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Review Article

Dengue Fever: A Narrative Review Article

Running title: Dengue Fever

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Abstract

Dengue fever (DF) is a mosquito-borne viral illness that has spread rapidly throughout the WHO region in recent years. Dengue virus is primarily transmitted by female mosquitoes (*Aedes aegypti*) species and also by (*Ae Arbopictus)*. Symptoms are usually flu-like but can progress to severe dengue haemorrhagic fever, a life-threatening condition. The incidence of DF has increased dramatically over the past few decades. The true number of dengue cases is underestimated because the vast majority of infected patients are asymptomatic or with mild and self-limited disease. Many patients were misdiagnosed to be other febrile illnesses. It is estimated that 2.5 billion people are at risk of having the disease, making dengue fever a major international public health concern. With an aim to gather and spread knowledge on Dengue fever early management, mode of transmission and reduction of its infectivity, this review provides insights on dengue fever transmission, complications, treatment and impact on the healthcare system.

Key words: dengue fever; haemorrhagic fever; aedes aegypti; transmission; mosquitoes

Introduction:

Dengue fever is acute arthropod-borne viral disease that is caused by four serotypes (DENV-1, 2, 3, 4). dengue viruses are transmitted by Aedes mosquitoes, mainly *Aedes aegypti* and less commonly by *A. albopictus* [1]. Its symptoms range from asymptomatic and flu-like mild illness to a potentially fatal hemorrhagic fever, dengue shock syndrome. DF is a global health challenge, and it is the most common arboviral infection worldwide. WHO estimates that the annual incidence of DF is 100 to 400 million infections, with about half of the world's population is at risk of having the disease [2].

Recent studies showed a significant increase in the number of DF cases in the last two decades, and many regions have suffered seasonal outbreaks. During the period from 2000 to 2019, the number of dengue fever cases reported to the WHO, has increased over 8-fold [2]. This significant increase in incidences has placed a significant burden on the health systems of many countries, particularly those dealing with other health issues, such as the COVID-19 pandemic [3]. In 2016, the average annual dengue fever related cost in Latin America was more than 3 billion USD, including both the social and medical economic burden [4].

this review, aims to highlight the clinical presentation of DF and severe dengue to raise the level of clinical suspicion among healthcare workers to allow early detection and provide necessary treatment, as well as to raise awareness among community members about the disease and the importance of taking preventive measures. Furthermore, it will also review the different ways and strategies to prevent and control outbreaks of DF as well as how to mitigate its economic and social impact, especially on vulnerable communities.

Epidemiology:

In 1789, Benjamin Rush described the first cases of dengue fever and coined the term "break bone fever" Many years later, individual serotypes

were identified, but the epidemiology of these serotypes varies across the continental [5]. Since the discovery of dengue in Africa, it has become endemic in 15 African countries, and most epidemics were reported to be of the DENV-2 serotype, but all four serotypes were isolated in Africa [6]. The wide distribution of the dengue vector and the rapid population growth make the extensive transmission of the virus possible in Africa [7, 8]. The annual incidence of dengue is about 400 million per year [9]. Asian countries represent 75% of dengue fever burden, followed by Africa and south America [10].

Transmission:

The principal vector of dengue virus is Aedes Aegypti, which is a day pitting mosquito that is widely distributed throughout the world. Other Aedes species such as *A.blbopitus* and *A.luciocephalus* can act as potential vectors [11]. the transmission of dengue virus and other semilar mosquito borne diseases is sensitive to rainfall, temperature and humidity that favour the vector to develop the virus [12]. Mosquito bite can transmit all dengue serotypes but susceptibility of the vector to dengue virus varies geographically [12]. A non-vector transmission can occur as in blood transfusion and needlestick injuries [13].

Clinical picture of dengue fever:

Dengue fever it's acute viral infection, that is found to be due to 4 distinct serotypes, and is the most common virus spread to people by mosquitoes [16]. The virus can cause a variety of signs and symptoms, ranging from asymptomatic to fatal, e.g. haemorrhage (dengue haemorrhagic fever), shock (dengue shock syndrome) [17].

A. Dengue fever:

Dengue symptoms are thought to be caused by both viral and host factors in infected patients. The incubation phase lasts between 3 and 14 days, it's often an acute febrile illness that manifests as frontal headache, skin rash, muscle and joint pain, retroocular pain, nausea, and vomiting [18]. The febrile period its painful it takes 5-7 days [19], and patient may present with fatigability after fever terminate, the dengue virus is removed from the blood within five days, which again is correlated with the cessation of fever, and no carrier status arise [17].

most infections in children under 15 years old are asymptomatic and increase in severity as symptoms increase with age. Infants and adolescents DF typically present as undifferentiated febrile illness with a maculopapular rash (arise mainly on the 3rd or 4th day), whereas older children and adults typically present with mild fever and, in some cases, incapacitating disease [14]. Adults and children are more prone to develop skin eruption. In febrile period there is a presence of flashing of face, neck, and chest [17].

Leukopenia and mild thrombocytopenia are frequent [19]. While haemorrhagic symptoms such as gingival bleeding, epistaxis, microscopic haematuria, GIT bleeding, and hypermenorrhoea are less common [17].

B. Dengue haemorrhagic fever:

It's an acute febrile disease associated with bleeding, thrombocytopenia, and evidence of plasma leakage which is the main different from DF and determine the severity of the disease [14], and present as haemoconcentration, pleural or other effusions, or hypoalbuminemia, or hypoproteinemia [17]. The emergence of haemorrhagic dengue fever raises the risk of experiencing shock [14, 19].

C. Dengue shock syndrome:

It's a dengue hemorrhagic fever with the presence of features of circulatory failure e.g. narrow pulse pressure, hypotension, and shock [14, 17]. It has an extremely high mortality rate and occurs as a result of hemorrhagic dengue fever when there is excessive plasma leakage [20].

Diagnosis:

The symptoms and signs of dengue fever alone make it very difficult to differentiate it from other febrile diseases, and detection is also difficult since early symptoms are ambiguous, viremia may go undetected, and serological testing reveals dengue late in the disease's progression [16, 17]. When plasma leakage and thrombocytopenia are found, this is a highly definitive diagnosis [21]. Disease can be ruled out if sign and symptoms appear 2 weeks after leaving an endemic area or if the fever continues for 2 weeks or more.

A. Serological diagnosis:

There are five serological tests used to identify dengue infection, and they are based on virus isolation, viral antigen detection, or viral antibody detection in serum.

Hemagglutinin-inhibition test:

The benefits of this test include its high sensitivity and simplicity of disease execution, while the limitations include its lack of specificity and inability to identify viral genotypes. After a week of complaints, antibodies are identified in the acute phase, and antibody titers exceed 1:10. In the recovery phase of a primary infection, antibody titers drop to1:64; however, in a secondary or tertiary infection, titers exceed 5:120 [22].

Complement fixation test:

The limitation of this test is that it is extremely difficult to execute, requiring highly qualified and trained individuals to get the findings, while the benefits are very specific to primary infection and infection serotype determination. Test based on the utilization of complement during antigen-antibody interaction [22].

Neutralization test:

The limitations of this test include its high cost, lengthy execution time, and technical difficulties, while the benefits include its high sensitivity and specificity and the ability to detect the virus serotype in a primary infection and also detect asymptomatic infections [22, 23].

Enzyme-linked immunosorbent essay:

The benefits of this test include its high sensitivity and simplicity of use in identifying acute-phase (IgM) and recovery-phase (IgG) antibodies and antigens (Ag), and it is commonly used to diagnose. Production of IgM It differs. It may be detected from the 3 to5 days after symptoms appear [21], but it could also be undetectable until the eighth day of disease progression [22]. MAC-ELISA used for the qualitative detection of the virus antigen in the blood [21]. Its benefit is that it's used during epidemics since it has a quick detection of transmission progression, whereas in endemic areas a high number of clinical samples are examined [22]. IgG-ELISA is used to differentiate between primary and secondary dengue virus infections [21]. It is highly sensitive since it is performed in seroepidemiological research [22].

Molecular diagnosis:

It can identify dengue virus throughout the acute phase and, on some occasions, during the recovery phase [22].

Nucleic acid hybridization:

It's an RNA extract. It is employed in epidemiological research rather than diagnostic approaches; because it's hard to work with RNA, and it is also used in tissue autopsies for viral detection [22].

Reverse transcription-polymerase chain reaction (RT-PCR):

It is rapid, sensitive, and easy to use. Used to identify the genome in human tissue or mosquito also useful in quickly identifying novel serotypes in endemic areas [22, 24]. Several studies have found that RT-PCR is affected by the area of the genome chosen to be increased as well as the primers used to accomplish this purpose [22]. Capability of detecting the dengue serotype causing the continuing sickness and quick genomic categorization of dengue virus serotypes.

Treatment:

Up till this moment, there is no prescribed curing therapy for DF that the patient can take to recover from the disease. In severe cases, the patients may need to be hospitalized for supportive care, and for electrolyte replacement, the patient may need intravenous fluid, moreover, the blood pressure measurement is vital if the patient bleeds a blood transfusion is a must to avoid rapid blood pressure falls as well as the hypovolemic shock (x).

The availability of four antigenically different dengue serotypes, each capable of evoking cross-reactive and disease-enhancing antibody responses against the remaining three serotypes, has made dengue vaccine development a problematic undertaking [14].

Prevention has always been better than cure, especially in developing and low-income countries with insufficient resources and shaky healthcare infrastructures.

A. Symptomatic treatment:

Throughout the febrile period, lavish oral fluid administration is advised, as is antipyretic prophylaxis with paracetamol as needed [15]. The patient should avoid any other nonsteroidal anti-inflammatory drugs to avoid the risk of dengue fever bleeding complications [15]. It is very advised to monitor the patient's daily whole blood count if there is a health care hospital or clinic nearby. Severe exhaustion, early bleeding signs, and dehydration indications such as severe diarrhea and vomiting are all indicators that the patient should be admitted to the hospital for close monitoring and follow-up [15].

Severe Dengue fever:

Medical care provided by health care professionals can reduce mortality rates and save lives in most countries around the world by less than 1%, which is quite alarming and necessitates the collaboration of many hands to bridge the gap, including medical students, government and non-governmental organizations, and, most importantly, communities [2].

Prevention:

In preventing dengue fever Several issues, such as poor understanding of the pathogenic mechanisms of dengue fever, incapability to manage the vector population, absence of therapeutic intervention against the disease, and biological challenges in developing a vaccine, impede efforts to reduce the burden of dengue [15]. If an individual becomes a well-known case of dengue fever or knows someone who has been diagnosed with the disease, the patient should avoid mosquito bites during the first week because the virus will be spread in the patient's blood and will subsequently transmit the disease to other uninfected mosquitoes, increasing the percentage of infected individuals and potentially increasing hospitalization and the burden in the health care services [2].To achieve effective dengue fever prevention, all community members must work together to combat mosquito vectors [2]. This can be achieved through the following actions: Furthermore, there is continuing research among many worldwide collaborators in pursuit of breakthrough tools and innovative techniques that will help global efforts to stop dengue transmission. WHO encourages the combination of vector management practices in order to establish long-term, successful locally tailored vector control programs [2].

Discussion

This is one of the first narrative review articles performed in Sudan involving dengue fever perception. It underlines the importance of Epidemiological surveillance to track seasonal patterns, distribution trends to report dengue Control and its affection on the national health system here.

Globally, there is a considerable risk of dengue outbreaks, particularly in non-endemic areas with sensitive populations. Dengue infection represents a new global health security hazard as the Aedes mosquito population increases owing to global warming and globalization [25].

The probable source of the dengue outbreak has been determined to be stagnant water that serves as a breeding habitat for vectors. It is strongly advised to set up surveillance, an early reporting system, and implement protective measures against the vector [26].

Fever, haemorrhagic fever, and dengue shock syndrome are all possible symptoms of dengue infection (DSS). The term "expanded dengue syndrome" (EDS), which has been reported more frequently, was created by the World Health Organization (WHO) to describe cases that do not fit into either DHF or DSS and have unusual manifestations in other organs such as the cardiovascular system, nervous system, kidneys, gut, and hematological system. Additionally, EDS is spreading throughout the world with unusual characteristics and a greater severity. There are more and more reports of uncommon, little-reported presentations with serious organ involvement. This study provides information about clinical presentation which aids in diagnosing dengue quickly and preventing additional outbreaks, especially during active epidemics [27].

Patients with low knowledge scores concerning DF were substantially more likely to be illiterate, under 20, or between the ages of 21 and 30, to have non-skilled jobs, or to be unemployed. The two most frequent preventive actions mentioned by participants were covering water that had been stored (78.6%) and installing screens on the windows of the home (65.3%). 6.7% of participants had just 51–100% effective DF prevention behaviors. Low ratings of favorable sentiments toward DF were found to be a risk factor. Preventive actions against the disease were less likely to be taken because the study participants had low knowledge of DF and a limited understanding of how to cope with the many parts of DF prevention [28].

Previous study examines a mathematical model of dengue that is deterministic and is built on a set of fractional-order differential equations (FODEs). In this study, it examines dengue prevention measures that are pertinent to Malaysia's current circumstances. These include the use of adulticides and larvicides as well as the eradication of breeding grounds and personal protection. The Lyapunov function theory is used to build the global stability of the endemic equilibrium and the disease-free equilibrium. A quick analysis is done of the relationships between operator order and control parameters. To validate theoretical findings and assess the importance of each intervention method in limiting the spread of dengue in the community, numerical simulations are carried out. The model demonstrates that the most effective strategy for preventing the spread of dengue fever [29].

Further strains on the healthcare system are likely to be brought on by the overlapping diseases as well as the increased prevalence and high cost of dengue. Implementing integrated methods, such as immunization, is essential for effectively mitigating and controlling dengue and lowering its incidence [30].

The overall economic burden of DF in china in the three Provinces in 2019 was roughly 46,805,064 Chinese Yuan, 10,579,572 Chinese Yuan (CNY), and 36,927,380.00 Chinese Yuan (CNY), respectively. The costs for preventing and controlling dengue fever are 205,800.00 CNY,

731,180.00 CNY, and 6,934,378.00 CNY, respectively, for counties (or districts) without cases, counties (or districts) with imported cases, and counties (or districts) with local cases. About 3,166,660,240.00 CNY was spent on DF prevention and control in China's 30 counties overall in 2019.

Patients with dengue fever face a disproportionately high direct medical cost burden, hence medical insurance coverage needs to be expanded. The findings also imply that in order to stop the spread of dengue fever, China should improve funding for basic healthcare institutions [31].

In Taiwan: Dengue claimed an average of 115.3 DALYs per million people per year from 1998 to 2014 (range: 6.3 to 934.3). In dengue epidemic years, hospitalization (86.09%), emergency (7.77%), outpatient (6.10%), and medicine costs (0.03%) accounted for the majority of the direct costs associated with the disease. Death-related lost productivity (70.76%) was the main driver of indirect expenses. Overall, expenses were 12.3 times greater in years with epidemics than in years without epidemics [32].

Conclusion:

Our study represents that DF places a significant medical and economical strin in Sudan. With future rapid socioeconomic change and global warming, the rising DF risk may become an unavoidable threat to human health globally. Our findings indicate that strengthening dengue prevention and control efforts in Sudan is necessary in order to limit the disease's potential future effects. These efforts should focus on reducing emissions and pursuing more sustainable socioeconomic growth goals.

Recommendations:

Developing regionally specific models for the high-risk areas of dengue in Sudan, encouraging interdisciplinary collaboration between health ministry and health services, and improving public health education and management at national, regional, and local levels. Promoting more advanced research on the relationship between the impacts of dengue fever on the health system

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