Dengue
Acknowledgments

MAJ Leyi Lin, MD
Adult Infectious Diseases Physician
Viral Diseases Branch
Walter Reed Army Institute of Research

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Disclaimer

The views expressed in this presentation are those of the speaker and authors, and do not reflect the official policy of the Department of Army, Department of Defense, or U.S. Government.
Lecture Objectives

1. Understand the **global distribution** of dengue virus circulation and disease.
2. Appreciate the spectrum of **dengue clinical phenotypes** and recognize severe forms of the disease.
3. Understand the nuances of **treating dengue** and best management practices.
4. Become familiar with **countermeasure development** efforts.
Lecture Outline

• Introduction
• Epidemiology
• Clinical Phenotypes
• Pathophysiology
• Diagnostics
• Management
• Vaccine Development

Kuhn, R., Purdue University
Dengue

• Basics
  – Family Flaviviridae, Genus Flavivirus, Species Dengue
    • Same family as WNV, YF, JE, Zika
  – RNA virus, 3 structural and 7 non-structural genes
    • Different functions during infection process
    • Different targets for drugs/vaccines
  – 4 dengue virus types: DENV-1-4
    • Multiple genotypes within each dengue virus type
Dengue Epidemiology

Dengue Ward: QSNICH, Bangkok, Thailand (Photo: Christopher Brown, IHT)
Factors Driving Transmission

- Dengue viruses
  - Human travel
  - Viral evolution
- Naïve hosts
  - Population growth
  - Increased urbanization
- Vector
  - Ecologic changes
  - Evolution

These conditions create standing water in which the principal vector, the mosquito *Aedes aegypti*, breeds.
Mosquito Vectors

- **Aedes mosquitos**
  - Female bite, day time biter
  - Mosquito incubation period of 8-12 days and remains infective
  - Urban area, breed in or by houses
  - Man made or natural water containers
  - Short flyers

- **Aedes aegypti**
  - Principal vector
  - Multiple blood meals
  - Tropical and subtropical distribution

- **Aedes albopictus**
  - Less efficient vector
  - Wider distribution, better cold tolerance
  - Locally acquired cases in non endemic count (Japan in 2014)
Areas supporting dengue virus transmission.
Is dengue a threat to the blood supply?

D. Teo,* L. C. Ng† & S. Lam* *Blood Services Group, Health Sciences Authority, and †Environmental Health Institute, National Environment Agency, Singapore  Transfusion Medicine, 2009, 19, 66–77

- Laboratory acquired?
- Blood supply?
- Organ donation?

<table>
<thead>
<tr>
<th>Country</th>
<th>Donor deferral measures for dengue</th>
</tr>
</thead>
<tbody>
<tr>
<td>Singapore*</td>
<td>6 months deferral for history of dengue infection</td>
</tr>
<tr>
<td></td>
<td>3 weeks deferral for history of fever</td>
</tr>
<tr>
<td></td>
<td>No travel-related deferral for dengue</td>
</tr>
<tr>
<td>Hong Kong*</td>
<td>6 months deferral for history of dengue infection</td>
</tr>
<tr>
<td></td>
<td>2 weeks deferral for history of fever</td>
</tr>
<tr>
<td></td>
<td>No travel-related deferral for dengue</td>
</tr>
<tr>
<td>Sri Lanka*</td>
<td>No specific deferral for history of dengue infection</td>
</tr>
<tr>
<td></td>
<td>2 weeks deferral for history of fever</td>
</tr>
<tr>
<td></td>
<td>No travel-related deferral for dengue</td>
</tr>
<tr>
<td>Australia†</td>
<td>4 weeks deferral for history of dengue infection</td>
</tr>
<tr>
<td></td>
<td>No travel-related deferral for dengue</td>
</tr>
<tr>
<td>New Zealand‡</td>
<td>4 weeks deferral for history of dengue infection</td>
</tr>
<tr>
<td></td>
<td>No travel-related deferral for dengue</td>
</tr>
<tr>
<td>UK‡</td>
<td>2 weeks deferral for history of dengue infection</td>
</tr>
<tr>
<td></td>
<td>No travel-related deferral for dengue</td>
</tr>
<tr>
<td>United States‡</td>
<td>4 weeks deferral for history of dengue infection</td>
</tr>
<tr>
<td></td>
<td>No travel-related deferral for dengue</td>
</tr>
</tbody>
</table>

*Endemic for dengue.
†Non-endemic except parts of Northern Australia.
‡Non-endemic.
DENV Type Distribution - 1970

D. Gubler
Global Air Travel Flight Plans

http://upload.wikimedia.org/wikipedia/commons/a/ac/World-airline-routemap-2009.png
DENV Type Distribution - 2004

D. Gubler
Dengue Burden

Under-estimated and under-reported

Table 1 | Estimated burden of dengue in 2010, by continent

<table>
<thead>
<tr>
<th>Type</th>
<th>Apparent</th>
<th>Inapparent</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Millions (credible interval)</td>
<td>Millions (credible interval)</td>
</tr>
<tr>
<td>Africa</td>
<td>15.7 (10.5–22.5)</td>
<td>48.4 (34.3–65.2)</td>
</tr>
<tr>
<td>Asia</td>
<td>66.8 (47.0–94.4)</td>
<td>204.4 (151.8–273.0)</td>
</tr>
<tr>
<td>Americas</td>
<td>13.3 (9.5–18.5)</td>
<td>40.5 (30.5–53.3)</td>
</tr>
<tr>
<td>Oceania</td>
<td>0.18 (0.11–0.28)</td>
<td>0.55 (0.35–0.82)</td>
</tr>
<tr>
<td>Global</td>
<td>96 (67.1–135.6)</td>
<td>293.9 (217.0–392.3)</td>
</tr>
</tbody>
</table>

389.9M infections/year

GLOBAL STRATEGY
FOR DENGUE PREVENTION AND CONTROL

Figure 3. Average number of dengue cases in 30 most highly endemic countries/territories as reported to WHO, 2004–2010

© World Health Organization 2012
Average dengue incidence /100,000 by country, 1980–2007
### Middle East Pakistan

**Table 1 — Confirmed cases and deaths from 2006 to 2011 in the affected areas of Pakistan.**

<table>
<thead>
<tr>
<th>Year</th>
<th>Khyber Pakhtunkhwa</th>
<th>Sindh</th>
<th>Punjab</th>
<th>Lahore</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Cases</td>
<td>Deaths</td>
<td>All parts Cases</td>
<td>Deaths</td>
</tr>
<tr>
<td>2006</td>
<td>31</td>
<td>1</td>
<td>1500</td>
<td>50</td>
</tr>
<tr>
<td>2007</td>
<td>0</td>
<td>0</td>
<td>950</td>
<td>22</td>
</tr>
<tr>
<td>2008</td>
<td>30</td>
<td>4</td>
<td>585</td>
<td>6</td>
</tr>
<tr>
<td>2009</td>
<td>100</td>
<td>7</td>
<td>550</td>
<td>7</td>
</tr>
<tr>
<td>2010</td>
<td>0</td>
<td>0</td>
<td>5000</td>
<td>35</td>
</tr>
<tr>
<td>2011</td>
<td>296</td>
<td>8</td>
<td>952</td>
<td>18</td>
</tr>
</tbody>
</table>

*a* Data collected from National Institute of Health Islamabad.  
*b* Data collected from provincial health departments.
Figure. Dengue and *Aedes aegypti* mosquitoes in Africa. Brown indicates 34 countries in which dengue has been reported, including dengue reported only in travelers, and *Ae. aegypti* mosquitoes. Light brown indicates 13 countries (Mauritania, The Gambia, Guinea-Bissau, Guinea, Sierra Leone, Liberia, Niger, Chad, Central African Republic, Republic of the Congo, Malawi, Zimbabwe, and Botswana) in which dengue has not been reported but that have *Ae. aegypti* mosquitoes. White indicates 5 countries (Western Sahara, Morocco, Algeria, Tunisia, and Libya) for which data for dengue and *Ae. aegypti* mosquitoes are not available.

**Brown – dengue reported**

**Light Brown – dengue not reported but vector exists**

**White – data not available**
High Financial and Human Cost

Economic Impact of Dengue Illness in the Americas

Donald S. Shepard,* Laurent Coudeville, Yara A. Halasa, Betzana Zambrano, and Gustavo H. Dayan
Brandeis University, Waltham, Massachusetts; Sanofi Pasteur, Lyon, France; Sanofi Pasteur, Swiftwater, Pennsylvania

Figure 1. Number of dengue reported cases in the Americas from 2000 to 2007.

Figure 3. Annual economic burden in the Americas from 2000 to 2007 (in 2010 US$).

Economic and Disease Burden of Dengue in Southeast Asia


Figure 3. Aggregate values of dengue episodes and economic burden by year for 12 countries in SEA (2001–2010).
CDC Dengue Map – 01MAY – 01NOV 2014

Note Cases in Temperate Climates!

Reporting sources – WHO, MOHs, ProMed, GeoSentinel, EuroSurveillance, World Org
Dengue fever in Brazil

When it rains, it pours

The welcome return of wet weather has a nasty side-effect

Mar 28th 2015 | SÃO PAULO | From the print edition

A MOIST March, combined with the wettest February in 20 years, has brought respite to Brazil’s parched south-east. Last year’s record drought in the region, where two in five Brazilians live and where more than half the country’s output is produced, had stretched into January. So the drenching is welcome. But the rains have also stirred up an old scourge: dengue fever, a disease transmitted by mosquitoes. Its early symptoms resemble flu but it can cause fatal internal and external bleeding.

At least 224,000 cases had been registered across Brazil by March 7th, 162% more than in the same period in 2014, when the dry weather left fewer stagnant puddles in which mosquitoes could breed. The situation is gravest in the state of São Paulo, where 124,000 people have been diagnosed since January, an eightfold increase on last year. Infections have reached epidemic levels in nearly half the state’s municipalities (mostly the smaller ones). São Paulo has seen 67 confirmed fatalities. Mercifully, things in the rest of the country are better, meaning that the situation is less severe than the full-blown epidemic that infected 1.5m people in 2013.

Malaysia

As of 25 April 2015, there were 38,517 cases of dengue reported in Malaysia for 2015. This is 33.7% higher compared with the same reporting period of 2014 (n=28,814) (Figure 2). From 19 to 25 April 2015, there were 1,446 cases of dengue reported, 5.2% higher than the same period of the previous week (n=1,370).

Alternative herbal drink introduced to combat dengue fever

BY PRIYA PUDALAN - 11 MAY 2015 @ 2:44 PM

BUTTERWORTH: An alternative herbal drink to cure the escalating dengue fever has been introduced.

Thanks to Al Faris Herbs, the ‘Sari Daun Betik’ is rich in Vitamin C and minerals, made with papaya leaf extract to increase blood platelets in human body.

Al Faris advisor Datuk Dr Shuib Saedlin, who is also a medical practitioner, said the drink helps to increase low level of platelets in human body.

“The papaya leaf juice is probably the most well-known alternative treatment for dengue.

“However, it is bitter to consume, especially for children.

“We carried out scientific studies in the past few months and produced this herbal remedy which consists of dates, honey and other vitamins combined with the papaya leaf extract to combat dengue fever,” he told reporters today.

Dr Shuib said the results cannot be said to be definitive, due to their small study size, but they are certainly promising.

The product will be available in market starting today and can be found in sundry and retail shops.

It is priced at RM55 per bottle and could last more than a month.

Meanwhile, the latest report from the Health Ministry states that as of May 5, the number of dengue cases has increased to 41,450 cases and 126 deaths nationwide.
Dengue in the U.S.

Dengue Fever, Hawaii, 2001–2002

Emerging Infectious Diseases • www.cdc.gov/eid • Vol. 11, No. 5, May 2005

Paul V. Effler,* Lorrin Pang,* Paul Kitsutani,† Vance Vorndam,† Michele Nakata,* Tracy Ayers,* Joe Elm,* Tammy Tom,* Paul Reiter,† José G. Rigau-Perez,† John M. Hayes,† Kristin Mills,* Mike Napier,‡ Gary G. Clark,† and Duane J. Gubler* for the Hawaii Dengue Outbreak Investigation Team†
Dengue in the U.S.

Identification of Dengue Fever Cases in Houston, Texas, with Evidence of Autochthonous Transmission Between 2003 and 2005


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


Epidemic Dengue and Dengue Hemorrhagic Fever at the Texas–Mexico Border: Results of a Household-based Seroepidemiologic Survey, December 2005
Locally Acquired Dengue — Key West, Florida, 2009–2010

onset and method of identification — Key West, Florida, 2009–2010

Week of illness onset

* Two cases identified in both household serosurvey and medical record review are shown as record review cases.
† Week of illness onset in index patient.

acquired dengue — Key West, Florida, 2009–2010

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>No.</th>
<th>(%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>19</td>
<td>(68)</td>
</tr>
<tr>
<td>Female</td>
<td>9</td>
<td>(32)</td>
</tr>
<tr>
<td>Age group (yrs)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;20</td>
<td>1</td>
<td>(4)</td>
</tr>
<tr>
<td>21–40</td>
<td>11</td>
<td>(39)</td>
</tr>
<tr>
<td>41–60</td>
<td>11</td>
<td>(39)</td>
</tr>
<tr>
<td>&gt;60</td>
<td>5</td>
<td>(18)</td>
</tr>
<tr>
<td>Race</td>
<td></td>
<td></td>
</tr>
<tr>
<td>White</td>
<td>24</td>
<td>(86)</td>
</tr>
<tr>
<td>Black</td>
<td>3</td>
<td>(11)</td>
</tr>
<tr>
<td>Asian/Pacific Islander</td>
<td>1</td>
<td>(4)</td>
</tr>
<tr>
<td>Ethnicity</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Non-Hispanic</td>
<td>25</td>
<td>(89)</td>
</tr>
<tr>
<td>Hispanic</td>
<td>3</td>
<td>(11)</td>
</tr>
<tr>
<td>Symptoms</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fever</td>
<td>28</td>
<td>(100)</td>
</tr>
<tr>
<td>Headache</td>
<td>22</td>
<td>(79)</td>
</tr>
<tr>
<td>Myalgia</td>
<td>23</td>
<td>(82)</td>
</tr>
<tr>
<td>Arthralgia</td>
<td>18</td>
<td>(64)</td>
</tr>
<tr>
<td>Eye pain</td>
<td>14</td>
<td>(50)</td>
</tr>
<tr>
<td>Rash</td>
<td>15</td>
<td>(54)</td>
</tr>
<tr>
<td>Bleeding</td>
<td>6</td>
<td>(21)</td>
</tr>
</tbody>
</table>

* Percentages might not add to 100% because of rounding.
Dengue in the U.S. - Florida 2013

• 2013:
  • 26% of all dengue in the US
  • All 4 serotypes, mostly DENV-1
  • 120 travel related cases
  • 23 locally acquired cases
    • 22 from Martin County

• 2014
  • Few cases
  • Both travel and locally acquired

CDC Dengue Map, 15 OCT 2013
Puerto Rico: 2014 epidemic compared to 2015
(through 6/24/15, CDC)

References: CDC Website
Puerto Rico 2014 Epidemic

Total viral identifications in the last 12 months

Month of first symptoms

Municipios with suspected cases in weeks 11-14

References: CDC Website
"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 3. Etiologic Diagnoses within Selected Syndrome Groups, According to Travel Region.*

<table>
<thead>
<tr>
<th>Syndrome and Cause</th>
<th>All Regions</th>
<th>Caribbean</th>
<th>Central America</th>
<th>South America</th>
<th>Sub-Saharan Africa</th>
<th>South Central Asia</th>
<th>Southeast Asia</th>
<th>Other or Multiple Regions†</th>
</tr>
</thead>
<tbody>
<tr>
<td>Systemic febrile illness (n=3907)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Specific pathogen or cause reported‡:</td>
<td>594</td>
<td>459</td>
<td>527</td>
<td>446</td>
<td>718</td>
<td>522</td>
<td>547</td>
<td>454</td>
</tr>
<tr>
<td>Malaria†</td>
<td>352</td>
<td>65</td>
<td>133</td>
<td>133</td>
<td>622</td>
<td>139</td>
<td>130</td>
<td>234</td>
</tr>
<tr>
<td>Dengue‡</td>
<td>104</td>
<td>238</td>
<td>123</td>
<td>138</td>
<td>7</td>
<td>142</td>
<td>315</td>
<td>35</td>
</tr>
<tr>
<td>Mononucleosis (due to Epstein–Barr virus or cytomegalovirus)‡:</td>
<td>32</td>
<td>70</td>
<td>69</td>
<td>79</td>
<td>10</td>
<td>17</td>
<td>32</td>
<td>63</td>
</tr>
<tr>
<td>Rickettsial infection‡:</td>
<td>31</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>56</td>
<td>10</td>
<td>16</td>
<td>24</td>
</tr>
<tr>
<td>Salmonella typhi or S. paratyphi infection‡:</td>
<td>29</td>
<td>22</td>
<td>25</td>
<td>17</td>
<td>7</td>
<td>141</td>
<td>26</td>
<td>24</td>
</tr>
<tr>
<td>No specific cause reported‡:</td>
<td>406</td>
<td>541</td>
<td>473</td>
<td>554</td>
<td>282</td>
<td>478</td>
<td>453</td>
<td>546</td>
</tr>
</tbody>
</table>

‡ P<0.01 for the comparison among regions.
Dengue and US Military Operations from the Spanish–American War through Today

Robert V. Gibbons, Matthew Streitz, Tatyana Babina, and Jessica R. Fried
Emerging Infectious Diseases • www.cdc.gov/eid • Vol. 18, No. 4, April 2012

Figure 1. Captain Percy Ashburn.

Figure 2. Third Lieutenant Charles Craig.

Figure 3. Lieutenant Commander J.F. Siler.

Figure 4. Major Albert Sabin.

Figure 6. Airplane spraying of DDT over Manila, the Philippines, 1945.
Dengue U.S. Military Impact

- WWII: >85,000 U.S. cases
  Outbreaks: 80% attack rate
  Saipan: 20,000 cases in a 3 month period

- Vietnam (1966): most prevalent cause of FUO

- Somalia (1992-93): 59 cases/289 febrile troops

- Haiti (1994): Most common infectious cause of hospital admission
Dengue Risk / Threat to DoD

• Prevalence and Risk to Soldiers (2003-2012)
  – **Total Cases:** 631
    • Active Duty: 177; Reserve: 35; MHS Beneficiaries: 419
    • No record of attributable deaths
  – **Dengue Mission Impact Projections**
    • Not severe: hospitalized ~5-7 days, low functioning ~14-28 days
    • Severe: evacuation to MTF, ICU care?, death?, LDD >1 month
  – **Deployment**
    • DODSR: 500 samples, deployed between 2006-2008
      – 11.2% seroprevalence of dengue antibody
      – 2.4% with monovalent profile (high risk with next infection)

References: *Dengue Tetravalent Vaccine CDD; †DMSS*
Seroprevalence of DENV Exposure in Deployed Personnel

- DODSR, 1000 samples, first time deployers, 2008-2011
- 250 samples selected per COCOM
- Tested for presence of neutralizing antibody by microneut assay
- Overall 7.6% seroprevalence rate of past dengue exposure
- 1.5% seroconversion rate during deployment (first infection)
- Increased self report of fever during deployment in those with antibodies

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

<table>
<thead>
<tr>
<th>Region</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>
DENV Exposure in USASOC Personnel

• USASOC and WRAIR Viral Diseases threat characterization

• 1027 samples tested since 2010

• Pre/post-deployment sample collection in SOC personnel
  • Tested for presence of neutralizing antibody by MN assay
  • 13.73% are seropositive to at least one DENV serotype
  • 9.35% are tetravalent responses
  • 4.38% are monolavent, bivalent or trivalent responses
  • Ongoing testing

• USASOC personnel are highly primed to dengue, a proportion are in high risk category for severe disease with secondary infection
# DOD Infectious Disease Threats

<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 / 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>
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<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>
Case Presentation

• 18 year old native from Thailand (moved to US at 10 years of age) presents in August with 2 days of illness including fever, headache, bone pain, and nausea 3 days after returning from a vacation in Puerto Rico. You suspect he has a dengue infection. He is tolerating PO intake without vomiting and is urinating. Vital signs except for temperature (102.5F) are in the range of normal. Mucous membranes are moist, skin turgor is normal, abdominal exam is normal, and lungs are clear. A CBC reveals a low WBC (3.5k) but otherwise is within normal limits. Electrolytes are normal.

• What is the most reasonable initial management strategy?

  – 1. treat as outpt, provide NSAIDS, encourage PO fluids
  – 2. treat as inpt, provide 1L NS bolus, monitor in ICU setting
  – 3. treat as outpt, provide acetaminophen, encourage po fluids, F/U
  – 4. treat as inpt, encourage PO fluids, perform q6 hr HCT evaluations
Clinical Phenotype

AN ACCOUNT OF THE Biliary 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.
Suspecting Dengue

- Travel to endemic region
- Incubation: 4-7 days, range 3-14 days
  - Travel > 14 days prior = other dx
- Classic “Breakbone fever”
  - 15-60% of patients
- Myalgias, arthralgias
- Headache, retro-orbital pain
- Rash
  - 2-5 days AFTER fever onset
  - More common in primary infection
- Nausea, vomiting, abdominal pain
  - More common in secondary infection


Diagnosing Dengue

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

• History and physical
  – Clinical presentation
  – Vital signs (HR, BP, Temp)
  – Dengue tourniquet test (TT)

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

• Dengue tests in US
  – IgM capture ELISA
  – CDC RT-PCR

• Dengue area, +Clinical, +TT, WBC<5k = High PPV (~70%)
Dengue Tourniquet Test

• Measure BP
• SBP + DBP / 2 = target insufflation pressure for test
• Inspect area near antecubital fossa
  – You will assess delta before / after
• Inflate to target pressure
• Hold for 5 minutes
• Remove cuff
• Reassess antecubital fossa
• Count # of petechiae in 2.5 cm² area
• ≥10 new petechiae is positive
• TT measures capillary fragility, severe disease predictor?
1997 WHO Dengue Fever Case Definition

- **Dengue Fever (DF)** = Acute febrile illness + fever and AT LEAST 2 of:
  - Retro-orbital or ocular pain, headache, rash, myalgia, arthralgia, leukopenia, or hemorrhagic manifestations but not meeting the case definition of dengue hemorrhagic fever.

- **Dengue Hemorrhagic Fever (DHF)** = DF + ALL bellow
  - Fever 2-7 days,
  - hemorrhagic manifestation or a positive tourniquet test
  - Thrombocytopenia (≤100,000 cells per mm3)
  - Evidence of plasma leakage shown by hemoconcentration

- **Dengue Shock Syndrome (DSS)** = DHF + circulatory failure

- Definition revised to improve care to those not meeting DHF definition, emphasize plasma leakage as a sign, and improve disease capture and reporting.
Clinical Phenotypes

![Diagram showing clinical phenotypes]


OCID course 2015
Dengue haemorrhagic fever

Diagnosis, treatment, prevention and control

SECOND EDITION

World Health Organization
Geneva
1997

Suggested Dengue Case Classification and Levels of Severity

**DENGUE ± WARNING SIGNS**

**SEVERE DENGUE**

1. Severe plasma leakage
2. Severe haemorrhage
3. Severe organ impairment

**CRITERIA FOR DENGUE ± WARNING SIGNS**

**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)*

**CRITERIA FOR SEVERE DENGUE**

**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
Pathophysiology

Dengue Ward: QSNICH, Bangkok, Thailand (Photo: Christopher Brown, IHT)
Exposure Determinants – Infection Risk

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

• Immune profile (dengue, other flavivirus)
• Vector exposure dynamics (duration, concentration)
  • “Neighbors” infection status
• Activities of daily living (who, what, where, when)

Virus

Vector

Host

• Response to ecology
  - Temperature
  - Rain
• Infection resistance
  - Co-infection
• Evolutionary capacity
Infection Outcome Determinants – Disease Risk

- DENV type
- DENV genotype
- Replicative kinetics
- Immune evasion
- Target cell tropism
- Evolutionary capacity
- Sequence of infection

- Immune profile (first infection, humoral, cellular)
- Demographic (age, race, genetic background [HLA])
- Co-morbidities
- Medical system sophistication treating dengue

- Salivary proteins
Figure 4 | A balance between favourable and unfavourable factors determines the clinical outcome of dengue virus infection. Virus inoculation by *Aedes aegypti* mosquitoes results in viral dissemination, which in turn results in disease manifestations; high virus titres are necessary but not sufficient to cause severe disease. Viral and host factors affect early viral replication and influence the level of viraemia. Other host factors affect the levels of production of various cytokines (such as interferon-γ (IFNγ) and tumour necrosis factor (TNF)) and determine the severity of illness for any given level of viraemia. APL, altered peptide ligand.
Disease Risk – What We Know

- Virulence likely serotype (DENV 2) and genotype (Asian strains) specific

- Risk for severe disease declines with age

- Severe disease appears less common in malnourished children

- Host (human) genetic variation such as HLA type
Secondary Infection

- Increased risk of severe dengue if infected with a different serotype
- Heterotypic antibodies protective against all 4 serotypes for a brief period
  - At least 3 months
- Antibody Dependent Enhancement
- Serotype sequence and virus genotype may be important
  - DENV 1 followed by DENV 2
    - Asian DENV 2 genotype but not American (Watts 1999)
- Host Specific
- 3rd or more heterotypic infections have much lower rates of severe disease
- Multiple serotypes / genotypes circulating in one area
- Interaction between dengue and immune system is complicated

Stimulation of complement system and cells of the innate immunity

- Increased virus titers
  - Enhancing antibodies
  - Antibodies cross-react with plasmin
  - Antibodies cross-react with platelets
    - Production of specific and cross-reactive antibodies
      - DENV
        - Mononuclear cells: replication in Langerhans cells and splenic macrophages
          - Stimulation of cross-reactive, low avidity T cells
            - Stimulation of regulatory T cells
              - Stimulation of specific and highly cross-reactive T cells

- Endothelial cell dysfunction
  - Endothelial cells: infection and replication in selective endotheliocytes
  - Liver: replication in hepatocytes and Kupffer cells
  - Tissue macrophages
  - Bone marrow: replication in stromal cells

Development of coagulation disorder
Endothelial cell dysfunction

- Endothelial cells: infection and replication in selective endotheliocytes
  - Apoptosis

- Liver: replication in hepatocytes and kupffer cells
  - Necrosis and/or apoptosis in liver and breach of its function
  - Release of toxic products into the blood
  - Increase of coagulation
  - Activation of fibrinolytic system
  - Consumption of platelets

- Tissue macrophages
  - Apoptosis

- Bone marrow: replication in stromal cells
  - Suppression of haemopoiesis
  - Soluble mediators: TNF-α, IFN-γ, IL-1, IL-2, IL-6, IL-8, IL-10, IL-13, IL-18, TGF-β, C3a, C4b, C5a, MCP-1, CCL2, VEGF, NO
  - Imbalance profile of cytokine and other mediators

Development of coagulation disorder

OCID course 2015
Dengue Clinical and Lab Parameters

24 hr period around defervescence = danger period
Dengue Fever

6 year old male with acute primary den-1, DF

- Negative tourniquet test
- Pleural effusion index 0.0

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

- Platelet count
- Hematocrit (%)
- Albumin
- AST
- ALT

Clinical illness day
Fever day
Dengue Hemorrhagic Fever

7 year old male with acute secondary den-1, grade III DHF

Positive tourniquet test

Pleural effusion index 25.5

Fever (°C)

Hematocrit (%)

Pulse pressure (mm Hg)

Platelet count

White blood cell count

500x10^3
400x10^3
300x10^3
200x10^3
100x10^3

Liver

Clinical illness day

Fever day

WBC

Platelet

AST

ALT

Albumin
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
Diagnosing Dengue

- FDA-cleared
  - DENV 1-4 Real Time RT PCR (June 2012)
  - DENV Detect IgM Capture ELISA (April 2011)

- RDT, Filter Paper Cards
  - No FDA-cleared RDT yet
    - FY17?
  - NS1 antigen detection
  - Antibody detection
    - IgM and IgG ELISA
    - Ideally combined with NS1 detection
Evaluation of diagnostic tests: dengue

Rosanna W. Peeling, Harvey Artsob, Jose Luis Pelegrino, Philippe Buchy, Mary J. Cardosa, Shamala Devi, Delia A. Enria, Jeremy Farrar, Duane J. Gubler, Maria G. Guzman, Scott B. Halstead, Elizabeth Hunsperger, Susie Kliks, Harold S. Margolis, Carl M. Nathanson, Vinh Chau Nguyen, Nidia Rizzo, Susana Vázquez and Sutee Yoksan

Direct methods

- Virus isolation
- Genome detection
- Antigen detection

Indirect methods

- Serology IgM
- Serology IgG

Specificity

Opportunity

Figure 1 | Comparative merits of direct and indirect laboratory methods for the diagnosis of dengue infections. Opportunity refers to the fact that antibody testing is usually the most practical diagnostic option available.
Case Presentation

• 18 year old native from Thailand (moved to US at 10 years of age) presents in August with 2 days of illness including fever, headache, bone pain, and nausea 3 days after returning from a vacation in Puerto Rico. You decide to manage him as an outpatient. He fails to follow up as requested but does return day 6 of his illness afebrile with resolution of some symptoms but he now has abdominal pain, slight shortness of breath, and lethargy.

• What is the most reasonable management strategy at this point?
  – 1. Continue close follow up as outpatient, encourage PO fluid intake, this is the natural history of a resolving dengue infection
  – 2. Admit to the hospital, approach as a critically ill patient, this is a severe dengue virus infection
  – 3. Admit to the hospital, evaluate for another infectious disease process, these new symptoms represent a new medical problem
  – 4. Prescribe doxycycline, he probably has leptospirosis
Suggested Dengue Case Classification and Levels of Severity

**DENGUE ± WARNING SIGNS**

- with warning signs
- without

**SEVERE DENGUE**

1. Severe plasma leakage
2. Severe haemorrhage
3. Severe organ impairment

**CRITERIA FOR DENGUE ± WARNING SIGNS**

**Probable dengue**
- live in / travel to dengue endemic area
- Fever and 2 of the following criteria:
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**Laboratory-confirmed dengue**
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- Laboratory: increase in HCT concurrent with rapid decrease in platelet count

*(requiring strict observation and medical intervention)*

**CRITERIA FOR SEVERE DENGUE**

**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
**Dengue Treatment**

**Dengue without warning signs**

**Group A**
(May be sent home)

**Group criteria**
Patients who do not have warning signs AND who are able:
- to tolerate adequate volumes of oral fluids
- to pass urine at least once every 6 hours

**Laboratory tests**
- full blood count (FBC)
- haematocrit (HCT)

**Treatment**
Advice for:
- adequate bed rest
- adequate fluid intake
- Paracetamol, 4 gram maximum per day in adults and accordingly in children.

Patients with stable HCT can be sent home.

**Monitoring**
Daily review for disease progression:
- decreasing white blood cell count
- defervescence
- warning signs (until out of critical period).

Advice for immediate return to hospital if development of any warning signs, and
- written advice for management (e.g. home care card for dengue).
Dengue Treatment

DENGUE WITH WARNING SIGNS

Group B
(Referred for in-hospital care)

Group criteria
Patients with any of the following features:
- co-existing conditions such as pregnancy, infancy, old age, diabetes mellitus, renal failure
- social circumstances such as living alone, living far from hospital

Monitoring
Monitor:
- temperature pattern
- volume of fluid intake and losses
- urine output (volume and frequency)
- warning signs
- HCT, white blood cell and platelet counts

Laboratory tests
- full blood count (FBC)
- haematocrit (HCT)

Treatment
- Encouragement for oral fluids. If not tolerated, start intravenous fluid therapy 0.9% saline or Ringer’s Lactate at maintenance rate.
Algorithm for Fluid Management in Compensated Shock

Compensated shock (systolic pressure maintained but has signs of reduced perfusion)
Fluid resuscitation with isotonic crystalloid
5–10 ml/kg/hr over 1 hour

- Assess
- Intervene
- Re-assess
Algorithm for Fluid Management in Hypotensive Shock

Hypotensive shock
Fluid resuscitation with 20 ml/kg isotonic crystalloid or colloid over 1.5 minutes
Try to obtain a HCT level before fluid resuscitation

Improvement

YES

Crystallloid/colloid 10 ml/kg/hr for 1 hour, then continue with:
IV crystalloid 5-7 ml/kg/hr for 1-2 hours;
reduce to 3-5 ml/kg/hr for 2-4 hours;
reduce to 2-3 ml/kg/hr for 2-4 hours.

If patient continues to improve, fluid can be further reduced.
Monitor HCT 6-hourly.

If the patient is not stable, act according to HCT levels:
if HCT increases, consider bolus fluid administration or increase fluid administration;
if HCT decreases, consider transfusion with fresh whole blood.
Stop at 48 hours.

NO

Review 1st HCT

HCT ↑ or high

Administer 2nd bolus fluid (colloid)
10-20 ml/kg over ½ to 1 hour

Improvement

YES

Consider significant occult/overt bleed
Initiate transfusion with fresh whole blood

NO
• Assess
• Intervene
• Re-assess

Consider occult / overt bleed

Repeat 2nd HCT

HCT↑ or high

Administer 3rd bolus fluid (colloid)
10-20 ml/kg over 1 hour

Improvement

Repeat 3rd HCT

HCT↓

YES

NO
<table>
<thead>
<tr>
<th></th>
<th>Good practice</th>
<th>Bad practice</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Assessment and follow-up of patients with non-severe dengue and careful instruction of warning signs to watch out for</td>
<td>Sending patients with non-severe dengue home with no follow-up and inadequate instructions</td>
</tr>
<tr>
<td>2</td>
<td>Administration of paracetamol for high fever if the patient is uncomfortable</td>
<td>Administration of acetylsalicylic acid (aspirin) or ibuprofen</td>
</tr>
<tr>
<td>3</td>
<td>Obtaining a haematocrit level before and after fluid boluses</td>
<td>Not knowing when haematocrit levels are taken with respect to fluid therapy</td>
</tr>
<tr>
<td>4</td>
<td>Clinical assessment of the haemodynamic status before and after each fluid bolus</td>
<td>No clinical assessment of patient with respect to fluid therapy</td>
</tr>
<tr>
<td>5</td>
<td>Interpretation of haematocrit levels in the context of fluid administered and haemodynamic assessment</td>
<td>Interpretation of haematocrit levels independent of clinical status</td>
</tr>
<tr>
<td>6</td>
<td>Administration of intravenous fluids for repeated vomiting or a high or rapidly rising haematocrit</td>
<td>Administration of intravenous fluids to any patient with non-severe dengue</td>
</tr>
<tr>
<td>7</td>
<td>Use of isotonic intravenous fluids for severe dengue</td>
<td>Use of hypotonic intravenous fluids for severe dengue</td>
</tr>
<tr>
<td>8</td>
<td>Giving intravenous fluid volume just sufficient to maintain effective circulation during the period of plasma leakage for severe dengue</td>
<td>Excessive or prolonged intravenous fluid administration for severe dengue</td>
</tr>
<tr>
<td>9</td>
<td>Avoiding intramuscular injections in dengue patients</td>
<td>Giving intramuscular injections to dengue patients</td>
</tr>
<tr>
<td>10</td>
<td>Intravenous fluid rate and frequency of monitoring and haematocrit measurement adjusted according to the patient’s condition</td>
<td>Fixed intravenous fluid rate and unchanged frequency of monitoring and haematocrit measurement during entire hospitalization for severe dengue</td>
</tr>
<tr>
<td>11</td>
<td>Close monitoring of blood glucose, i.e. tight glycaemic control</td>
<td>Not monitoring blood glucose, unaware of the hyperglycaemic effect on osmotic diuresis and confounding hypovolaemia</td>
</tr>
<tr>
<td>12</td>
<td>Discontinuation or reducing fluid therapy once haemodynamic status stabilizes</td>
<td>Continuation and no review of intravenous fluid therapy once haemodynamic status stabilizes</td>
</tr>
</tbody>
</table>
Dengue Vaccine Development
Dengue Vaccine Pipeline 2013

- **Sanofi Pasteur (CYD)**
- **WRAIR/GSK - LAV**
- **NIH/JHU - ∆30 mut**
- **NMRC – Tetra DNA + Vaxf.**
- **WRAIR/GSK – PIV + AS**
- **Takeda – DENVax**
- **Merck / HBI – r80E + ISCO**
- **GenPhar – Cad-Vax**
- **NMRC/Genvec – Adv5_DNA**
- **Mahidol - LAV**
- **FDA – mutF**
- **Carolina – alphavirus vector**
- **VaxInnate – flagellin E**
- **Altravax – flagellin E**
- **Arbovax - mutant**

**Pre-clinical**

- Development halted *
- Development halted
- Tetravalent product to endemic regions
- US and Puerto Rico
- Ongoing trial in PR, other endemic regions
- Tetravalent study ongoing
- Exploring future
- NHP studies completed
- DENV-3 component derailed initial effort, reformulating
- NHP study completed, no further development
- NHP study completed
- NHP study underway
- NHP study underway
- NHP study underway

**Green** = human testing;
**Red** = pre-clinical
NMRC & others: DNA (preM+E) + adjuvant

Merck: 80% E recombinant
Expressed in Drosophila cells

NIH: Directed mutagenesis,
deletions, point mutations
Stand alone and chimeras

Various: Domain III antigen

Sanofi P: YF 17D backbone
Dengue prM and E
Monovalents formulated as tetra-

Takeda: DENV-2 PDK backbone,
Directed mutagenesis, DENV-2/-1, -2/-3, -2/-4

WRAIR/GSK: PIV + adjuvant system
Full genome, inactivated, formalin
Sanofi Pasteur’s CYD Tetravalent Dengue Vaccine (TDV)

- Three doses at 0, 6, 12 months
- Completed two large phase 3 studies in Latin America and Asia among mostly seropositive children exposed to all 4 serotypes.
- Vaccine is efficacious against dengue fever
- Substantial protection against severe dengue
- Protection varied by serotype (DENV 2 worst)
- Lowest efficacy in 2-5 year olds
- Poor efficacy for subjects seronegative at baseline
- Marketing and licensure?
- Fit for US travelers and military personnel?
Development Challenges

• Each DENV type may cause severe disease/death
  – Viable vaccine requires efficacy against multiple types
  – Immune interference may prevent balanced response

• Incomplete understanding of protection / pathology
  – Will a poor dengue vaccine increase / worsen disease?
  – Extrapolating wild type infection data to immunization?

• No validated immune correlate of protection
  – No metrics or benchmarks for vaccine developers
  – Increases need for larger scale clinical trials
Development Challenges

• No validated animal model of disease
  – NHPs develop viremia and Nab but not disease

• No validated human infection model
  – Advancing vaccines based on Nab and NHP data
  – Efficacy trials may not capture efficacy vs. all DENVs

• Biologic assays used for endpoint determinations
  – Inter-assay variability notorious
  – Neutralizing antibody’s ability to predict efficacy?

• Numerous indications with unique challenges
  – Needs vary at the time, space, and population level
Conclusions

• The world needs a dengue vaccine!
• Global dengue burden is increasing
• Maintain a high index of suspicion in febrile traveler
• High financial and societal cost associated with disease
• Numerous factors continue to drive transmission
• Numerous vaccine development challenges exist
• Dengue vaccine pipeline robust
• Numerous areas for expanded study exist
Questions?