ISSN 0976 – 3333

Available Online at www.ijpba.info

International Journal of Pharmaceutical & Biological Archives 2013; 4(6): 1075 - 1085

REVIEW ARTICLE

A Review on Dengue

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Received 12 May 2013; Revised 18 Nov 2013; Accepted 27 Nov 2013

ABSTRACT

Dengue is an infectious tropical disease which is a life threatening disease nowadays. Dengue is the sixteenth neglected disease. The prevention of disease is focused due to unavailability of therapy, diagnosis which involves laboratory test for early detection of disease. The present review comprises symptomatic treatment for saving life of patient. It also comprises information about research of vaccine. Also the present review addresses briefly the history, transmission, prevention with respect to dengue. Dengue is on the rise nowadays..Dengue disease's must detected at the time, so review comprises recent & well equipped techniques for diagnosis .In dengue disease, "prevention is better than cure."

Key words: Dengue, Aedes.

INTRODUCTION

Aedes, principally an aegypti .The virus has four different types; infection with one type usually gives lifelong immunity to that type, but only short-term immunity to the others. Subsequent infection with a different type increases the risk of severe complications. As there is no commercially available vaccine, prevention is sought by reducing the habitat and the Dengue fever is an infectious tropical disease caused by the dengue virus. Symptoms include fever headache, muscle and joints pain, and a characteristic skin rash that is similar to measles. In a small proportion of cases the disease develops into the life-threatening dengue hemorrhagic fever, resulting in bleeding low level blood platelet and blood plasma leakage, or into dengue shock syndrome, where dangerously low blood pressure occurs. Dengue is transmitted by several species of mosquito within the genus number of mosquitoes and limiting exposure to bites [2].

1.1**Defination:-**

"Dengue is infectious tropical disease which caused by virus Aedes agypeti mosquitoes, usually live between the latitudes of 35^0c, north and 35^0c south below [2]. Which typically during the day, particularly in early morning and in evening [15,16].

2. HISTORY

The first record of a case of probable dengue fever is in a Chinese medical encyclopedia from the Jin Dynasty (265–420 AD) which referred to a "water poison" associated with flying insects [42,43]. The primary vector, *A. aegypti*, spread out of Africa in the 15th to 19th centuries due in part to increased globalization secondary to the slave trade [7]. There have been descriptions of epidemics in the 17th century, but the most plausible early reports of dengue epidemics are from 1779 and 1780, when an epidemic swept Asia, Africa and North America [43]. From that time until 1940, epidemics were infrequent [43]. In 1906, transmission by the *Aedes* mosquitoes was confirmed, and in 1907 dengue was the second disease (after yellow fever) that was shown to be caused by a virus [44]. Further investigations by John Burton Cleland and Joseph Franklin Siler completed the basic understanding of dengue transmission [44]. The marked spread of dengue during and after the Second World War has been attributed to ecologic disruption. The same trends also led to the spread of different serotypes of the disease to new areas, and to the emergence of dengue hemorrhagic fever. This severe form of the disease was first reported in the Philippines in 1953; by the 1970s, it had become a major cause of child mortality and had emerged in the Pacific and the Americas [43] Dengue hemorrhagic fever and dengue shock syndrome

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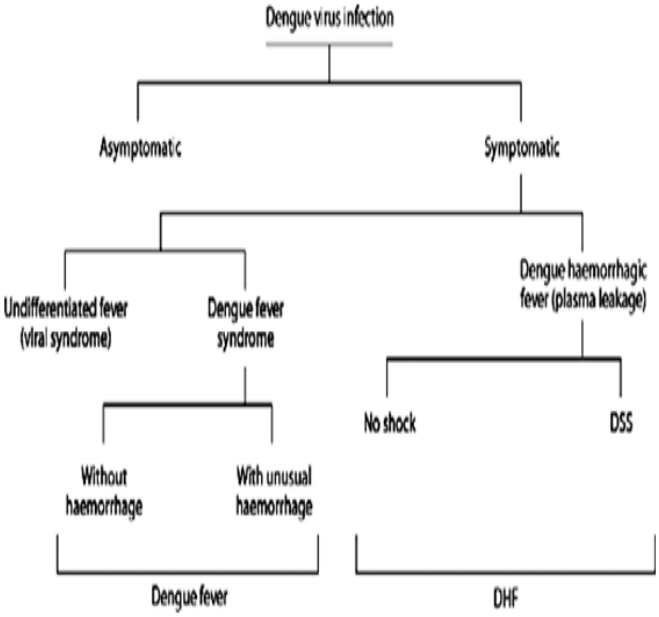
were first noted in Central and South America in 1981, as DENV-2 was contracted by people who had previously been infected with DENV-1 several years earlier. The World Health Organizations' 2009 classification divides dengue fever into two groups: uncomplicated and severe [1,27]. This replaces the 1997 WHO classification which needed to be simplified as it had been found to be too restrictive, though the older classification is still widely used [27]. Severe dengue is defined as that associated with severe bleeding, severe organ dysfunction, or severe plasma leakage while all other cases are uncomplicated [27]. The 1997 classification divided dengue into undifferentiated fever, dengue fever, and dengue hemorrhagic fever [5, 31]. Dengue hemorrhagic fever was subdivided further into grades I–IV. Grade I is the presence only of easy bruising or a positive tourniquet test in someone with fever, grade II is the presence of spontaneous bleeding into the skin and elsewhere, grade III is the clinical evidence of shock, and grade IV is shock so severe that blood pressure and pulse cannot be detected [31]. Grades III and IV are referred to as "dengue shock syndrome."

3. TRANSMISSON:

Figure 1: The mosquito *Aedes aegypti*

The mosquito *Aedes aegypti* feeding on a human hostDengue virus is primarily transmitted by *Aedes* mosquitoes, particularly *A. aegypti* [2]. These mosquitoes usually live between the latitudes of 35° North and 35° South below an elevation of 1,000 meters (3,300 ft).[2]They typically bite during the day, particularly in the early morning and in the evening[16,17] Other *Aedes* species that transmit the disease include *A. albopictus A. polynesiensis* and *A.scuellaris* [2] Humans are the primary host of the virus,[2,12] but it also circulates in nonhuman primate [18]An infection can be acquired via a single bite [19] A female mosquito that takes a blood meal from a person infected with dengue fever, during the initial 2–10 day febrile period, becomes itself infected with the virus in the cells lining its gut [20] About 8–10 days later, the virus spreads to other tissues including the mosquito's salivary gland and is subsequently released into its saliva. The virus seems to have no detrimental effect on the mosquito, which remains infected for life. *Aedes aegypti* prefers to lay its eggs in artificial water containers, to live in close proximity to humans, and to feed on people rather than other vertebrate [21] Dengue can also be transmitted via infected blood products and through organ donation,[22,23] In countries such as Singapore where dengue is endemic, the risk is estimated to be between 1.6 and 6 per 10,000 transfusion [24]vertical transmission (from mother to child) during pregnancy or at birth has been reported.[25]Other person-to-person modes of transmission have also been reported, but are very unusual [9]. The genetic variation in dengue viruses is region specific, suggestive that establishment into new territories is relatively infrequent, despite dengue emerging in new regions in recent decades.

4. CLASSIFICATION



5. MECHANISM

When a mosquito carrying dengue virus bites a person, the virus enters the skin together with the mosquito's saliva. It binds to and enters white blood cells, and reproduces inside the cells while they move throughout the body. The white blood cells respond by producing a number of signaling proteins, such as cytokines and interferon's, which are responsible for many of the symptoms, such as the fever, the flu-like symptoms and the severe

pains. In severe infection, the virus production inside the body is greatly increased, and many more organs (such as the liver and the bone marrow) can be affected. Fluid from the bloodstream leaks through the wall of small blood vessels into body cavities due to endothelial dysfunction As a result, less blood circulates in the blood vessels, and the blood pressure becomes so low that it cannot supply sufficient blood to vital organs. Furthermore, dysfunction of the bone marrow due to infection of the stromal cells leads to reduced numbers of platelets, which are necessary for effective blood clotting; this increases the risk of bleeding, the other major complication of dengue fever [26].

6. VIROLOGY

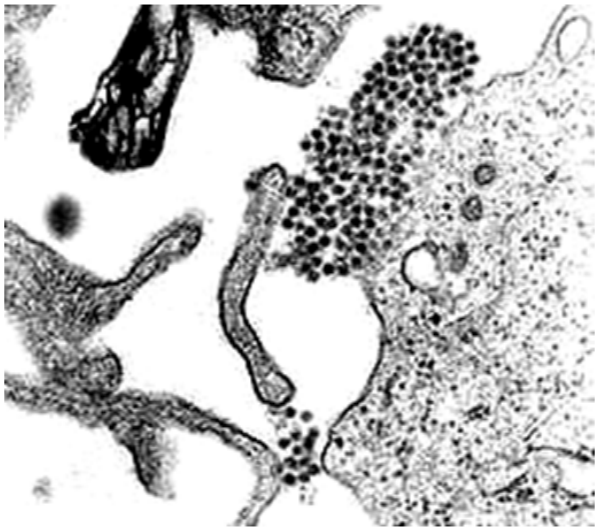


Figure 2:- A TEM micrograph showing dengue virus virions (the cluster of dark dots near the center)

Dengue fever virus (DENV) is an RNA virus of the family Flaviviridae; genus Flavivirus. Other members of the same genus include yellow fever virus, West Nile virus, St. Louis encephalitis virus, Japanese encephalitis virus, tick-borne encephalitis virus, Kyasanur forest disease virus, and Omsk hemorrhagic fever virus [12]. Most are transmitted by arthropods (mosquitoes or ticks), and are therefore also referred to as arboviruses (arthropod-borne viruses) [12]. The dengue virus genome (genetic material) contains about 11,000 nucleotide bases, which code for the three different types of protein molecules (C, prM and E) that form the virus particle and seven other types of protein molecules (NS1, NS2a, NS2b, NS3, NS4a, NS4b, NS5) that are only found in infected host cells and are required for replication of the virus [13,14]. There are four strains of the virus, which are called serotypes, and these are referred to as DENV-1, DENV-2, DENV-3 and DENV-4 [2]. The distinctions between the serotypes are based on the antigenicity [1].

7. SIGN AND SYMPTOMS

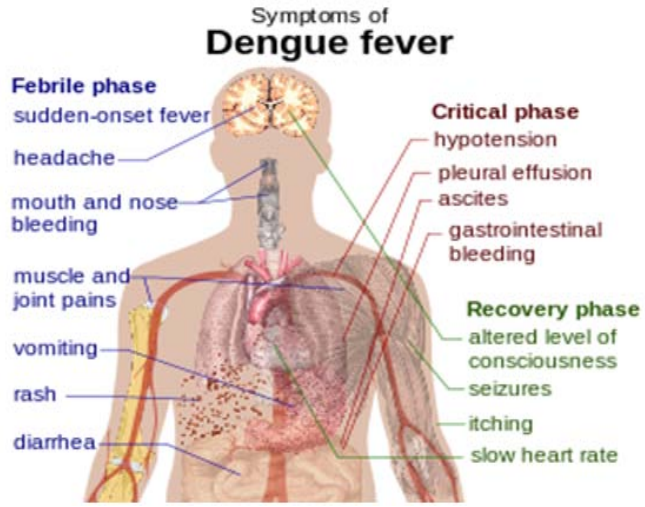


Figure 3:- Schematic depiction of the symptoms of dengue fever

CLINICAL FEATURES OF DENGUE FEVER
Prodame.
•2days of malaise & headache
Acute onset
Fever, backache, arthralgias, headache, generalized pains ("break bone fever"), pain on Eye movement lacrimation , anorexia, nausea, vomiting, relative bradycardia prostration depression, lymphadenopathy.
Fever
• Continuous or "saddle- back", with break on 4th or 5th day, usually lasts 7-8 days.
Rash
Transient muscular in first 1-2 days maculo- papular, scarlet morbilliform from days 3-5 on trunk, spreading centrifugally and sparing palms and soles may desquamate on resolution.
Convalescence-: • slow.[61]

Typically, people infected with dengue virus are asymptomatic (80%) or only have mild symptoms such as an uncomplicated fever [1,3]Others have more severe illness (5%), and in a small proportion it is life-threatening The incubition period time between exposure and onset of symptoms) ranges from 3–14 days, but most often it is 4–7 days [4]. Therefore, travelers returning from endemic areas are unlikely to have dengue if

fever or other symptoms start more than 14 days after arriving home.[5] Children often experience symptoms similar to those of the common cold and gastroenteritis (vomiting and diarrhea)[6] and have a greater risk of severe complications [5,7], though initial symptoms are generally mild but include high fever The characteristic symptoms of dengue are sudden-onset fever, headache (typically located behind the eyes), muscle and joint pains, and a rash. The alternative name for dengue, "breakbone fever", comes from the associated muscle and joint pains [1,9]. The course of infection is divided into three phases: febrile, critical, and recovery.[8] The febrile phase involves high fever, potentially over 40 °C (104 °F), and is associated with generalized pain and a headache; this usually lasts two to seven days.[8-9] Vomiting may also occur [7]. A rash occurs in 50–80% of those with symptoms [9,10] in the first or second day of symptoms as flushed skin, or later in the course of illness (days 4–7), as a measles- like rash.[10-11] Some petechiae (small red spots that do not disappear when the skin is pressed, which are caused by broken capillaries) can appear at this point,[8] as may some mild bleeding from the m mucous membranes of the mouth and nose [5,9]. The fever itself is classically biphasic in nature, breaking and then returning for one or two days, although there is wide variation in how often this pattern actually happens [11,12].

In some people, the disease proceeds to a critical phase around the time fever resolve [7] and typically last one to two days [8]. During this phase there may be significant fluid accumulation in the chest and abdominal cavity due to increased capillary permeability and leakage. This leads to depletion of fluid from the circulation and decreased blood supply to vital organ [8]. During this phase, organ dysfunction and severe bleeding, typically from the gastrointestinal tract, may occur [5,8]. shock (dengue shock syndrome) and hemorrhage (dengue hemorrhagic fever) occur in less than 5% of all cases of dengue [5] however those who have previously been infected with other serotype of dengue virus ("secondary infection") are at an increased risk [5,13] This critical phase, while rare, occurs relatively more commonly in children and young adults [7].The recovery phase occurs next, with resorption of the leaked fluid into the bloodstream [8]. This usually lasts two to three days [5]. The improvement is often striking, and can be accompanied with severe itching and a slow heart rate [5,8]. Another rash may occur with either a maculopapular or a vasculitis appearance, which is followed by peeling of the skin [7] During this stage, a fluid overload state may occur; if it affects the brain, it may cause a reduced level of consciousness or seizures [5]. A feeling of fatigue may last for weeks in adults.

8. ASSOCIATED PROBLEM

Dengue can occasionally affect several other body system [8], either in isolation or along with the classic dengue symptoms.[6] A decreased level of consciousness occurs in 0.5–6% of severe cases, which is attributable either to infection of the brain by infection of the brain by the virus or indirectly as a result of impairment of vital organs, for example, the liver [6,12]. Other neurological disorders have been reported in the context of dengue, such as transverse myelitis and guillain – barrel syndrome [6]. Infection of the heart and acute liver failure are among the rarer complications.

9. PREVENTION

A 1920s photograph of efforts to disperse standing water and thus decrease mosquito populations

There are no approved vaccines for the dengue virus. [1] Prevention thus depends on control of and protection from the bites of the mosquito that transmits it

The World Health Organization recommends an Integrated Vector Control program consisting of five elements:

1. Advocacy, social Mobilization and legislation to ensure that public health bodies and communities are strengthened.
2. Collaboration between the health and other sectors (public and private).
3. An integrated approach to disease control to maximize use of resources.

4. Evidence-based decision making to ensure any interventions is targeted appropriately.
5. Capacity-building to ensure an adequate response to the local situation.

The primary method of controlling *A. aegypti* is by eliminating its habitats

1). This is done by emptying containers of water or by adding insecticides or biological control agents to these areas [16]. Although spraying with organophosphate or pyrethroid insecticides is not thought to be effective [3].
2).Reducing open collections of water through environmental modification is the preferred method of control, given the concerns of negative health effect from insecticides and greater logistical difficulties with control agents [16].
3).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] [19].

10. DIAGNOSIS

- ✓ Warning signs
- ✓ Worsening abdominal pain,
- ✓ Ongoing vomiting,
- ✓ Liver enlargement,
- ✓ Mucosal bleeding,
- ✓ High hematocrit with low platelets,
- ✓ Lethargy or restlessness,
- ✓ Serosal effusions

The diagnosis of dengue is typically made clinically, on the basis of reported symptoms and physical examination; this applies especially in endemic areas [1] However, early disease can be difficult to differentiate from other viral infection [5]. A probable diagnosis is based on the findings of fever plus two of the following: nausea and vomiting, rash, generalized pains, low white blood cell count, positive tourniquet test, or any warning sign (see table) in someone who lives in an endemic area [27]. Warning signs typically occur before the onset of severe dengue [8].

The tourniquet test, which is particularly useful in settings where no laboratory investigations are readily available, involves the application of a blood pressure cufft between the diastolic and systolic pressure for five minutes, followed by the counting of any petechial hemorrhages; a higher number makes a diagnosis of dengue more likely with the cut off being more than 10 to 20 per 2.5 cm^2 (1 $inch^2$) [8,28,29].

The diagnosis should be considered in anyone who develops a fever within two weeks of being in the tropics or subtropics [7]. It can be difficult to distinguish dengue fever and chikungunya, a similar viral infection that shares many symptoms and occurs in similar parts of the world to dengue [9]. Often, investigations are performed to exclude other conditions that cause similar symptoms, such as malaria ,letospirosis ,viral hemorrhagic fever ,typhoid fever ,meningococcal disease ,measles, , and influenza [5,30]. The earliest change detectable on laboratory investigations is low white blood cell count, which may then be followed by low platelet and metabolic acidosis [5]. A moderately elevated level of aminotransferasaminotransferase (AST and ALT) from the liver is commonly associated with low platelets and white blood cells [7]. In severe disease, plasma leakage results in hemoconcentration (as indicated by a rising hematocrit) and hypoalbuminemia [5]. Pleural effusions or ascites can be detected by physical examination when large [5], but the demonstration of fluid on ultrasound may assist in the early identification of dengue shock syndrome [1,5]. The use of ultrasound is limited by lack of availability in many settings [1].

Dengue shock syndrome is present if pulse pressure drops to ≤ 20 mm Hg along weietatith peripheral vascular collapse [7]. Peripheral vascular collapse is determined in children via delayed capillary refill, rapid heart rate, or cold extremities [8].

10.1. Laboratory Test:

The diagnosis of dengue fever may be confirmed by microbiological laboratory testing:

10.2. Culture Test:

This can be done by virus isolation in cell cultures, nucleic acid detection by PCR, viral antigen detection (such as for NS1) or specific antibodies (serology) [14,30]. Virus isolation and nucleic acid detection are more accurate than antigen detection, but these tests are not widely available due to their greater cost.[30]Detection of NS1 during the febrile phase of a primary infection may be greater than 90% however is only 60-80% in subsequent infections [7]. All tests may be negative in the early stages of the disease [5,14]. PCR and viral antigen detection are more accurate in the first seven days [7]. In 2012 a PCR test was introduced that can run on equipment used to diagnose influenza; this is likely to improve access to PCR-based diagnosis [34].

These laboratory tests are only of diagnostic value during the acute phase of the illness with the exception of serology. Tests for dengue virus-specific antibodies, types IgG and IgM, can be useful in confirming a diagnosis in the later stages of the infection. Both IgG and IgM are produced after 5–7 days. The highest levels of IgM are detected following a primary infection, but IgM is also produced in reinfection. IgM becomes undetectable 30–90 days after a primary infection, but earlier following re-infections. IgG, by contrast, remains detectable for over 60 years and, in the absence of symptoms, is a useful indicator of past infection. After a primary infection IgG reaches peak levels in the blood after 14–21 days. In subsequent re-infections, levels peak earlier and the titres are usually higher. Both IgG and IgM provide protective immunity to the infecting serotype of the virus [9,35]. The laboratory test for IgG and IgM antibodies can cross-react with other flaviviruses and may result in a false positive after recent infections or vaccinations with yellow fever virus or Japanese encephalitis [7].

The detection of IgG alone is not considered diagnostic unless blood samples are collected 14 days apart and a greater than fourfold increase in levels of specific IgG is detected. Ultrasonography was the sensitive technique to add evidence most of plasma leakage up to 100%. Platelet < 100,000 cellslmm3 was found in 93.5%.

10.3 PCR:

PCR.Reverse transcriptase PCR (RT-PCR) has been developed for a number of RNA viruses in recent years and has the potential to revolutionize laboratory diagnosis; for dengue, RT-PCR provides a rapid serotype-specific diagnosis. The method is rapid, sensitive, simple, and reproducible if properly controlled and can be used to detect viral RNA in human clinical samples, autopsy tissues, or mosquitoes [29,55,98,148]. Although RT-PCR has similar sensitivity to virus isolation systems that use C6/36 cell cultures, poor handling, poor storage, and the presence of antibody usually do not influence the outcome of PCR as they do virus isolation. A number of methods involving primers from different locations in the genome and different approaches to detect the RT-PCR products have been developed over the past several years [29,55,148].

It must be emphasized, however, that RT-PCR should not be used as a substitute for virus isolation. The availability of virus isolates is important for characterizing virus strain differences, since this information is critical for viral surveillance and pathogenesis studies. Unfortunately, many laboratories are now conducting RT-PCR tests without proper quality control, i.e., virus isolation or serologic testing. Since RT-PCR is highly sensitive to amplicon contamination, without proper controls false-positive results may occur. Improvements in this technology, however, should make it even more useful in the future [63, 65]

10.4 Hybridization probes:

The hybridization probe method detects viral nucleic acids with cloned hybridization probes [29, 148]. Probes with variable specificity ranging from dengue complex to serotype specific can be constructed depending on the genome sequences used. The method is rapid and relatively simple and can be used on human clinical samples as well as fixed autopsy tissues. Unfortunately, hybridization probes have not been widely used or evaluated in the diagnostic laboratory. Preliminary data suggest that this method is less sensitive than RT-PCR, but like PCR, the outcome of the test is not influenced by the presence of neutralizing antibodies or other inhibitory substances. Even so, the difficulties of working with RNA and the technical expertise required to obtain reproducible results make this method more suitable as a research tool than as a routine diagnostic test [63-65].

11. TREATMENT

There are no specific anti-viral tablets or injections that can kill the dengue virus, but a lot of care treatment cans help to save a patient suffering from dengue fever.

1. Fever is treated by anti-pyretic like paracetamol.
2. Pain in the bone can be treated by analgesics or pain killing tablets.
3. In case a patient is suffering from dengue hemorrhagic fever or dengue shock syndrome then hospitalization is a must.
4. The survival rate in the absence of hospitalization can be as high as 50%. With proper treatment the mortality reduces to 3%
5. A few days of intravenous fluids can be administered in the form of normal saline or dextrose saline.
6. For some patients, oxygen is helpful Laboratory test.
7. When laboratory tests for dengue fever become positive where day zero is the start

of symptoms, 1st refers to in those with a primary infection, and 2nd refers to in those with a secondary infection.

12. W.H.O. ACTIVITIES

The WHO Initiative for Vaccine Research (IVR), in collaboration with a wide range of partners, aims to facilitate the development and future introduction of safe, effective and affordable dengue vaccines. Activities focus on the following main objectives:

- ✓ Identify knowledge gaps and research needs related to the development, evaluation and implementation of dengue vaccines.
- ✓ Build scientific consensus and develop guidance on the evaluation of dengue vaccines.
- ✓ Review and evaluate the evidence base for policy recommendations related to the introduction and use of dengue vaccines.
- ✓ Develop guidance on vaccine implementation, including introduction strategies.

IVR is part of the Dengue Vaccine Initiative (DVI), a collaborative effort of partners to facilitate the introduction of future dengue vaccines. Scientists claim breakthrough on first vaccine against dengue.Kounteya Sinha, TNN Sep 11, 2012, 09.05AM IST.Scientists on Tuesday announced a major dengue vaccine breakthrough, with a candidate vaccine showing a 60%-90 % protection rate against three virus strains (DENV 1, 3 and 4) that causes the mosquito-borne disease. The vaccine CYD-TDV was also found to be safe and well tolerated, with no side-effects on those who received it. No vaccine is now available to protect against dengue, and efforts to develop one have been hampered by the fact that dengue is caused by four viruses —DENV 1, 2, 3 and 4. Animals can't be used for vaccine trials Dengue, which is now endemic in more than 100 countries, appears to be unique to humans. Hence, scientists cannot use animal models to test vaccine candidates.

NEW DELHI: The world's first effective vaccine against dengue could be available by 2015.On clinical examination, a maculo-papular erythematous rash was found to be present in 212 (69%) cases and petechiae were present in 118 (38%) of the cases. 25(8%) cases showed a tendency for spontaneous bleeding. The gastrointestinal tract was the most common site for the bleeding in 17 patients, followed by epistaxis (3 cases) and episodes of haemoptysis (5 cases). Among these 25 cases that had the bleeding tend, pleural effusions and shock developed in 4, 1, 1 and 1 cases respectively.

A platelet count of <1,00,000/cmm was found in 261 (84%) cases and 81 (26%) cases had a platelet count of less encies, 9 interesting cases showed normal platelet counts and prothrombin time. Renal failure, an altered sensoriumthan 20,000/cmm, out of which in 63 (20%) cases had platelet transfusion (Table 1/ Fig3). Haemoglobin was mildly reduced in most of the cases and 57% cases showed elevated liver enzymes With regards to vector control, a number of novel methods have been used to reduce mosquito numbers with some success including the placement of the guppy (Poecilia reticulate) or copepods in standing water to eat the mosquito larvae [47].

Attempts are ongoing to infect the mosquito population with bacteria of the Wolbachia genus, which makes the mosquitoes partially resistant to dengue virus [7]. There are also trials with genetically modified male A. aegypti that after release into the wild mate with females, and their offspring live through the larval stage but die as pupae, before reaching sexual maturity[48] [medical citation needed]. There are ongoing programs working on a dengue vaccine to cover all four serotypes.[31] One of the concerns is that a vaccine could increase the risk of severe disease through antibody-dependent enhancement (ADE) [49].

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 Seema Awasthi et al., The Changing Clinical Spectrum of Dengue Fever in the and cost-effective[49] As of 2012, a number of vaccines were undergoing testing[16-49]. The most developed is based on a weakened combination of the yellow fever virus and each of the four dengue serotypes [16-50]. It is hoped that the first products will be commercially available by 2015[31]. Apart from attempts to control the spread of the Aedes mosquito and work to develop a vaccine against dengue, there are ongoing efforts to develop antiviral drugs that would be used to treat attacks of dengue fever and prevent severe complications [51,52].

Discovery of the structure of the viral proteins may aid the development of effective drugs. [52] There are several plausible targets. The first approach is inhibition of the viral RNA-dependent

RNA polymerase (coded by NS5), which copies the viral genetic material, with nucleoside analogs. Secondly, it may be possible to develop specific inhibitors of the viral protease (coded by NS3), which splices viral proteins [53]. Finally, it may be possible to develop entry inhibitors, which stop the virus entering cells, or inhibitors of the 5′ capping process, which is required for viral replication.[51] off, which stop the virus entering cells, or inhibitors of the 5′ capping process, which is required for viral replication process, which is required for viral.

13.1 Signs of Recovery:

- Stable pulse, blood pressure and breathing rate.
- Normal temperature.
- No evidence of external or internal bleeding.
- No vomiting.
- Good urine output.
- Stable haematocrit.
- Convalescent confluent petechiae rash.

13.2 Criteria for Discharging Patients:

1. Absence of fever for at least 24 hours without the use of anti-fever therapy.
2. Return of appetite.
3. Visible clinical improvement.
4. Good urine output.
5. Minimum of three days after recovery form shock.
6. No respiratory distress from pleural effusion and no ascites.
7. Platelet count of more than 50,000/mm3.

13.3 Do's and Don'ts for Patients:

If you or any family member is suffering from suspected dengue fever, it is important to carefully. Watch yourself or relative for the next few days, since this disease can rapidly become very serious. And lead to a medical emergency. The complication associated with Dengue fever/ dengue hemorrhagic fever usually appears. Between the third and fifth day of illness you should there four watches the patient for 2 days even after fever disappears.

13.4 Signs of Recovery:

- Stable pulse, blood pressure and breathing rate.
- Normal temperature.
- No evidence of external or internal bleeding.
- No vomiting.
- Good urine output.
- Stable haematocrit.
- Convalescent confluent petechiae rash.

14. VACCINATION:

The scientists tested tetravalent combinations of the most effective vaccine candidates against each of the 4 viruses. The phase I clinical trial included 112 healthy men and women ranging from 18 to 50 years old. None had prior exposure to dengue or other related viruses. The participants were randomized into 4 groups. Within each group, 20 people received a single injection of 1 of the 4 combinations. With further development, the vaccine may help ease the burden of dengue fever in developing countries. Infectious Diseases. Scientists at an international research centre in New Delhi are claiming progress in their search for a dengue vaccine. Thousands have fallen victim to the virus this year alone.

14.1 Example of vaccine trial:-

At a local hospital in the Indian capital, Hiralal Pandey, a daily wage laborer, is being treated for dengue. Aside from the muscle aches, pains and fever, Pandey has gone through a phase of blood transfusions to kick up his dipping platelet.

But there could be hope as the International Centre for Genetic Engineering and Biotechnology (ICGEB) is currently developing a non-infectious dengue vaccine based on Hepatitis B vaccine While no licensed dengue vaccine is available, several vaccine candidates are currently being evaluated in clinical studies.The candidate currently at the most advanced clinical development stage, a live-attenuated tetravalent vaccine based on chimeric yellow fever-dengue virus (CYD-TDV), has progressed to phase III efficacy studies. Results from a phase IIb efficacy study in Thailand have been published in September 2012.Several other live-attenuated vaccines, as well as subunit, DNA and purified inactivated vaccine candidates, are at earlier stages of clinical development. Additional technological approaches, such as virus-vectored

and VLP-based vaccines, are under evaluation in preclinical studies.

14.2 Challenges to vaccine development:-

Infection by one of the four dengue virus serotypes has been shown to confer lasting protection against homotypic re-infection, but only transient protection against a secondary heterotypic infection. Moreover, secondary heterotypic infection is associated with an increased risk of severe disease. This and other observations suggest an immunopathological component in dengue pathogenesis, which is referred to as immune enhancement of disease. Due to these dengue-specific complexities, vaccine development focuses on the generation of a tetravalent vaccine aimed at providing long-term protection against all virus serotypes. Additional challenges are posed by the lack of an adequate animal disease model and the resulting uncertainty around correlates of protection. In spite of these challenges, vaccine development has made remarkable progress in recent years, and the current dengue vaccine pipeline is advanced, diverse and overall promising [66].

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