Introduction
Dengue is an acute mosquito-transmitted viral disease characterized by fever, headache, muscle and joint pain, rash, nausea and vomiting. The most severe form of the disease is dengue hemorrhagic fever, which is characterized by thrombocytopenia, bleeding, and shock. The hemorrhagic form continues to be the leading viral hemorrhagic fever in the world.

Dengue virus infection - Dengue fever - Dengue hemorrhagic fever - Dengue shock syndrome.

Other names
Break bone fever, named by Dr. Benjamin Rush in Philadelphia, 1780; Dandy fever: Seven-day fever, Duengero - from the Spanish duengo, Ki denga pepo – Swahili: “it is a sudden overtaking by a spirit”.

Dengue, a flavivirus in the family Arboviridae, has four known serotypes. Studies show that infection with and subsequent immunization from one dengue serotype actually increases the odds of developing dengue hemorrhagic fever during infection with a second serotype. This is especially notable in areas where multiple serotypes have overlapping, endemic regions. Essentially, exposure to a mild form of dengue (in some cases, there is no apparent illness) seems to sensitize the immune system to the hemorrhagic form of the disease.

Occurrence
As of the late 1990’s Dengue, a disease found in most tropical and subtropical areas of the world, has become the most common arboviral disease of humans. More than 2.5 billion persons now live in areas where dengue infections can be locally acquired. Reported attack rates for disease during epidemics range from 1 per hundred to 1 per thousand of the population.

However, because persons with milder illness may not seek medical attention and subsequently be reported, the actual number of infections in a population may be 5 to 10 times greater than the number reported. Epidemics caused by all four virus serotypes have become progressively more frequent and larger in the past 25 years. As of 2005, dengue fever is endemic in most tropical countries of the South Pacific, Asia, the Caribbean, the Americas, and Africa (see Map). The incidence of the severe disease, DHF, has increased dramatically in Southeast Asia, the South Pacific, and the American tropics in the past 25 years, with major epidemics occurring in many countries every 3-5 years.
World Distribution of Dengue 2007

- The eggs can lie dormant in dry conditions for up to about 9 months, after which they can hatch if exposed to favorable conditions, i.e. water and food.
- A. aegypti cannot withstand temperatures below 48°F, and will die after less than an hour of 32°F. It is currently limited to a range below 35N latitude.
- Global warming will likely expand the range of the vector mosquito.

Breeding Habit

- A puddle of water about the size and depth of 20-cent coin is sufficient for an Aedes mosquito to breed in.
- The Aedes mosquito can also breed in unusual places such as water trapped in the hardened soil in potted plates, and the rim of unwanted pails.

Favoured Breeding Places

Desert coolers, Drums, Jars, Pots, Buckets, Flower vases, Plant saucers, Tanks, Cisterns, Bottles, Tins, Tyres, Roof gutters, Refrigerator drip pans, Cement blocks, Cemetery urns, Bamboo stumps, Coconut shells, Tree holes and many more places where rainwater collects or is stored.

Virus

Fast facts about the mosquito

- Aedes aegypti is the principal vector of dengue / dengue hemorrhagic fever. Aedes albopictus also transmits the disease.
- Only the female aedes mosquito bites as it needs the protein in blood to develop its eggs.
- The mosquito becomes infective approximately 7 days after it has bitten a person carrying the virus. This is the extrinsic incubation period, during which time the virus replicates in the mosquito and reaches the salivary glands.
- Peak biting is at dawn and dusk.
- The average lifespan of an Aedes mosquito in Nature is 2 weeks.
- The mosquito can lay eggs about 3 times in its lifetime, and about 100 eggs are produced each time.
Resurging Infections: Dengue

Dengue viruses are members of the family Flaviviridae, which include the Japanese encephalitis virus and the yellow fever virus. Four dengue virus serotypes and various biotypes can be differentiated. Infection with one serotype provides life-long immunity to that virus but not to the others.

1. Mosquitoes transmit dengue to human dendritic cells
2. Dengue targets areas with high WBC counts (liver, spleen, lymph nodes, bone marrow, and glands)
3. Dengue enters WBCs and lymphatic tissue
4. Dengue enters blood circulation

The transmission cycle for dengue starts when:

• Infected Aedes mosquito bites a healthy person.
• 4-7 days later, the infected person develops fever (after the virus multiplies i.e., incubation period). The person usually then sees a doctor.
• When fever starts, the person becomes infectious for about 5 days.
• If an Aedes mosquito bites the person during this period when he is infectious, it will pick up the dengue virus in his blood.
• The virus takes 7-10 days to multiply in the second mosquito.
• The mosquito then becomes infective and the cycle starts again when it bites another person.

Clinical Features

This infectious disease is manifested by a sudden onset of fever. It persists for 5 to 6 days. Fever is characteristically biphasic and returns to almost normal in the middle of the febrile period giving rise to the saddleback temperature chart. It reaches its highest level during the last 24 hours before abatement. There is often a macular rash on the first day as well as adenopathy, palatal vesicles, and scleral injection. Other Symptoms include muscle pain, Bone pain, loss of appetite, Nausea, vomiting, Sore throat, abdominal pain, diarrhea, intense headache, usually frontal, and retroorbital pain, particularly when pressure is applied to the eyes. (“Fire is coming out of my eyes”). Epistaxis and scattered petechiae are often noted in uncomplicated
Dengue, and preexisting gastrointestinal lesions may bleed during the acute illness. Some cases develop much milder symptoms which can, when no rash is present, be misdiagnosed as influenza or other viral infection.

### Dengue Hemorrhagic Fever (DHF)

The incubation period of DHF is unknown but is probably similar to that of DF.

<table>
<thead>
<tr>
<th>DF/DHF</th>
<th>Grade</th>
<th>Clinical picture</th>
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<tbody>
<tr>
<td>DF</td>
<td></td>
<td>As described in dengue fever</td>
</tr>
<tr>
<td>DHF I</td>
<td>I</td>
<td>Above plus positive tourniquet test</td>
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<tr>
<td>DHF II</td>
<td>II</td>
<td>Above signs plus spontaneous bleeding in the form of skin and/or other hemorrhages</td>
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<tr>
<td>DHF III</td>
<td>III</td>
<td>Above signs plus circulatory failure (cold clammy skin, rapid pulse weak pulse pressure, restlessness</td>
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<tr>
<td>DHF IV</td>
<td>IV</td>
<td>Profound shock with undetectable pulse and blood pressure</td>
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</table>

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### Dengue Shock Syndrome (DSS)

DHF grade III and IV are also called DSS. The four warning signs for impending shock are intense, sustained abdominal pain, persistent vomiting, restlessness or lethargy, and a sudden change from fever to hypothermia with sweating and prostration.

### Pathogenesis

DHF is almost always found in individuals who had a previous experience with at least one of the four serotypes of dengue virus. This leads to the hypothesis of heterotypic antibodies from a previous dengue infection promoting the viral replication within the mononuclear leucocytes – the phenomenon of antibody-dependent enhancement. Furthermore, the immunologic processes aimed at eliminating dengue virus infected cells can result in release of histamine and substances with vasoactive and procoagulant properties, the release of interferon-gamma, and the activation of complement.
DHF results from an infection by a more virulent biotype of the virus or even from unfavorable host factors such as concomitant bacterial infections. DHF is known to be more common in Southeast Asia compared to Africa and America. Black individuals are relatively resistant to DHF / DSS due to a speculated "resistant gene". The cause of bleeding in DHF appears to be due to thrombocytopenia, platelet dysfunction, disseminated intravascular coagulation and micro vascular injury.

**Diagnosis**

**Total White Blood Cell Count:** In case of dengue, this test will reveal leukopenia. The presence of leukocytosis and neutrophilia excludes the possibility of dengue and bacterial infections (leptospirosis, meningocencephalitis, septicemia, pyelonephritis etc).

**Thrombocytopenia (< 100.00 / mm$^3$):** Total platelet count must be obtained in every patient with symptoms suggestive of dengue for three or more days of presentation. Leptospirosis, measles, rubella, meningococcemia and septicemia may also present with thrombocytopenia.

**Hematocrit (micro-hematocrit):** According to the definition of DHF, the presence of hemoconcentration (hematocrit elevated by > 20%) is necessary; when it’s not possible to know the previous value of hematocrit, we must regard as significantly elevated the results > 45%.

Thrombocytopenia with concurrent high hematocrit levels differentiates DHF from classic DF.

Currently routine laboratory diagnosis of dengue infections depend on virus isolation or the detection of dengue virus-specific antibodies. The isolation of viruses from clinical specimens can be carried out in cultured mosquito cells, such as AP-61 or C6/36 cells cultures. When dengue virus serotype specific monoclonal antibodies are used, virus identification by indirect immunofluorescence can be achieved within 2 weeks.

The commonly used serologic test is the hemagglutination inhibition test. In a primary infection dengue hemagglutination inhibition antibody titer is generally less than 1:20 in a sample collected within the first 4 days after the onset of symptoms. In the convalescent phase sample (collected 1 to 4 weeks after the onset of symptoms) a fourfold or greater rise in antibody titer is detected, with antibody titer $\geq 1.1280$

A secondary dengue infection is characterized by the rapid appearance of broadly cross-reactive antibodies. Hemagglutination inhibition titers of 1:20 in the acute-phase sample rise to 0 to 1:2560 in the convalescent phase sample. An improved and less time-consuming method is a capture enzyme-linked immunosorbent assay that can detect specific anti-dengue IgM in a single acute-phase sample.

Recently commercial kits for the detection of specific IgG as well as IgM antibodies have become available. They are based on a dot enzyme assay or a nitrocellulose membrane-based capture format, respectively. An alternative to virus isolation is the detection of viral RNA by reverse transcription polymerase chain reaction. Reverse transcription polymerase chain reaction is a highly sensitive technique of particular value in the early diagnosis of dengue infection.

**Suspect Cases:** Acute onset and high fever of 2-7 days duration, and two or more of the following:

- Headache, retro-orbital pain, myalgia, arthralgia, rash, hemorrhagic manifestations, and leukopenia.

**Probable case:** Suspect case and one or more of the following:

- Occurrence of confirmed cases of dengue in the same place and time. Detection of IgM antibody.

**Confirmed case:** Suspect or probable case and one or more of the following:

- Isolation of virus or detection of viral genomic sequences. Fourfold rise in titers of IgG or IgM antibody.
**Differential Diagnosis**

Physicians should consider dengue in the differential diagnosis of all patients who have fever and a history of travel to a tropical area within 2 weeks of onset of symptoms.

**Leptospirosis** – Increased erythrocyte sedimentation rate, total WBC elevated with neutrophilia, transaminases levels slightly elevated and increased BUN and serum creatinine. The presence of jaundice (indicative of severe forms of leptospirosis) + epidemiologic data practically exclude the diagnosis of dengue.

**Respiratory Infections** – ‘Common Cold’ is seldom mistaken with dengue due to the absence of fever. In relation to the ‘influenza – like syndromes’, differential diagnosis is made by the presence of respiratory symptoms (cough, sore throat, nasal discharge), with higher incidence in the winter; Bacterial pneumonias usually present with chest pain (pleurodynia), productive cough and total WBC elevated with neutrophilia. Diagnosis can be made by chest radiography and sputum bacterioscopy by the method of Gram.

**Measles** - The pre exanthematic phase (cough, nasal discharge, and conjunctivitis) doesn’t occur in dengue. The morbilliform rash usually begins on the face, with a cefalo-caudal progression. The presence of ‘koplik’ lesions in the jugal mucous membrane just before the exanthematic phase is a pathognomonic sign of measles. A positive vaccination history doesn’t exclude the diagnosis, because an inadequate immunization may have occurred.

**Rubella (German Measles)** – Fever with an insidious onset, absence of systemic symptoms and lymphoadenomegalgy (retroauricular, suboccipital, cervical) preceding a rash which usually begins on the face are typical of rubella. The diagnosis of rubella cannot be made on clinical basis, but by serologic method.

**Malaria** – Diagnosis is made by detection of *Plasmodium* forms on serial blood examination. Fever in malaria is initially of daily presentation, and spleen may be enlarged and tender; jaundice may also be present.

**Yellow Fever** – The initial clinical manifestations are indistinguishable from dengue. However, the period of incubation usually doesn’t exceed 6 days. Laboratory findings include leukopenia and neutrophilia, a very low erythrocyte sedimentation rate (near by) mm) and a marked increase in the serum transaminases levels. A positive vaccination history practically excludes the diagnosis of yellow fever.

**Meningoencephalitis** – Headache, presence of petechiae and shock with an onset < 24-48 hours indicate the obligatory exclusion of meningococcemia (in the severe forms of dengue these manifestations usually occur after the third day of disease). Leukocytosis and neutrophilia, thrombocytopenia and hemoconcentration may be present. Besides, neurologic manifestations tend to be absent in dengue fever, in contrast with meningoencephalitis. The evaluation of the cerebral spinal fluid is the basis of diagnosis, because in dengue fever the CSF is usually normal.

**Pyelonephritis** – The diagnosis is made based on the urine bacterioscopy by the method of Gram and Urinocultures. Urinalysis is inadequate for the evaluation of the urinary tract infections. WBC may show leukocytosis and neutrophilia.

**Septicemia** – The onset of symptoms is more insidious and it’s usually possible for the clinician to detect a primary infectious focus. Splenomegaly, leukocytosis / leukopenia, metabolic acidosis and neurologic disturbances may be present. Related diseases like diabetes mellitus, alcoholism, neoplasms and malnutrition may lead to the correct diagnosis, which is made by hemocultures.

**Management of Dengue Fever**

- Early reporting of the suspected dengue fever
- Management of dengue fever is symptomatic and supportive. Give Paracetamol but no aspirin or brufen. In cases with severe pain
analgesics or mild sedatives are to be given. Bed rest is essential. Oral fluids and electrolyte therapy are required for patients with excessive sweating or vomiting. Follow up for any change in platelet/hematocrit. During afebrile phase (2-3 days after febrile period) check platelet/hematocrit. In convalescent phase no special instructions. Normal diet. Patients almost always recover but often have prolonged asthenia and depression.

Management of DHF Grade I and II
Duration is 2-3 days after the febrile phase. Treat on OPD/ inpatient basis. Give ORS. Check platelet/hematocrit. If Hct > 20% start IV therapy. Monitor vitals, urine output, and hematocrit.

Management of DHF Grade III and IV
Duration is 2-3 days after the febrile phase. Check platelet/hematocrit. Start IV therapy (isotonic solutions). Monitor vitals, urine output, and hematocrit.

If hematocrit is increasing change IV fluid to colloidal solution preferably Dextran or plasma. If hematocrit is decreasing from initial value, give fresh whole blood transfusion. In case of profound shock give IV fluid bolus one or two times. Give oxygen therapy. Steroids in DSS are not helpful. In some cases platelet transfusion may be necessary.

Emerging treatments
Emerging evidence suggests that mycophenolic acid and ribavirin inhibit dengue replication. Initial experiments showed a fivefold increase in defective viral RNA production by cells treated with each drug. In vivo studies, however, have not yet been done.

Prevention
a. preventive surveillance and control;
b. public education and community involvement;
c. enforcement; and
d. research.

Personal Prevention
- Use of mosquito repellent creams, liquids, coils, mats etc.
- Wearing of full sleeve shirts and full pants with socks
- Use of bednets for sleeping infants and young children during day time
- Flywire/screening on doors and windows.
- None of these are effective by themselves alone, use combination.

Vector Control
- As Aedes aegypti breeds in containers and receptacles detection and elimination of mosquito breeding sources is the most important activity.
- Management of roof tops, porticos and sunshades
- Proper covering of stored water
- Reliable water supply
- Observation of weekly dry day
- Check no larvae swimming in water.
- Can treat with Abate® (temephos) (or use fish in ponds).
Control of case

- Instruct patient and immediate room-mates to use anti-mosquito measures for 12 days post onset.
- Investigate source of infection.

Control of contacts

Patient asked about sick family members, work colleagues or room-mates, follow up interview with these and suggest sera samples sought if dengue suspected.

Tyres collect rainwater
- dispose or cover

Overhead storage need tight covers

Cover water jars, drums, coolers and tanks

Flower pot with water collection – empty weekly

Health Education and Community Participation

Impart knowledge to common people regarding the disease and vector through various media sources like T.V., Radio, Cinema slides, etc. Sensitizing and involving the community for detection of Aedes breeding places and their elimination.

Vaccine Development

There is no commercially available vaccine for the dengue flavivirus.

An effective vaccine will have to be tetravalent because pre-existing heterotypic dengue antibody is a risk factor for DHF. Live attenuated vaccine viruses have been evaluated in phase I and II trials in Thailand, and a tetravalent formulation is currently undergoing repeat phase I and II trials. Advances have also been made with second generation recombinant dengue vaccines.

Vaccine Update

In a journal published 24 March 2006, by Zhou H. and Deem M.W., a novel vaccine procedure known as a polytopic injection can be used to elicit a host immune response to dengue fever and reduce immunodominance. Using the polytopic injection, different vaccine serotypes are injected into different regions of the body. These injections contain epitopes of different dengue serotypes (1-4) that are subdominant; therefore eliciting T cell responses in separate regional lymph nodes. This will then prime the immune system to seek out the subdominant determinants instead of the cross-reactive dominant epitopes for each of the 4 dengue serotypes. This will allow for the avoidance of an immunodominance reaction and provide the host immunity against each serotype of dengue virus.

Prognosis

With early detection and proper case management and symptomatic treatment, mortality can be reduced substantially.

The case fatality rate in DHF can be as low as 0.2% if detected early and treated. Once shock has set in, the fatality rate may be as high as 12% to 44%.

Conclusion

Future dengue incidence in specific locales cannot be predicted accurately, but a high level of dengue transmission is anticipated in all tropical areas of the world for the indefinite future. As there is no Vaccine for dengue, it can be prevented and controlled only with the full support and cooperation of Government, NGOs, Medical Team and the Public.
Resurging Infections: Dengue

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