Dengue

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Walter Reed Army Institute of Research (WRAIR)

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Dengue Lecture Outline

• Dengue Virus
• Dengue Epidemiology
• Military Significance
• Clinical Presentation and Management
• Diagnosis
• Pathophysiology
Dengue Virus (DENV)

• Virus
  – Positive-polarity, single-stranded RNA genome
  – Flavivirus (YF, JE, WNV, DENV)
  – 4 serotypes: DENV-1-4
    • Multiple genotypes

• Vector
  – Mosquito (*Aedes aegypti/albopictus*)

• Transmission
  – Feeding mosquito vector
  – Laboratory
Dengue Virus

(a) Gene structure of Dengue Virus, showing the order and functions of the structural and non-structural proteins. The diagram highlights the 5' to 3' orientation of the viral genome.

(b) A detailed illustration of the Dengue virus capsid, showing the glycoprotein domains and their functions:
- **Domain I** — central structure
- **Domain II** — dimerization
- **Domain III** — receptor binding
- **Fusion peptide**

Additional protein activities include protease with NS2B, helicase, NTPase, and RNA polymerase methyltransferase.
Dengue Epidemiology

Dengue Ward: QSNICH, Bangkok, Thailand (Photo: Christopher Brown, IHT)
Facts

• Leading arboviral infection of humans
• >120 countries reporting indigenous transmission
• >3.5 billion people living at risk for infection
• >50 million infections annually
• >500,000 severe cases annually
• >30,000 deaths annually
• No licensed vaccine / therapeutic
• Effective vector control very difficult
Areas supporting dengue virus transmission.
Factors Driving Transmission

- Population increases
- Migration
- Urbanization
- Poverty
- Vector expansion
- International travel

- Changing global ecology
- Vector evolution
- Viral evolution
Figure 1: Approximate global distribution of dengue and Aedes aegypti in 2005
Reprinted with permission of the US Centers for Disease Control and Prevention.
DENV Type Distribution - 1970

D. Gubler
Global Air Travel Flight Patterns
DENV Type Distribution - 2004
Figure 1.2 Average annual number of dengue fever (DF) and dengue haemorrhagic fever (DHF) cases reported to WHO, and of countries reporting dengue, 1955–2007.
The Epidemiology of Dengue in the Americas Over the Last Three Decades: A Worrisome Reality

Figure 1. Number of dengue fever (DF) and dengue hemorrhagic fever (DHF) cases, Region of the Americas, 1980–2007.

Figure 4. Percentage of countries reporting serotypes 1–4 to the Pan American Health Organization by year, Region of the Americas, 1995–2007.

José Luis San Martín, Olivia Brathwaite, Betzana Zambrano, José Orlando Solórzano, Alain Bouckenooghe, Gustavo H. Dayan, and María G. Guzmán

Dengue Regional Program, Pan American Health Organization (PAHO), Panama, Republic of Panama; Clinical Department, Samofl Parot, Sewickley, Pennsylvania; General Directorate of Health Surveillance, Secretariat of Health, Tegucigalpa, Honduras; Virology Department, PAHO/World Health Organization Collaborating Center for the Study of Dengue and its Vector, Institute of Tropical Medicine Pedro Kouri, Havana, Cuba

Average dengue incidence per 100,000 by country, Region of the Americas, 1980–2007.
Figure 1.3 Outbreaks of dengue fever in the WHO Eastern Mediterranean Region, 1994–2005

DENGUE (DEN-2):
- 1994: 673 suspected cases, 289 confirmed cases
- 1995: 136 suspected cases, 6 confirmed cases
- 1996: 57 suspected cases, 2 confirmed cases
- 1997: 62 suspected cases, 15 confirmed cases
- 1998: 31 suspected cases, 0 confirmed cases
- 1999: 26 suspected cases, 3 confirmed cases
- 2000: 17 suspected cases, 0 confirmed cases
- 2001: 7 suspected cases, 0 confirmed cases
- 2005: 32 suspected (confirmed)

AL-HUDAYDHAH, MUKKALA, SHAABWA
(1994, DEN-3, no data)

AL-HUDAYDHAH, YEMEN
(September 2000, DEN-2, 653 suspected cases, 80 deaths [CFR = 12%])

AL-HUDAYDHAH, YEMEN
(March 2004, 45 suspected cases, 2 deaths)

AL-HUDAYDHAH, MUKKALA
(March 2005, 403 suspected cases, 2 deaths)
## Pakistan

<table>
<thead>
<tr>
<th>13 October 2011 (02:00 pm)</th>
<th>13 October 2011 (02:00 pm)</th>
<th>13 October 2011 (02:00 pm)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>No. of reported cases</strong></td>
<td><strong>No. of reported cases</strong></td>
<td><strong>No. of reported cases</strong></td>
</tr>
<tr>
<td>208,837</td>
<td>208,837</td>
<td>208,837</td>
</tr>
<tr>
<td><strong>No. of confirmed cases</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>18,768</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>No. of identified cases</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1,232</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>No. of total cases</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>221,837</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>No. of total deaths</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>21</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Identification of the disease:**

The presence of virus in this disease in the body can only be ascertained through blood test in the laboratory.

**Indications:**

The specific indications of this disease include fever with:
- Pain in back, body and joints
- Presence of spots on the body
- Pain in eyes
- Shortage of white cells in the blood
- Severe headache, cold and flu
- In case of serious illness, blood may be emitted from different parts of the body like mouth and the nose.

**Treatment:**

This disease neither has a specific cure nor a vaccine available. Therefore, as soon as there are any such indications, give the patient as much liquids as possible and contact the nearest health centre.

**Precautionary Measures:**

- Keep your homes and offices protected against mosquitoes
- Keep homes and offices airy, bright and safe from moisture
- Keep doors and windows closed
- Wear full sleeves clothes
- Use mosquito nets while sleeping
- Don’t leave the overhead tanks open
- Don’t keep water in containers
- Keep the water in containers, and let them dry and then fill again
- Don’t let the water fall from the overhead tanks to accumulate permanently, instead dry it.
- Don’t let the water accumulate in any case both inside or outside the home.
- Be mindful of your home and mahallah’s cleanliness.
- Be mindful of the hedge boundaries duly cut both inside and outside the home, and spray them with insecticides, particularly in the evening.
- Don’t let the water stay all the time in the flowers pots, garlands of plants.
- Instead water them only in the morning every alternate day.

**Health Education Cell, Health Group of Offices**

CITY DISTRICT GOVERNMENT KARACHI

Reconstruction of Karachi – City Government’s Resolve
Brown – dengue reported

Light Brown – dengue not reported but vector exists

White – data not available
Dengue Fever, Hawaii, 2001–2002
DENGUE SURVEILLANCE IN TEXAS, 1995

JULIE A. RAWLINGS, KATHERINE A. HENDRICKS, CHRISTINE R. BURGESS, RICHARD M. CAMPMAN, GARY G. CLARK, LAURA J. TABONY, AND MARY ANN PATTERSON

Infectious Disease Epidemiology and Surveillance Division and Bureau of Laboratories, Texas Department of Health, Austin, Texas; Dengue Branch, Centers for Disease Control and Prevention, San Juan, Puerto Rico

Dengue Hemorrhagic Fever --- U.S.-Mexico Border, 2005


UNCLASSIFIED Slide 21
"With respect to specific diagnoses, malaria was one of the three most frequent causes of systemic febrile illness among travelers from every region, although travelers from every region except sub-Saharan Africa and Central America had confirmed or probable dengue more frequently than malaria."

**Table 1. Dengue and malaria diagnoses as a proportion of all morbidity in ill returned travelers according to region or country of acquisition**

<table>
<thead>
<tr>
<th>Region* or country of exposure</th>
<th>No. ill returned travelers with dengue</th>
<th>No. ill returned travelers with malaria</th>
<th>Total no. ill returned travelers</th>
<th>Dengue proportionate morbidity†</th>
<th>Malaria proportionate morbidity†</th>
</tr>
</thead>
<tbody>
<tr>
<td>Southeast Asia</td>
<td>264</td>
<td>103</td>
<td>3,694</td>
<td>71</td>
<td>28</td>
</tr>
<tr>
<td>Thailand</td>
<td>154</td>
<td>9</td>
<td>1,523</td>
<td>101</td>
<td>5</td>
</tr>
<tr>
<td>Indonesia</td>
<td>38</td>
<td>53</td>
<td>652</td>
<td>58</td>
<td>81</td>
</tr>
<tr>
<td>South Central Asia</td>
<td>90</td>
<td>70</td>
<td>3,303</td>
<td>27</td>
<td>21</td>
</tr>
<tr>
<td>India</td>
<td>66</td>
<td>57</td>
<td>2,118</td>
<td>31</td>
<td>27</td>
</tr>
<tr>
<td>Caribbean</td>
<td>47</td>
<td>14</td>
<td>1,470</td>
<td>32</td>
<td>9</td>
</tr>
<tr>
<td>South America</td>
<td>40</td>
<td>49</td>
<td>2,427</td>
<td>16</td>
<td>20</td>
</tr>
<tr>
<td>Brazil</td>
<td>22</td>
<td>12</td>
<td>685</td>
<td>32</td>
<td>18</td>
</tr>
<tr>
<td>Central America</td>
<td>37</td>
<td>27</td>
<td>1,867</td>
<td>20</td>
<td>14</td>
</tr>
<tr>
<td>Africa</td>
<td>25</td>
<td>1,216</td>
<td>7,231</td>
<td>3</td>
<td>168</td>
</tr>
<tr>
<td>Sub-Saharan Africa</td>
<td>23</td>
<td>1,201</td>
<td>6,201</td>
<td>4</td>
<td>194</td>
</tr>
<tr>
<td>Oceania</td>
<td>11</td>
<td>91</td>
<td>303</td>
<td>36</td>
<td>300</td>
</tr>
<tr>
<td>Other‡ or multiple regions of exposure</td>
<td>7</td>
<td>23</td>
<td>4,443</td>
<td>2</td>
<td>5</td>
</tr>
<tr>
<td>Country missing</td>
<td>1</td>
<td>12</td>
<td>182</td>
<td>5</td>
<td>66</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>522</strong></td>
<td><strong>1,605</strong></td>
<td><strong>24,920</strong></td>
<td><strong>21</strong></td>
<td><strong>64</strong></td>
</tr>
</tbody>
</table>

*Regions defined per (9).
†Proportionate morbidity expressed per 1,000 ill returned travelers seen at GeoSentinel clinics.
‡No cases were acquired in Canada, United States, Western Europe, Japan, or Australia.
Dengue’s Military Significance

- Philippines
- World War II
- Vietnam
- Philippines
- Haiti
- Somalia
<table>
<thead>
<tr>
<th>Disease</th>
<th>2010 COCOM panel rank</th>
<th>ID-IDEAL Rank</th>
</tr>
</thead>
<tbody>
<tr>
<td>Malaria</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td><strong>Dengue</strong></td>
<td><strong>2</strong></td>
<td><strong>3</strong></td>
</tr>
<tr>
<td>Diarrhea, bacterial</td>
<td>3</td>
<td>1</td>
</tr>
<tr>
<td>MDR wound pathogens</td>
<td>4</td>
<td>NA</td>
</tr>
<tr>
<td>Leishmaniasis</td>
<td>5</td>
<td>19</td>
</tr>
<tr>
<td>Q fever (Coxiella burnetti)</td>
<td>6</td>
<td>26</td>
</tr>
<tr>
<td>Norovirus and other viral diarrhea</td>
<td>7</td>
<td>NA</td>
</tr>
<tr>
<td>Influenza</td>
<td>8</td>
<td>NA</td>
</tr>
<tr>
<td>Leptospirosis</td>
<td>10</td>
<td>7</td>
</tr>
<tr>
<td>Diarrhea, protozoal</td>
<td>11</td>
<td>11</td>
</tr>
<tr>
<td>TB</td>
<td>12</td>
<td>NA</td>
</tr>
<tr>
<td>CCHF</td>
<td>13</td>
<td>10</td>
</tr>
<tr>
<td>HIV</td>
<td>14</td>
<td>8</td>
</tr>
<tr>
<td>HFRS</td>
<td>15</td>
<td>17</td>
</tr>
<tr>
<td>Chikungunya</td>
<td>16</td>
<td>4</td>
</tr>
<tr>
<td>Meningococcal meningitis</td>
<td>17</td>
<td>20</td>
</tr>
<tr>
<td>Plague</td>
<td>18</td>
<td>27</td>
</tr>
<tr>
<td>Rickettsioses</td>
<td>19</td>
<td>18</td>
</tr>
<tr>
<td>Viral encephalitides</td>
<td>20</td>
<td>NA</td>
</tr>
</tbody>
</table>
### Table 1: Dengue Disease Incidence in US Military Personnel

<table>
<thead>
<tr>
<th>Year</th>
<th>Incidence Rate</th>
<th>Incidence Count</th>
<th>Breakdown</th>
</tr>
</thead>
<tbody>
<tr>
<td>2000</td>
<td>12.3/100,000</td>
<td>123</td>
<td>US troops</td>
</tr>
<tr>
<td>2001</td>
<td>15.4/100,000</td>
<td>154</td>
<td>US troops</td>
</tr>
<tr>
<td>2002</td>
<td>10.7/100,000</td>
<td>107</td>
<td>US troops</td>
</tr>
<tr>
<td>2003</td>
<td>11.2/100,000</td>
<td>112</td>
<td>US troops</td>
</tr>
<tr>
<td>2004</td>
<td>12.8/100,000</td>
<td>128</td>
<td>US troops</td>
</tr>
<tr>
<td>2005</td>
<td>13.9/100,000</td>
<td>139</td>
<td>US troops</td>
</tr>
</tbody>
</table>

*Note: Data includes all troops stationed in areas with Dengue transmission.*
### Dengue During Viet Nam War

<table>
<thead>
<tr>
<th>Date</th>
<th>Location</th>
<th>Cases</th>
<th>Mortality</th>
<th>Source</th>
</tr>
</thead>
<tbody>
<tr>
<td>1965-1966</td>
<td>South Vietnam</td>
<td>300</td>
<td>15</td>
<td>Report</td>
</tr>
<tr>
<td>1967-1968</td>
<td>Central Vietnam</td>
<td>250</td>
<td>2</td>
<td>Database</td>
</tr>
<tr>
<td>1969-1970</td>
<td>North Vietnam</td>
<td>100</td>
<td>1</td>
<td>Report</td>
</tr>
<tr>
<td>1971-1972</td>
<td>Southeast Vietnam</td>
<td>50</td>
<td>0</td>
<td>Database</td>
</tr>
</tbody>
</table>

### Additional Information

- Dengue virus has a wide distribution in Vietnam, affecting both urban and rural areas.
- The disease is predominantly transmitted by Aedes aegypti mosquitoes.
- Dengue epidemics have been observed during periods of increased population density and poor sanitation.

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**Note:** Further detailed analysis and data can be found in the associated sources provided.
Hospitalized troops with fever / Unit survey of 494

129 / 289 hospitalized w/ fever = no diagnosis
- 41 / 96 had DENV isolated (39 = DENV-2, 2 = DENV-3)
- 18 / 37 culture negative had IgM antibodies vs. dengue

Survey of 494 = 77% prevalence of dengue antibodies

PATIENTS: 101 US military personnel with acute febrile illnesses.

RESULTS: Febrile illnesses accounted for 103 (25%) of the 406 combat support hospital admissions during the first 6 weeks of deployment. A total of 30 patients had DF. Dengue virus serotypes 1, 2, and 4 were isolated from 22 patients, and 8 patients developed IgM antibody to dengue virus. Patients with DF could not be distinguished from other febrile patients on clinical grounds alone.

CONCLUSIONS: DF accounted for at least 30% of the febrile illnesses among hospitalized US troops.
USASOC

DODSR

500 samples

Dengue ELISA

11% seroprevalence
WRAIR USASOC DODSR Study - 2012

Seroprevalence Based on 1,000 Post-Deployment Samples in First Time Deployers

<table>
<thead>
<tr>
<th></th>
<th>Central America*</th>
<th>South America</th>
<th>Asia</th>
<th>Africa*</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Percent</td>
<td>4.8</td>
<td>12.4</td>
<td>7.2</td>
<td>6.0</td>
<td>7.6</td>
</tr>
</tbody>
</table>

- **Overall seroprevalence = 7.6%**
- Highest prevalence among those serving in the Army
- Positive association with older age
- No effect of deployment length
- Increased self-report of fever among those w/ antibodies
Dengue Infection Clinical Phenotypes

Dengue virus infection

- Asymptomatic
- Symptomatic
  - Undifferentiated fever (viral syndrome)
  - Dengue fever syndrome
    - Without haemorrhage
    - With unusual haemorrhage
      - No shock
      - Dengue shock syndrome

- Dengue haemorrhagic fever
  - (plasma leakage)
    - No shock
    - Dengue shock syndrome

Probable dengue
live in / travel to dengue endemic area.
Fever and 2 of the following criteria:
• Nausea, vomiting
• Rash
• Aches and pains
• Tourniquet test positive
• Leukopenia
• Any warning sign

Laboratory-confirmed dengue
(important when no sign of plasma leakage)

Warning signs*
• Abdominal pain or tenderness
• Persistent vomiting
• Clinical fluid accumulation
• Mucosal bleed
• Lethargy, restlessness
• Liver enlargement >2 cm
• Laboratory: increase in HCT concurrent with rapid decrease in platelet count
*(requiring strict observation and medical intervention)

Severe plasma leakage
leading to:
• Shock (DSS)
• Fluid accumulation with respiratory distress

Severe bleeding
as evaluated by clinician

Severe organ involvement
• Liver: AST or ALT >= 1000
• CNS: Impaired consciousness
• Heart and other organs
## Table 1. WHO Classification of DHF

<table>
<thead>
<tr>
<th>Grades</th>
<th>Increase in Hematocrit*</th>
<th>Hemorrhage†</th>
<th>Shock‡</th>
<th>Profound Shock§</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>+</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>2</td>
<td>+</td>
<td>+</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>3</td>
<td>+</td>
<td>±</td>
<td>+</td>
<td>-</td>
</tr>
<tr>
<td>4</td>
<td>+</td>
<td>±</td>
<td>+</td>
<td>+</td>
</tr>
</tbody>
</table>

*Hematocrit increased by at least 20%.
†Spontaneous bleeding in skin and/or other sites.
‡Hypotension and/or narrowing of pulse pressure to 20 mmHg or less, with cold clammy skin and restlessness.
§Undetectable blood pressure or pulse.
Dengue Fever in US Military Personnel in Haiti

JAMA 1997; 277:19:1546-1548

Symptoms in Febrile Patients Admitted to the 28th Combat Support Hospital, Port-au-Prince, Haiti, SEP 27, 1994 - NOV 4, 1994

<table>
<thead>
<tr>
<th>Symptoms</th>
<th>Dengue Fever, No. of Patients (%) (n=30)</th>
<th>Non-dengue Fever, No. of Patients (%) (n=40)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Malaise</td>
<td>30 (100)</td>
<td>40 (100)</td>
</tr>
<tr>
<td>Headache</td>
<td>27 (90)</td>
<td>38 (95)</td>
</tr>
<tr>
<td>Chillies</td>
<td>26 (87)</td>
<td>34 (85)</td>
</tr>
<tr>
<td>Backache</td>
<td>22 (73)</td>
<td>24 (60)</td>
</tr>
<tr>
<td>Loss of appetite</td>
<td>21 (70)</td>
<td>30 (75)</td>
</tr>
<tr>
<td>Rigors</td>
<td>19 (63)</td>
<td>20 (50)</td>
</tr>
<tr>
<td>Arthralgia</td>
<td>18 (60)</td>
<td>21 (53)</td>
</tr>
<tr>
<td>Myalgia</td>
<td>18 (60)</td>
<td>27 (68)</td>
</tr>
<tr>
<td>Nausea</td>
<td>17 (57)</td>
<td>31 (78)</td>
</tr>
<tr>
<td>Neck stiffness</td>
<td>11 (37)</td>
<td>24 (60)</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>11 (37)</td>
<td>25 (63)</td>
</tr>
<tr>
<td>Conjunctival irritation</td>
<td>10 (33)</td>
<td>21 (30)</td>
</tr>
<tr>
<td>Abdominal pain</td>
<td>10 (33)</td>
<td>23 (58)</td>
</tr>
<tr>
<td>Coryza</td>
<td>10 (33)</td>
<td>24 (60)</td>
</tr>
<tr>
<td>Photophobia</td>
<td>8 (27)</td>
<td>15 (38)</td>
</tr>
<tr>
<td>Cough</td>
<td>7 (23)</td>
<td>16 (40)</td>
</tr>
<tr>
<td>Sore throat</td>
<td>6 (20)</td>
<td>18 (45)</td>
</tr>
<tr>
<td>Altered taste</td>
<td>5 (17)</td>
<td>2 (5)</td>
</tr>
<tr>
<td>Vomiting</td>
<td>5 (17)</td>
<td>11 (28)</td>
</tr>
</tbody>
</table>
### Physical Findings in Febrile Patients

Febrile Patients Admitted to the 28th Combat Support Hospital, Port-au-Prince, Haiti, September 27, 1994 to November 4, 1994*

<table>
<thead>
<tr>
<th>Finding</th>
<th>Dengue Fever (n=30)</th>
<th>Non-dengue Fever (n=40)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Maximum temperature, mean °C (range)</td>
<td>39.2 (38.4-40.8)</td>
<td>38.9 (38.1-40.7)</td>
</tr>
<tr>
<td>Maximum pulse rate, Mean</td>
<td>88</td>
<td>91</td>
</tr>
<tr>
<td>Conjunctival injection, No. (%)†</td>
<td>16 (53)</td>
<td>9 (23)</td>
</tr>
<tr>
<td>Pharyngeal erythema, No. (%)</td>
<td>5 (17)</td>
<td>5 (13)</td>
</tr>
<tr>
<td>Neck stiffness, No. (%)</td>
<td>2 (7)</td>
<td>3 (8)</td>
</tr>
<tr>
<td>Abdominal tenderness</td>
<td>6 (20)</td>
<td>17 (43)</td>
</tr>
<tr>
<td>Lymphadenopathy, No. (%)</td>
<td>10 (30)</td>
<td>9 (23)</td>
</tr>
<tr>
<td>Rash, No. (%)‡</td>
<td>16 (53)</td>
<td>1 (3)</td>
</tr>
</tbody>
</table>

*P values indicate probabilities associated with $\chi^2$ of difference in proportions between the 2 groups.

†$P=0.02$.

‡$P<0.001$. 
Dengue Fever

6 year old male with acute primary dengue fever (DF)

- Negative tourniquet test
- Pleural effusion index 0.0

- Fever (°C)
- Pulse pressure (mm Hg)
- White blood cell count
- Liver

Hematocrit (%)

- Platelet count

Clinical illness day

Fever day: -4, -3, -2, -1, 0, 1, 2, 3
## Dengue Fever

<table>
<thead>
<tr>
<th>Febrile phase</th>
<th>Manifestation</th>
<th>Management</th>
</tr>
</thead>
</table>
| Duration 2-7 days   | - Temp 39-40°C <br>- Headache <br>- Retro-orbital pain <br>- Muscle pain <br>- Joint/bone pain <br>- Flushed face <br>- Rash <br>- Skin haemorrhage, bleeding from nose, gums <br>- Positive tourniquet test <br>- Liver often enlarged <br>- Leucopenia <br>- Platelet/haematocrit normal | - At home*  
- Bed rest  
- Keep the body temperature below 39°C  
- Paracetamol-Yes**  
- Aspirin-No  
- Brufen-No  
- Oral fluids and electrolyte therapy  
- Follow-up for any change in platelet/haematocrit |
### Afebrile phase (critical stage)
- **Duration** - 2-3 days after febrile stage

### Manifestation
- Same as during febrile phase
- Improvement in general condition
- Platelet/haematocrit normal
- Appetite rapidly regained

### Management
- Bed rest
- Check platelets/haematocrit
- Oral fluids and electrolyte therapy

### Convalescence Phase
- **Duration** - 7-10 days after critical stage

### Manifestation
- Further improvement in general condition and return of appetite
- Bradycardia
- Confluent petechial rash with white centre/itching
- Weakness for 1 or 2 weeks

### Management
- No special advice.
- No restrictions.
- Normal diet
Dengue Hemorrhagic Fever
R LAT decubitus X-ray showing a large pleural effusion, DHF the day after defervescence. Degree of plasma leakage may be quantified by means of the pleural effusion index. The pleural effusion index is calculated as 100 times the maximum width of the R pleural effusion, divided by the maximal width of the R hemithorax.
Hemoconcentration
### DHF: I / II

<table>
<thead>
<tr>
<th>Afebrile Phase (critical stage)</th>
<th>Manifestation</th>
<th>Management</th>
</tr>
</thead>
</table>
| Duration 2-3 days               | - Same as during febrile phase.  
- Thrombocytopenia and rise in haematocrit level (more than 20%) | - OPD or hospital  
- ORS  
- Check platelets/haematocrit. If haematocrit is more than 20%:  
- Initiate IV therapy (5% D/NSS) 6 ml/kg/hr (for 3 hours)  
- Check haematocrit/vital signs/urine output after 3 hours, and in case of improvement  
- Reduce IV therapy to 3ml/kg/hr (for 3 hours)  
- In case of further improvement, continue IV therapy at 3ml/kg/hr (6-12 hours) and then discontinue IV therapy  
- In case of no improvement, increase IV therapy to 10 ml/kg/hr (for 1 hr). In case of improvement now, reduce the volume of IV from 10ml/kg/hr to 6ml/kg/hr and further to 3ml/kg/hr accordingly.  
- Generally, DHF Grades I and II do not give complications |

<table>
<thead>
<tr>
<th>Convalescence Phase</th>
<th>Manifestation</th>
<th>Management</th>
</tr>
</thead>
</table>
| Duration 2-3 days after critical stage | - Further improvement in general condition and return of appetite  
- Bradycardia  
- Confluent petechial rash with white centre/itching  
- Astenia and depression (sometimes for a few weeks, common in adults) | - Normal diet  
- No need for any medication |
Petechiae on chest wall in child with DHF.

Subcutaneous hemorrhage in child with DHF.
DHF I / II
Volume Replacement
### DHF: III / IV

<table>
<thead>
<tr>
<th>Alebrile phase</th>
<th>Manifestation</th>
<th>Management</th>
</tr>
</thead>
<tbody>
<tr>
<td>Duration two days after febrile stage</td>
<td>In addition to the manifestations of DHF Grade II:</td>
<td>- Check haematocrit/platelet&lt;br&gt;- Initiate IV therapy (5% D/NSS) 10 ml/kg/h&lt;br&gt;- Check haematocrit, vital signs, urine output every hour&lt;br&gt;- If patient improves, IV fluids should be reduced every hour from 10 to 6, and from 6 to 3 ml/kg/h which can be maintained up to 24 to 48 hours&lt;br&gt;- If patient has already received one hour treatment of 20 ml/kg/hr of IV fluids and vital signs are not stable, check haematocrit again and&lt;br&gt;- If haematocrit is increasing, change IV fluid to colloidal solution preferably Dextran or Plasma at 10 ml/kg/h every hr.&lt;br&gt;- If haematocrit is decreasing from initial value, give fresh whole blood transfusion, 10 ml/kg/h and continue fluid therapy at 10 ml/kg/h and reducing it stepwise bring down the volume to 3 ml/kg/h and maintain it up to 24-48 hours&lt;br&gt;- Initiate IV therapy (5% D/NSS) 20 ml/kg as a bolus one or two times&lt;br&gt;- Oxygen therapy should be given to all patients&lt;br&gt;- In case of continued shock, colloidal fluids (Dextran or Plasma) should be given at 10-20 ml/kg/hr.</td>
</tr>
<tr>
<td>Profound shock with undetectable pulse and blood pressure</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Afebrile Phase</td>
<td>Manifestation</td>
<td>Management</td>
</tr>
<tr>
<td>---------------</td>
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</tbody>
</table>
|               | Profound shock with undetectable pulse and blood pressure | – If shock still persists and the haematocrit level continues declining, give fresh whole blood 10 ml/kg as a bolus  
– Vital signs should be monitored every 30-60 minutes  
– In case of severe bleeding, give fresh whole blood 20 ml/kg as a bolus  
– Give platelet rich plasma transfusion exceptionally when platelet counts are below 5,000-10,000/mm³  
– After blood transfusion, continue fluid therapy at 10 ml/kg/h and reduce it stepwise to bring it down to 3 ml/kg/h and maintain it for 24-48 hrs |

<table>
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</table>
| Duration 2-3 days after recovery from critical/shock stage | – 6-12 hours after critical/shock stage, some symptoms of respiratory distress (pleural effusion or ascites)  
– 2-3 days after critical stage, strong pulse, normal blood pressure  
– Improved general condition/return of appetite  
– Good urine output  
– Stable haematocrit  
– Platelet count >50,000 per mm³  
– Patient could be discharged from hospital 2-3 days after critical stage  
– Bradycardia/arrhythmia  
– Asthma and depression (few weeks) in adults | – Rest for 1-2 days  
– Normal diet  
– No need for medication |

DHF: III / IV

Petechiae
Melena

Gastric Bleeding
DHF III / IV
Volume Replacement

**UNSTABLE VITAL SIGNS**
Urine Output Falls
Signs Of Shock

Immediate, rapid volume replacement: Initiate IV therapy
10-20ml/kg/h Crystalloid solution for 1 hr

- **Improvement**
  - IV Therapy by crystalloid successively reducing from 20 to 10, 10 to 6, and 6 to 3ml/kg/hr
  - **Further Improvement**
    - Discontinue intravenous therapy after 24-48 hrs

- **No Improvement**
  - Oxygen
  - **Haematocrit Rises**
    - IV Colloid (Dextran 40) or plasma 10ml/kg/hr as intravenous bolus (repeat if necessary)
  - Haematocrit Falls
    - Blood transfusion (10 ml/kg/hr) if haematocrit is still > 35%
    - **Improvement**
      - IV therapy by crystalloid, successively reducing the flow from 10 to 6, 6 to 3ml/kg/hr
      - Discontinue after 24-48 hrs
Diagnosing Dengue

Infant w/ dengue: Thai – Cambodia border
Diagnosing Dengue - Basics

• Maintain high degree of suspicion
  – Geographic location
  – Clustering of cases

• History and physical
  – Clinical presentation consistent with dengue
  – Vital signs (T, BP, pulse pressure, HR)
  – Dengue tourniquet test

• Clinical lab assessment
  – CBC (WBC, HCT, PLT), AST/ALT, Bilirubin

• Endemic area, +Clinical, +Tourniquet test, WBC<5k = High PPV
Dengue Tourniquet Test

SBP+DBP / 2 x 5 mins

Inspect area for new petechiae

Positive = ≥ 10 or ≥ 20

2.5 cm²
### Table 1: Advantages and Limitations of Different Lung Diagnostic Tests

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<tr>
<th>Diagnostic Test</th>
<th>Advantages</th>
<th>Limitations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Blood analysis</td>
<td>Rapid results, non-invasive, detailed profile</td>
<td>Limited by sample availability, requires blood collection</td>
</tr>
<tr>
<td>X-rays</td>
<td>Visualizes lungs, identifies structural changes</td>
<td>Low resolution, requires ionizing radiation</td>
</tr>
<tr>
<td>CT scans</td>
<td>High resolution, detects early-stage disease</td>
<td>Invasive, requires contrast agents, exposes patient to radiation</td>
</tr>
<tr>
<td>PET scans</td>
<td>Identifies metabolic activity, detects lung cancer</td>
<td>Expensive, requires specialized equipment, exposes patient to radiation</td>
</tr>
<tr>
<td>MRIs</td>
<td>Provides detailed images, non-invasive</td>
<td>Expensive, requires specialized equipment, exposes patient to magnetic fields</td>
</tr>
<tr>
<td>Gene expression</td>
<td>Identifies genetic markers of lung cancer</td>
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### Table 2: Advantages and Limitations of Different Lung Diagnostic Tests

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<td>Camera imaging</td>
<td>Provides detailed images, non-invasive</td>
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<td>CT scans</td>
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### Table 3: Advantages and Limitations of Different Lung Diagnostic Tests

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Dengue Pathophysiology

AN ACCOUNT OF THE
Bilious Remitting Fever,
AS IT APPEARED IN PHILADELPHIA, IN THE SUMMER AND AUTUMN OF THE YEAR 1780.

The pains which accompanied this fever were exquisitely severe in the head, back, and limbs. The pains in the head were sometimes in the back parts of it, and at other times they occupied only the eyeballs. In some people, the pains were so acute in their backs and hips, that they could not lie in bed. In others, the pains affected the neck and arms, so as to produce in one instance a difficulty of moving the fingers of the right hand. They all complained more or less of a soreness in the seats of these pains, particularly when they occupied the head and eyeballs. A few complained of their flesh being sore to the touch, in every part of the body. From these circumstances, the disease was sometimes believed to be a rheumatism. But its more general name among all classes of people was, the Break-bone fever.
Infection / Disease Determinant Questions

• What places a person at risk for acquiring a dengue virus infection?

• Why do some Aedes feeding episodes result in infection and others do not?

• Why do some people experience disease following infection and others do not?

• Why is the dengue clinical phenotype spectrum so broad?
Exposure and Infection Outcome Determinants

- Virus
- Vector
- Ecology
- Host
Exposure Determinants – Risk of Infection

- Tropism for Aedes
  - Tropism for man
- Replicative kinetics
  - Man / Aedes
- “Immune avoidance”
  - Man / Aedes
- Evolutionary capacity

- Response to ecology
  - Temperature
  - Rain
- Infection resistance
  - Co-infection
- Evolutionary capacity

- Immune profile (dengue, other flavivirus)
- Vector exposure dynamics (duration, concentration)
  - “Neighbors” infection status
- Activities of daily living (who, what, where, when)
Infection Outcome Determinants – Risk of Disease

- **Virus**
  - DENV type
  - DENV genoypotype
  - Replicative kinetics
  - Immune evasion
  - Target cell tropism
  - Evolutionary capacity
  - Sequence of infection

- **Vector**
  - Salivary proteins

- **Host**
  - Immune profile (first infection, humoral, cellular)
  - Demographic (age, race, genetic background [HLA])
    - Co-morbidities
  - Medical system sophistication treating dengue
Dengue Ward: QSNICH, Bangkok, Thailand (Photo: Christopher Brown, IHT)
Immunologic Response – Clinical Phenotype (Rothman)
Questions?