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Pharmacy

OVERVIEW OF DENGUE FEVER

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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 flavivirus.[1] Health Organization (WHO) estimates an annual incidence of approximately 100 million infections, with approximately 500,000 people with dengue hemorrhagic fever (DHF) requiring hospitalization, a large proportion being children. DHF may develop into dengue shock. Syndrome (DSS) whereof the mortality rate is approximately1_2.5%. Successful treatment of patients with DHF and DSS is labor intensive and expensive, but without proper treatment, fatality rates may exceed 20%.[2] The diseases range in severity from undifferentiated acute febrile illness, classical dengue fever (DF), to the life-threatening conditions DHF/DSS.[3] Dengue illness was previously categorized on a I_IV grade scale, but a simplified categorization for dengue case classification has been proposed by WHO's Special Program for Research and Training in Tropical Diseases (TDR) in 2009 where DHF and DSS cases are grouped together as 'severe dengue' (group C) to avoid false negative DHF/DSS diagnosis.[4] After an incubation period of 3_15 days (usually 5 to8), classical DF begins with an abrupt onset of high fever. During the febrile phase, dehydration may cause neurological disturbances and febrile seizures in young children.[5] A macularpapular recovery rash appears 3_5 days after the onset of fever, and it usually starts on the trunk before spreading peripherally.[6] plasma leakage resulting from an increased vascular permeability, and thrombocytopenia (B100,000 platelets/mm3). Thrombocytopenia is not necessarily restricted to severe dengue, and minor bleeding may occur in mild infections, which can be severe in those with peptic ulcer disease.[7]

1.1Epidemiology

The global epidemiology of dengue fever/dengue hemorrhagic fever (DF/DHF) is changing fast.[8] The Indian encounter with this disease is interesting and intriguing. Dengue infection has been known to be endemic in India for over two centuries as a benign and self limited disease. Delhi, a city in North India, has experienced seven outbreaks of dengue virus infection since 1967 with the last reported in 2003.[9] The 1996 epidemic in India was mainly due to the virus dengue.[9] While in 2003 all four serotypes of dengue viruses were found in co-circulation.[10]

1.2 Symptoms

Symptoms, which usually begin four to six days after infection and last for up to 10 days, may include

- Sudden, high fever
- Severe headaches
- Pain behind the eyes
- Severe joint and muscle pain
- Fatigue
- Nausea
- Vomiting
- Skin rash, which appears two to five days after the onset of fever
- Mild bleeding (such a nose bleed, bleeding gums, or easy bruising)

Sometimes, symptoms are mild and can be mistaken for those of the flu or another viral infection. Younger children and people who have never had the infection before tend to have milder cases than older children and adults. However, serious problems can develop. These include dengue hemorrhagic fever, a rare complication characterized by high fever, damage to lymph and blood vessels, bleeding from the nose and gums, enlargement of the liver, and failure of the circulatory system. The symptoms may progress to massive bleeding, shock, and death. This is called dengue shock syndrome (DSS).[11]

People with weakened immune systems as well as those with a second or subsequent dengue infection are believed to be at greater risk for developing dengue hemorrhagic fever.

1.3 Diagnosis

Laboratory diagnosis of dengue virus infection can be made by the detection of specific virus, viral antigen, genomic sequence, and/or antibodies.[12] At present, the three basic methods used by most laboratories for the diagnosis of dengue virus infection are viral isolation and characterization, detection of the genomic sequence by a nucleic acid amplification technology assay, and detection of dengue virus-specific antibodies. After the onset of illness, the virus is found in serum or plasma, circulating blood cells, and selected tissues, especially those of the immune system, for approximately 2 to 7 days, roughly corresponding to the period of fever.[13] Molecular diagnosis based on reverse transcription (RT)-PCR, such as one-step or nested RT-PCR, nucleic acid sequence-based amplification (NASBA), or real-time RT-PCR, has gradually replaced the virus isolation method as the new standard for the detection of dengue virus in acute-phase serum samples.

Two patterns of serological response can be observed in patients with dengue virus infection: primary and secondary antibody responses, depending on the immunological status of the infected individuals. A primary antibody response is seen in individuals who are not immune to flaviviruses. A secondary antibody response is seen in individuals who have had a previous flavivirus infection. For acute- and convalescent-phase sera, serological detection of antibodies based on capture immunoglobulin M (IgM) and IgG enzyme-linked immunosorbent assay (ELISA) has become the new standard for the detection and differentiation of primary and secondary dengue virus infections.[14] This is important, since a sensitive and reliable assay for the detection and differentiation of primary versus secondary or multiple dengue virus infection is critical for the analysis of data for epidemiological, pathological, clinical, and immunological studies.

Virus isolation and characterization: For virus detection, virus isolation by cell culture and from mosquitoes remains the “gold standard,” although it has gradually been replaced by the RT-PCR method for rapid diagnosis. This is mainly due to its lower sensitivity and the fact that a longer time for detection is required if in direct immunofluorescence is performed to identify the isolated virus with dengue- or serotype-specific monoclonal antibodies.[15]However, the molecular method based on RT-PCR has been combined with the cell culture method to improve the sensitivity and reduce the time needed to identify the cultured viruses.[16] The latter method was reported to detect the cultured virus at day 1 (versus day 4 by the indirect immunofluorescence method) if 10^4viruses/ml were inoculated into the culture. It is obvious that viral isolation is indispensable for most laboratories interested in studies of the basic virology, molecular epidemiology and pathogenesis of dengue virus. The isolation of viruses from clinical samples can be conveniently carried out with cultured mosquito cells, such as the AP-61, Tra-284, C6/36, AP64, and CLA-1 cell lines, or mammalian cells, such as the LLCMK2, Vero, and BHK21 cell lines.[17] Because of its higher sensitivity, the mosquito inoculation technique is still the method of choice for attempting

dengue virus isolation from deceased patients with fatal cases or patients with severe hemorrhagic disease.[18] *Aedes albopictus* and *Toxorhynchites spendens*[19] have been shown to be useful for dengue virus recovery. At present, virus isolation with the C6/36 cell line with acute-phase serum or plasma from patients is the method of choice for routine dengue virus isolation.

1.4 Treatment

No specific antiviral medication is currently available to treat dengue. The treatment of dengue fever is symptomatic and supportive in nature. Bed rest and mild analgesic-antipyretic therapy are often helpful in relieving lethargy, malaise, and fever associated with the disease. Acetaminophen (Paracetamol) is recommended for treatment of pain and fever. Aspirin, other salicylates, and nonsteroidal anti-inflammatory drugs (NSAIDs) should be avoided.

Patients with dengue hemorrhagic fever or dengue shock syndrome may require intravenous volume replacement. Plasma volume expanders can be used in patients who do not respond to isotonic fluids.[20]

- **Analgesics**

These agents are used to reduce fever. They inhibit prostaglandin synthesis in the central nervous system. The also inhibit hypothalamic heat-regulating center, which in turn promotes the return of the set-point temperature to normal.

- **Acetaminophen (Tylenol, Fever all, Acephen, Mapap)**

Acetaminophen (Paracetamol) reduces fever by acting directly on hypothalamic heat-regulating centers, which increases dissipation of body heat via vasodilation and sweating. It is used in dengue infections to relieve pain and lower temperature when fever is thought to contribute to patient discomfort.

- **Crystalloids for Fluid Therapy**

Isotonic (0.9%) sodium chloride solution or lactated Ringer solution is administered intravenously to maintain intravascular volume, blood pressure, and urine output.

- **Lactated Ringer solution/isotonic sodium chloride solution**

These fluids are used to expand intravascular volume. Both fluids are essentially isotonic and have equivalent volume restorative properties. Although administration of large quantities of either fluid may lead to some differences in metabolic changes, for practical purposes and in most situations, these differences are clinically irrelevant. Importantly, no demonstrable difference in hemodynamic effect, morbidity, or mortality exists with either product.

- **Volume Expanders**

Plasma volume expanders are used in the treatment of intravascular volume deficits or shock to restore intravascular volume, blood pressure, and tissue perfusion**.**

- **Dextran 40 (LMD)**

Dextran 40 is a polymer of glucose. When infused, it increases intravascular volume, blood pressure, and capillary perfusion. It is used to restore intravascular volume when isotonic crystalloid administration is inadequate for that purpose.

1.5 Prevention

Prevention depends on control of and protection from the bites of the mosquito that transmits it.[31][51] The World Health Organization recommends an Integrated Vector Control program consisting of five elements:[21]

- Advocacy, social mobilization and legislation to ensure that public health bodies and communities are strengthened;
- Collaboration between the health and other sectors (public and private);
- An integrated approach to disease control to maximize use of resources;
- Evidence-based decision making to ensure any interventions are targeted appropriately; and
- Capacity-building to ensure an adequate response to the local situation.

The primary method of controlling *A. aegypti* is by eliminating its habitats.[31] This is done by getting rid of open sources of water, or if this is not possible, by adding insecticides or biological control agents to these areas[21] Generalized spraying with organophosphate or pyrethroid insecticides, while sometimes done, is not thought to be effective.[17] Reducing open collections of water through environmental modification is the preferred method of control, given the concerns of negative health effects from insecticides and greater logistical difficulties with control agents.[21] People can prevent mosquito bites by wearing clothing that fully covers the skin, using mosquito netting while resting, and/or the application of insect repellent(DEET being the most effective).[22] However, these methods appear not to be sufficiently effective, as the frequency of outbreaks appears to be increasing in some areas, probably due to urbanization increasing the habitat of *A. aegypti*. The range of the disease appears to be expanding possibly due to climate change.[23]

Vaccine

In 2016 a partially effective vaccine for dengue fever became commercially available in the Philippines and Indonesia. It has also been approved for use by Mexico, Brazil, El Salvador, Costa Rica, and Paraguay. In Indonesia it costs about US$207 for the recommended three doses.[24]

The vaccine is produced by Sanofi and goes by the brand name Dengvaxia. It is based on a weakened combination of the yellow fever virus and each of the four dengue serotypes.[32][54] Two studies of a vaccine found it was 60% effective and prevented more than 80 to 90% of severe cases. This is less than wished for by some.

There are ongoing programs working on a dengue vaccine to cover all four serotypes. Now that there is a fifth serotype this will need to be factored in. One of the concerns is that a vaccine could increase the risk of severe disease through antibody-dependent enhancement (ADE). The ideal vaccine is safe, effective after one or two injections, covers all serotypes, does not contribute to ADE, is easily transported and stored, and is both affordable and cost-effective.[25]

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 laboratory diagnosis of dengue virus infection has been greatly improved during the last decade. The rapid detection of the dengue virus genomic sequence by real-time one-step RTPCR has become a trend. This assay has the advantages of simplicity, rapidity, and a low contamination rate compared to the characteristics of the nested RT-PCR method, which, however, has a sensitivity similar to that of the real-time RT-PCR

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