DEN-2 serotype. Interestingly, no children were affected during the 1997 DHF epidemic. Since viral transmission had been interrupted over a 16 year period, children may have only had a primary infection at the time, hence arguing for the importance of secondary dengue infections in the subsequent development of DHF [73]. During the last two decades the incidence of dengue fever has increased significantly in this region. In 2002, more than 30 Latin American countries reported over one million cases of dengue fever. DHF occurred in 20 countries with more than 17 000 cases reported, including 225 fatalities [75]. The current epidemiological trend is similar to that seen in Asia, with DHF epidemics occurring every three or four years, with increasing numbers of cases seen with each epidemic [74]. Interestingly, DHF is absent in Haiti despite there being hyper-endemic dengue virus transmission.

Epidemiological Trends in Africa

Although the mosquito vector and all four dengue viral serotypes are present in the African region, to date an epidemic of DHF has not occurred [62]. Since DHF is less frequent among black persons living in areas that experience epidemics of DHF, it is possible that individuals of African origin may have a degree of inherent resistance to the disease.

MANAGEMENT OF DENGUE INFECTIONS

Management of dengue infections is mainly symptomatic, as there are no specific drugs effective against the dengue virus. Proper maintenance of fluid balance is a cornerstone in management. Early identification of the leakage phase with prompt resuscitation helps to

reduce complications and improve outcome. Mortality rates have been low in patients admitted early to hospital before the onset of shock [76].

Management of Dengue Fever

Both dengue fever and the febrile phase of DHF are managed similarly. Paracetamol is the only antipyretic recommended for use, since other non-steroidal anti-inflammatory drugs such as aspirin or diclofenac sodium may result in gastric irritation or provoke gastrointestinal bleeding. The recommended dose of paracetamol (60 mg/kg/day) should not be exceeded, as otherwise liver injury that accompanies dengue viralinfections may be aggravated. If the temperature still remains high despite administration of paracetamol, tepid sponging is recommended [77]. A soft, balanced, and nutritious diet is recommended changing to oral rehydration fluids if a soft diet is refused. An antiemetic such as domperidone may be used to treat vomiting. A gastric mucosal protective agent such as cimetidine may be given to patients with evidence of gastrointestinal bleeding or at risk of such bleeding due to very low platelet counts.

Management of DHF

Adequate fluid administration, regular assessment of fluid and electrolyte balance, andmonitoring for development of complications is vital. Vital signs should be monitored every 1–2 hours to detect early progression to shock. The packed cell volume should ideally be monitored every 4–6 hours (or at least twice a day if this is not possible). The rate of fluid administration depends on body weight and degree of plasma leakage [78]. This rate should be adjusted by frequent assessment of vital signs, urine output, and packed cell volume. Liver enzymes should be measured, as acute liver failure and hepatic encephalopathy are known complications.Platelet transfusions may be given to patients that develop serious haemorrhagic manifestations or have very low platelet counts, although the exact platelet count at which platelet transfusions should be given is debatable. Transfusion requirements correlate with the occurrence of bleeding in the gastrointestinal tract, but not with platelet counts [79].

Management of Dengue Shock Syndrome

The management of dengue shock syndrome is a medical emergency needing prompt and adequate fluid replacement. The patient should be kept flat and oxygen administered. Vital signs (blood pressure, pulse rate and pressure, capillary refill time) should be monitored every 10–15 minutes. Oxygen saturation may be monitored by a pulse oxymeter. Intravenous fluid should be infused using a wide bore cannula, with another wide bore cannula sited on the opposite arm/leg. Blood should be sent for grouping and cross match, urea and electrolytes, full blood count, and liver function tests. Electrolyte abnormalities, hypoglycemia, and metabolic acidosis are commonly seen during refractory shock and need to be looked for and corrected. Disseminated intravascular coagulation is usually present and may lead to worsening of shock or massive bleeding. Hence, prothrombin time and partial thromboplastin time should be measured [80].

PREVENTION AND CONTROL OF DHF

Since there is no effective vaccine against dengue, the prevention and control of dengue infections depends largely on preventing man-vector contact. Numerous strategies have been adopted and include: environmental control, biological control, chemical control, and active case surveillance.

Environmental Control Methods

These include: reducing vector breeding sites, solid waste management, modification of man-made breeding sites, and improvements in house design. Public education programmes play

a vital part if they are to be effective [81]. Personal protection is important in preventing man-vector contact. Sufficiently thick and loose fitting clothes reduce contact with the mosquitoes, but may not be the most practical clothes to wear in hot tropical climates. Other measures such as using household insecticidal products (mosquito mats and liquid vaporizers) or mosquito repellents may also be effective. Naturally occurring repellents (citronella oil, lemon grass) or chemical repellents (DEET) are available. However, unlike in the control of malaria, insecticide treated mosquito nets have limited utility in dengue control programmes as the vector is chiefly a day biting mosquito.

Biological Control of the Vector

Biological control methods are targeted against the larval stages of the dengue vector. They include the use of larvivorous fish such as *Gambusia affinis* and *Poecilia reticulate*, endotoxin producing bacteria (*Bacillus thuringiensis* serotype H-14 and *Bacillus sphaericus* are currently used), and copepod crustaceans. *Bacillus thuringiensis* serotype H-14 is more effective against *A aegypti* with very low levels of mammalian toxicity, and has therefore been accepted for use in house- hold containers storing water [23]. The use of mesocyclops (a copepod crustacean) in the Northern Province of Vietnam led to the eradication of the vector in a many areas [82]. They are most suitable for use in large containers (wells or concrete tanks) that are not cleaned regularly, as frequent cleaning leads to depletion of nutrients required by them. However, mainly due to their high cost, most of these methods have been restricted to small scale field operations [23].

Chemical Control

This includes the application of larvicidal insecticides or space spraying. Space spraying is more widely used as larvicidal insecticides cost more. Insecticides used for treating containers that hold water includes Temephos 1% sand granules and insect growth regulators. Regular monitoring of resistance patterns is essential as resistance to Temephos has been reported among some Aedes mosquito species in the South East Asian Region [23]. Insect growth regulators interfere with the development of the immature forms of the mosquito and have extremely low mammalian toxicity. Space spraying may be applied as thermal fogs or as ultra-low volume sprays. Although both methods are equally effective in killing adult mosquitoes, thermal fogging tends to be used more widely [83]. Although insecticides such as malathion 4%, fenitrothion 1%, or pirimiphos-methyl have proved to be very effective in many control programmes, mosquito vectors develop different patterns of resistance to them [83, 84, 85].Ultra-low volume applied bifenthrin, which has both adulticidal and larvicidal activities, was originally shown to be more effective than thermal fogging in the control of dengue vectors [86]. Subsequent contradictory reports suggest ultra-low volume spraying have no effect on the oviposition of A aegypti mosquitoes, possibly because very low amounts of the aerosol reach the primary resting sites of the vector [25, 87, 88].

CONCLUSION

The DENVs are old viruses that have re-emerged during the latter half of the 20th century. Regarded as a tropical fever disease affecting more than two thirds of the world's population, dengue is also the main cause after malaria of tropical fever among travelers and ranks as the most important mosquito-borne viral disease in the world. The lack of potent antiviral drugs and an effective vaccine results in 500,000 individuals, mainly children, being hospitalized with severe dengue every year and causes tremendous economic losses for both households and whole nations. The pathogenesis of the DENVs are not well understood, partly due to the absence of good animal models.

RECOMMENDATIONS

Effective vector control measures are the sole weapon against dengue today, while there is hope for improved diagnostics, clinical treatment, and effective vaccine.Government agencies and other non-government organizations should strengthen its programs on massive educational campaign to increase awareness and knowledge regarding dengue and preventive measures to reduce mosquito and prevent dengue.

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