Achy, Breaky, and Sneaky

Chikungunya, Dengue, and Zika…

With a touch of MERS and Hemorrhagic Fevers
Zika virus (ZIKV) History-1

- On 18 Apr 1947, a rhesus monkey that researchers identified as 766 ran a fever of 39.7 °C [103.5 °F].
- The monkey (part of a study on yellow fever virus) was living in a cage on a platform built into the tree canopy in the Zika Forest, adjacent to Lake Victoria in Uganda.
- Then, the investigators took a blood sample from Rhesus 766 and injected it into the brains of Swiss albino mice.
- The mice "showed signs of sickness" after 10 days, and the researchers isolated a filterable transmissible agent from the harvested brains.
- They harvested mosquitos and ground them up and again injected into the brains of mice.
- The animals "appeared inactive" after 7 days, and the same transmissible agent that had sickened Rhesus 766 was identified and called their "hitherto unrecorded virus" Zika.
ZIKV History-2

- 1970-80’s: Evidence of Zika antibodies in humans and monkeys and reports of human Zika virus infections from Nigeria and Indonesia
- 2007: Outbreak of a disease on Yap Island in Micronesia that resembled mild dengue but was distinct because people had a rash
- 2009: NEJM publication of 49 confirmed and 59 probable Zika cases.
- 2 U.S. scientists diagnosed in Colorado were infected in Senegal, one of them infected his wife, presumably through sex, when he returned home
- They only tested for Zika because of a chance meeting with a grandson of Alexander Haddow, one of the researchers who discovered the virus.
- 2013, outbreak in French Polynesia, with 333 confirmed cases and an estimated 19,000 suspected. The disease was associated with serious symptoms: mainly neurological disorders, including Guillain-Barre syndrome.
- Also, 2 babies also were infected in utero or during delivery but were healthy
• Cases of traveler-associated Zika: A Norwegian who vacationed in Tahiti, a Canadian in Thailand, Japanese tourists in Bora Bora, a German in Malaysian Borneo.
• 2014 World Cup soccer in Brazil
• The 1st published report of "autochthonous" cases in Brazil — meaning they were not imported — appeared in June 2015....
• 22 other countries have reported Zika virus infections, under which Colombia (20,000 cases)

• End of 2015, Brazilian clinicians started reporting an unusually high number of babies born with microcephaly.
• Many causes of microcephaly (CMV, rubella, toxins (alcohol))
• Of 4200 reported, 1313 analyzed;
  only 404 (30%) confirmed microcephaly
  
• Only 3 cases of sexual transmission documented
• Blood transfusion, organ transplantation?
Countries with Past or Current Evidence of Zika Virus Transmission as of January 2017
Many people infected with Zika virus won’t have symptoms or will only have mild symptoms. The most common symptoms of Zika are:

- Fever
- Rash
- Joint pain
- Conjunctivitis (red eyes)
- Other symptoms include:
  - Muscle pain
  - Headache
Local / Regional Transmission Risk
Zika virus (ZIKV)

- Flavivirus, only causing *symptoms in 1/5 patients*:
  - Fever, rash, joint pain, or conjunctivitis
  - Rare Guillain-Barre syndrome, microcephaly

- WHO declared it in 2016: "public health emergency of international concern."

1) All pregnant women are advised to consider postponing travel to areas with transmission
2) Avoid mosquito bites (daytime and dawn/dusk, both indoors/outdoors)
3) Avoid any mosquito bite when recovering from Zika
Aedes aegypti and albopictus mosquitos

Dengue is transmitted by infected female
Primarily a daytime feeder

• Lays eggs preferentially in containers
Dengue
Learning Objectives

- Know epidemiology of Dengue and lookalikes in returning traveler with a fever
- Diagnosis and pathogenesis of Dengue
- New classification and management of Dengue
- Review algorithm of returning traveler
Dengue Virus

- RNA virus
- Flaviviridae family
- 4 serotypes
  - DEN-1, DEN-2, DEN-3, DEN-4
- Each serotype provides specific lifetime immunity, and short-term cross-immunity
- All serotypes can cause severe and fatal disease
Dengue Fever

Epidemiology

- 50,000,000
  - Dengue cases per year worldwide
- 250,000 (0.5%)
  - Dengue Hemorrhagic Fever (DHF) per year
- 25,000 (0.05%)
  - Dengue-related deaths annually
- USA (Miami-Dade county, Florida).
- 28 Sep 2011. Miami-Dade County Health Department officials received confirmation of the 2nd **locally acquired case** of dengue fever for 2011, in a 44 year-old male resident of Miami-Dade county. The individual was diagnosed with dengue fever based on symptoms and confirmed by laboratory tests. The patient fully recovered from his illness.
Global Dengue Risk

Suitability for Dengue Transmission
- High suitability
- Low suitability
- Unsuitable or nonendemic

Undifferentiated Fever is the most common manifestation of Dengue

- Prospective study found that 87% of students infected were either asymptomatic or only mildly symptomatic

- Retrospective study in travelers estimates 1 symptomatic vs 3.3 asymptomatic infections

Clinical Dengue

- 3-7 days Incubation
- Day 1: Fever
  - Headache (retro-orbital), myalgia, arthralgia’s
  - Petechiae, bruising
  - Elevated ALT/AST
  - Leukopenia, thrombocytopenia
- Day 3-6: Afebrile
  - Complications (0.5%)
    or
  - Recovery (macular rash)

1. Systemic vascular leak
   - Hemoconcentration
     - Rising Hct
   - Hypoproteinemia
     - Pleural effusions
     - Ascites
   - Bleeding
     - Decreasing Plts

2. Hypotension and sudden shock
Pathogenesis

• 90% of DHF cases occur in secondary heterologous dengue infection.
  - 10% only in primary infection

• Cells targeted by the dengue virus are predominantly the cells of the reticulo-endothelial system.
  - Spleen, liver, bone marrow
  - Monocytes, lymphocytes, alveolar macrophages
Immunopathogenesis of Severe Dengue

Risk factors for Severe Dengue

- Secondary infection
- Other serotype
- Sub-neutralizing Ab may induce viral replication
- Capillary leak
- Coagulopathy
- Young age
Hemorrhagic Manifestations of Dengue

- Skin petechiae, purpura, ecchymoses
- Gingival bleeding
- Nasal bleeding
- GI hematemesis, melena, hematochezia
- Hematuria
- Increased menstrual flow
Hemorrhagic Manifestations of Dengue Infection.


Petechiae
Bleeding
Hemorrhage
Macular rash
Laboratory Diagnostic Options in a Patient with Suspected Dengue Infection

<table>
<thead>
<tr>
<th>Dengue Serologies</th>
<th>CDC-Arbovirus Branch</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Acute phase titers</strong></td>
<td></td>
</tr>
<tr>
<td>&lt;5 days from onset of symptoms</td>
<td></td>
</tr>
<tr>
<td>Neutralization assay</td>
<td><strong>Convalescent titers</strong></td>
</tr>
<tr>
<td>Neutralization assay</td>
<td></td>
</tr>
<tr>
<td><strong>Serotype 1</strong></td>
<td>1:80</td>
</tr>
<tr>
<td><strong>Serotype 2-4</strong></td>
<td>1:40</td>
</tr>
<tr>
<td><strong>Serotype 3</strong></td>
<td>1:20</td>
</tr>
<tr>
<td><strong>IgM</strong></td>
<td>Positive</td>
</tr>
<tr>
<td><strong>IgG</strong></td>
<td>Equivocal</td>
</tr>
</tbody>
</table>
# Dengue classifications

<table>
<thead>
<tr>
<th>Old criteria</th>
<th>New 2009 WHO criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Undifferentiated fever</td>
<td>• Uncomplicated Dengue</td>
</tr>
<tr>
<td>2. Dengue fever</td>
<td>- Recovery without complications</td>
</tr>
<tr>
<td>3. Dengue hemorrhagic fever (DHF)</td>
<td>• Dengue with warning signs</td>
</tr>
<tr>
<td>• Fever 2-7 days</td>
<td>• Severe Dengue</td>
</tr>
<tr>
<td>• Tourniquet test positive or bleeding</td>
<td></td>
</tr>
<tr>
<td>• Plts&lt;100,000</td>
<td></td>
</tr>
<tr>
<td>• Plasma leak</td>
<td></td>
</tr>
<tr>
<td>• Effusions and/or elevated Hct</td>
<td></td>
</tr>
<tr>
<td>4. Dengue shock syndrome (DSS)</td>
<td></td>
</tr>
</tbody>
</table>
Dengue classifications

Old criteria

1. Undifferentiated fever
2. Dengue fever
3. Dengue hemorrhagic fever (DHF)
   - Fever 2-7 days
   - Tourniquet test positive or bleeding
   - Plts<100,000
   - Plasma leak
   - Effusions and/or elevated Hct
4. Dengue shock syndrome (DSS)

New 2009 WHO criteria

- Uncomplicated Dengue
  - Recovery without complications
- Dengue with warning signs
  - Decreased plts, increased Hct
  - abdominal pain, dyspnea
- Severe Dengue
  - Plasma leakage-shock
  - Serosal fluid accumulation and/or dyspnea
  - Severe bleeding
  - Severe organ impairment
A tourniquet test determines capillary fragility. A blood pressure cuff is applied and inflated to a point between the systolic and diastolic blood pressures for five minutes.

Prospective study of 234 patients with clinically suspected dengue infection on admission

73% were serologically confirmed

Tourniquet test was positive in 30% of all patients

Does not distinguish DF and DHF

Positive tourniquet test

20 or more petechiae per inch² (6.25 cm²)
In Severe Dengue

Careful crystalloid fluid management

No evidence of benefit for use of:

- Corticosteroids
- IVIG
- Chloroquine
- Platelet transfusions
Dengue
Take home messages (DEET!)

• Bite of daytime mozzie
• Dengue vs Chikungunya
  - Dengue worldwide (USA!), risk Severe Dengue 0.5%
  - Chikungunya NOW in America’s; weeks/months of arthralgia’s (about 30% of infections)
• Severe Dengue on Day 4-7 of illness:
  - Bleeding, hypotension and shock
  - Thrombocytopenia and hemoconcentration
• Prevent mosquito bites by netting and DEET!!!
Chikungunya

Achy....
Global Chikungunya Risk

The boundaries and names shown and the designations used on this map do not imply the expression of any opinion whatsoever on the part of the World Health Organization concerning the legal status of any country, territory, city or area or of its authorities, or concerning the delimitation of its frontiers or boundaries. Dotted and dashed lines on maps represent approximate border lines for which there may not yet be full agreement.

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Outbreaks occurring in SE Asia and Africa

2005-2006
- Reunion/Mauritius (Indian Ocean)
- 266,000 of 1,000,000 inhabitants ill (30%)

2007 Italy few autochthonous cases

2010 South France few autochthonous cases
Geography as of April 2016

[Map showing current or previous local transmission of chikungunya virus]
Differential diagnosis

Chikungunya
Also Now in the America’s

- 2-5 days fever
- Defervescence
- Day 5-6
  - fever and rash
  - Mortality very low

• Arthralgia’s (distal) lasts weeks-months

Dengue
Worldwide

- 1-4 days fever
  - Myalgia, arthralgias
- Defervescence
- Day 3-6:
  - Recovery (macular rash) or
  - Complications (0.5%)

• Severe Dengue
  - Plasma leakage-shock
  - Serosal fluid accumulation and/or dyspnea
  - Severe bleeding
  - Severe organ impairment
Algorithm
Fever in returning traveler

Fever >48 hours? **YES**

- Endemic area for viral hemorrhagic fever? **NO**
  - Sick within 21 days of exposure?
  - Health care worker?
  - Contact with patients bleeding diathesis?

- Endemic area for malaria (*P. falciparum*)? **YES**
  - Sick within 7-90 days of exposure? **YES**
  - Evaluate with thick smear!
Differential diagnosis

Serious-treatable:
• Malaria
• Typhoid fever
• Rickettsial diseases
• Leptospirosis
• Influenza

Public Health alert:
• Viral hemorrhagic fevers
• SARS
• Acute HIV syndrome
• Measles

Nothing to be done:
• Dengue
• Chikungunya
• Zika
• West Nile virus
Incubation Time

- **Short <10 days**
  - Dengue
  - Chikungunya
  - Zika
  - Rickettsia
  - Legionella

- **Intermediate 10-21 days**
  - Malaria
  - Typhoid fever

- **Long >21 days**
  - Hepatitis A
  - Schistosomiasis
  - Tuberculosis
Hints from CBC

- **High WBC**
  - Leptospirosis
  - Amebic liver abscess

- **Low WBC**
  - Viral infections
    - Dengue
    - Chikungunya
  - Typhoid fever
  - Malaria

- **Thrombocytopenia**
  - Malaria
  - Dengue
  - Chikungunya
  - Viral hemorrhagic fever

- **Eosinophilia:**
  - Parasites

- **Low eosinophil count:**
  - Typhoid fever
Dengue
Laboratory diagnosis

• In primary infection
  - Increase in IgM antibodies 4-5 days after onset of fever and are detectable for 3-6 months.
  - Increase in IgG antibodies only after 7-10 days and remain detectable for life.

• In secondary infection
  - Level of IgM is lower than primary infection.
  - IgM antibodies are sometimes even absent.
  - IgG antibodies rises rapidly in secondary infections, even during the acute phase.
Prevention and Control

• *Eradication of vector mosquitoes*
  - Use of insecticides
  - Eradication of breeding sources (tires)
  - Limit travel to endemic areas

• *Vaccination???*
  - Difficult because of 4 serotypes
  - Protection to 1 or 2 viruses could actually increase risk of more serious disease
  - Trials in progress
<table>
<thead>
<tr>
<th>Virus transmission</th>
<th>Dengue</th>
<th>Zika</th>
<th>Chikungunya</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mosquitoes</td>
<td><em>Aedes aegypti</em>&lt;br&gt;<em>Aedes a/bop/chus</em></td>
<td><em>Aedes aegypti</em>&lt;br&gt;<em>Aedes a/bop/chus</em></td>
<td><em>Aedes aegypti</em>&lt;br&gt;<em>Aedes a/bop/chus</em></td>
</tr>
<tr>
<td>From mother to child</td>
<td>Evidence of transmission from an infected mother to her fetus</td>
<td>Rarely around time of birth, but it is possible that the virus could be passed to her fetus during pregnancy</td>
<td>Rarely from mother to newborn around the time of birth</td>
</tr>
<tr>
<td>Breastfeeding</td>
<td>No evidence</td>
<td>No evidence</td>
<td>No evidence</td>
</tr>
<tr>
<td>Blood</td>
<td>Rare cases known of transmission via blood transfusions from infected donors</td>
<td>Spread of the virus through blood transfusion have been reported</td>
<td>No evidence, but in theory possible</td>
</tr>
<tr>
<td>Sexual</td>
<td>No evidence</td>
<td>Spread of the virus through sexual contact have been reported</td>
<td>No evidence</td>
</tr>
</tbody>
</table>
Clinical features: Zika virus compared with dengue and chikungunya

<table>
<thead>
<tr>
<th>Feature</th>
<th>Zika</th>
<th>Dengue</th>
<th>Chikungunya</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fever</td>
<td>++</td>
<td>+++</td>
<td>+++</td>
</tr>
<tr>
<td>Rash</td>
<td>+++</td>
<td>+</td>
<td>++</td>
</tr>
<tr>
<td>Conjunctivitis</td>
<td>++</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Arthralgia</td>
<td>++</td>
<td>+</td>
<td>+++</td>
</tr>
<tr>
<td>Myalgia</td>
<td>+</td>
<td>++</td>
<td>+</td>
</tr>
<tr>
<td>Headache</td>
<td>+</td>
<td>++</td>
<td>++</td>
</tr>
<tr>
<td>Hemorrhage</td>
<td>-</td>
<td>++</td>
<td>-</td>
</tr>
<tr>
<td>Shock</td>
<td>-</td>
<td>+</td>
<td>-</td>
</tr>
</tbody>
</table>

Red Flag 1

- Pt from Saudi Arabia comes to Pittsburgh for evaluation of liver transplantation.

- 11 days after arrival in Pittsburgh he is short of breath and is admitted for pneumonia

- Keywords: Middle East, pneumonia, < 14 days
Middle East Respiratory Syndrome Coronavirus or MERS-CoV

- Coronavirus similar to SARS
- 1,638 cases, 587 deaths; mortality 36%
- Transmission: bats to camels to humans?
  - Incidental cases
  - Dromedary camels (NEJM Jun 26 2014)
  - Family clusters (NEJM Jun 27 2013)
  - Health Care workers (NEJM Aug 1 2013)
- Incubation time <14 days
- Fever, cough, pneumonia, lymphopenia
D.W. is a 58/F who was part of an expedition team in the Amazon River who presents with a 5 day history of fever, malaise, headache, and low back pain.

She felt some improvement yesterday but today, she felt worse and her symptoms returned.

She was seen in the hospital with jaundice, persistent fever, and oliguria.

VS: T=103.1°C   HR=78   RR=20

Exam showed jaundice and some bleeding in the IV sites as well as epistaxis.

Lab tests show leukopenia/neutropenia, elevated transaminases, and proteinuria.

What does this patient have and how will you manage her case?
**Arbovirus; Aedes and Haemogogus vector**

**Sub-Saharan Africa and tropical South America**

3-6 day incubation period; 15-50% develop illness and 15-25% of these people develop classic yellow fever symptoms

**Abrupt onset fever, chills, headache**

**Triad: jaundice, hemorrhagic fever, and renal dysfunction (proteinuria a diagnostic clue)**

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**Table: Signs and Symptoms**

<table>
<thead>
<tr>
<th>Outcome:</th>
<th>50–85% will not develop symptoms or illness</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>3-6 days Incubation</td>
</tr>
<tr>
<td></td>
<td>3-6 days Infection</td>
</tr>
<tr>
<td></td>
<td>2-24 hours Remission</td>
</tr>
<tr>
<td></td>
<td>3-8 days Intoxication</td>
</tr>
</tbody>
</table>

**Laboratory findings:**
- Leukopenia
- Neutropenia
- TAST
- TALT
- Proteinuria

**Infection/Immunity:**
- Viremia present

**Outcomes:**
- 75–85% will not progress
- 15–25% progress to "classic" yellow fever

**Signs and symptoms:**
- Fever
- Myalgia
- Lumbarosacral pain
- Nausea
- Malaise
- Prostration
- Dizziness
- Conjunctival injection
- Hyperemic tongue
- Relative bradycardia (Fsego's sign)

**Signs and symptoms:**
- Fever and symptoms abate

**Laboratory findings:**
- Leukocytosis
- Thrombocytopenia
- TALT
- Proteinuria
- Azotemia
- Hypoproteinemia
- Acidosis

**Infection/Immunity:**
- Viremia usually absent
- Antibody usually present

**Outcomes:**
- 50% mortality of persons in this stage

---

Guerrant et al. ed. 2011
Diagnosis

- **Differentials:** hepatitis, dengue, severe malaria, other HF, lepto
- **Viral isolation from blood**
- **Serology:** most important diagnostic test (IgM on day 7 of illness then fourfold increase in titer)
- **Immunohistochemistry of tissue (on autopsy)**

Treatment/Management

- Largely supportive
- No specific antiviral treatment
Yellow Fever Vaccine

- Live attenuated virus given >10 years before entry
- One dose with a booster every 10 years
- Severe adverse effect: viscerotropic (multisystem organ failure) or neurotropic disease (meningoencephalitis, GBS)
- Risk for viscerotropic: 1 in 250,000 (but in >70 yr olds, 1:42,000)
- Risk higher in older patients and with thymus disease
- Give only when there is a TRUE risk or required by customs

Vaccine contraindications

- Transplant recipients
- Immunodeficiencies including immunosuppressive drugs
- Thymus disorders
N.L. is a 25/M grad student who visited his family in India for 2 weeks. He returned to the USA 3 days ago and now presents with a one day history acute onset high fever and chills.

He also complains of headache, photophobia, and severe joint pains.

Exam reveals a fever of 102.9°C. He also has a diffuse maculopapular rash.

He has swelling of joints in his hands and lymphadenopathy

Lab tests showed lymphopenia.

What test will you order to diagnose the disease?
An arbovirus, *Alphavirus*, transmitted by *Aedes* mosquitos

Southeast Asia, India, SubSaharan Africa

Incubation period typically 4 days but can be up to 12 days

Abrupt onset of fever, chills, headache, severe back pain and joint pain - typically symmetrical joints (hands, feet) with edema

Early disease: distal polyarthritis and edema

Chronic disease: distal arthritis and tenosynovitis

Diagnosis: viral RNA early in disease; serology

Treatment: primarily supportive; no specific antiviral therapy
Caused by several, distinct family of viruses

All are RNA viruses

Has an animal or insect host as the natural reservoir

Human outbreaks occur sporadically and irregularly
Arenavirus: Lassa

Filovirus: Ebola and Marburg

Bunyavirus: Hantavirus, Rift Valley

Flavivirus: Dengue and Yellow Fever

Incubation: less than 3 weeks

Febrile phase: Fevers, chills, headache, myalgia

Hemorrhagic phase: petechiae then epistaxis, bleeding from IV site, frank hemorrhage from other mucosal sites
No good therapy except for Arenaviruses (Lassa)-

Ribavirin; others mostly supportive

Arenaviruses: spread by rodents (droppings)

Lassa (West Africa) - most important because it’s common and HCW’s get it

- exposure to rats and stored grains as well
- very contagious in the hospital
- 20% can develop deafness
- diagnosis by viral isolation and/or serology (IgM)

Filoviruses (Central or West Africa)

- possible reservoir in bats
- incubation period ~1 week
- virus in the sweat glands - contagious
- supportive therapy
Rift Valley Fever
- Cattle-raising areas in Africa; mosquitoes
- Only a small number get hemorrhagic disease (0.5-1%)
- Can try Ribavirin or interferon

Hanta virus
- Different geographic areas worldwide
- Rodent to human transmission
- Hantaan virus- hemorrhagic fever and pulmonary and/or renal syndrome