Just a plane ride away: Chikungunya, Dengue, Zika

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Infectious Diseases

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DISCLOSURES

• I do not have any relevant financial relationships or affiliations that may have a direct bearing on the subject matter of this CME activity.
Objectives

- Describe the epidemiology, clinical features, treatment and complications of MERS, Chikungunya, Dengue, and Zika.
- Understand how to counsel someone going to an at risk area about these viruses.
- Understand current CDC recommendations for Zika
• 54 year old female with a past medical history of rheumatoid arthritis on a biologic agent just returned from St. Marten. She had many mosquito bites, and ate local food including raw conch off a dock.

• She hobbles into the post-travel clinic with 3 days of fever to 102, general malaise, and severe bilateral knee pain.

• There were signs at the airport warning of a “Chicken” disease, but she stayed away from poultry
Chikungunya

• The unrecognized epidemic
• Total Western Hemisphere Ebola cases: 4
• Total Western Hemisphere Chikungunya cases: 1.2 million
Countries and territories where chikungunya cases have been reported* (as of May 29, 2018)

*Does not include countries or territories where only imported cases have been documented.
US Distribution: 2014

http://www.cdc.gov/chikungunya/geo/united-states-2014.html
States reporting chikungunya virus disease cases – United States, 2018 (as of October 16, 2018)

https://www.cdc.gov/chikungunya/geo/united-states-2018.html
Chikungunya fever

• Spread by chickens
Chikungunya fever

- Spread by chickens
- Originally from West Africa
- Name comes from a Tanzanian language, and means “stooped walk”
- Reflective of the arthritis/arthralgias it causes
Chikungunya virus

- *Alphavirus* (Togaviridae family)
- Initially identified in a Tanzanian outbreak in 1952
March of a virus

Transmission

• Mosquitos! *Aedes aegypti, Ae. albopictus*
• Rarely blood transfusions
• Rarely Mother to Child (but not by breast feeding)
Symptoms and Labs

**Symptoms**

- Fever, usually lasts about 1 week (90% of patients)
- Myalgia, usually lasts 7–10 days (90% of patients)
- Polyarthralgia, polyarthritis, or both, can last weeks to months (95% of patients)
- Rash, lasts about 1 week (40–50% of patients)
- Headache, conjunctivitis, nausea/vomiting

**Infection**

- 2–6 days Incubation period
- Approximately 1 week
- Weeks to months
- Years

- Viremia, usually lasts 5–7 days
- Viral culture or PCR
- IgM detectable 3–8 days after symptom onset, usually persists for 1–3 months
- IgG detectable 4–10 days after symptom onset, persists for years

**Biomarkers**

- Leukopenia, Thrombocytopenia, Elevated Creatinine, Transaminitis

Treatment

• Supportive
• Acetaminophen (avoid NSAIDs until dengue ruled out for bleeding risk)
• Mosquito avoidance for 1 week (the period of viremia) to prevent further transmission
• Symptoms usually resolve in 7-10 days
• Joint symptoms can last for months (years?)
Complications

- Typically self-limiting
- Age >65 and chronic medical conditions increases risk
- Respiratory failure
- Shock
- Liver and renal failure
- CNS: meningoencephalitis, Guillain-Barré, and acute flaccid paralysis, sensorineural hearing loss
- Eye: iridocyclitis, retinitis, episcleritis, macular choroiditis
- Death
Pre-travel Counselling

- Mosquito avoidance!
- Stay in places with air-conditioning or nets on the windows
- Mosquito nets
- Wear long-sleeved shirts and pants
- Wear closed toe shoes
Mosquito Repellent

• Wear mosquito repellent: DEET, picaridin, IR3535, and oil of lemon eucalyptus or para-menthane-diol
• Mosquito repellent-impregnated clothing
• Mosquito repellent-impregnated nets
• Place mosquito repellent on outside of clothes, not under
• Wear sunscreen first, then mosquito repellent
• 52 year old physician returns from a trip to Laos. He taught at the university hospital in Vientiane, but did travel to rural areas as a tourist. He ate mostly the food provided by the NGO that sent him, but did occasionally eat out (mostly at tourist restaurants). Lots of mosquito bites.

• 1 week after returning develops high fevers, chills, nausea, diarrhea. He has severe myalgias and says “it hurts in my bones.”
Dengue

- Known since 1940s
- *Flavivirus*
- 4 strains (DENV1-4)
- Each strain does not provide protection against the other
- Infection with one strain followed by another increases the risk of a hemorrhagic fever syndrome
- 50-100 million infections annually
Dengue, countries or areas at risk, 2008*

The contour lines of the January and July isotherms indicate the potential geographical limits of the northern and southern hemispheres for year-round survival of Aedes aegypti, the principal mosquito vector of dengue viruses.

Countries or areas at risk

*As of 1 November 2008

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Data Source: World Health Organization
Map Production: Public Health Information and Geographic Information Systems (GIS)
World Health Organization

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Transmission

- Mosquitos! *Aedes aegypti, Ae. albopictus*
- Rarely blood transfusions
- Rarely Mother to Child (but not by breast feeding)
Dengue Fever: Clinical Features

• In children, majority of cases are asymptomatic
• In adults, 86% are symptomatic
Classic Dengue Fever: Clinical Features

- 3-14 days post bite
- “Break bone fever”
- High fever for 3-7 days, in 5% a second period of fever for 1-2 days after first episode
- Frontal headache
- Retroorbital pain
- Myalgias/arthralgias
- Rash, conjunctival injection
- Anorexia and nausea
- Hepatosplenomegaly
- Generalized lymphadenopathy
Lab findings

- Leukopenia
- Thrombocytopenia
- Transaminitis
Diagnosis

- Serology: widely available
- PCR: not so widely available
- Viral culture: research only

- PCR positive in first 5 days
- Serology positive starting at day 3, but more reliably after 5 days
Dengue Hemorrhagic Fever and Shock Syndrome

• Begins 3-7 days into the illness
• Defervescence of fever leading to hypothermia
• Severe abdominal pain
• Hemorrhage: spontaneous bleeding or petechiae, “tourniquet test”
• Mental status change
• Shock (plasma leakage syndrome): hemoconcentration, pleural effusion, ascites
• Mortality without treatment 10%, with treatment 1%
Other complications of Dengue

• Heart: Myocarditis, cardiomyopathy
• Liver: Hepatitis/hepatic failure (may be more from shock than the virus)
• CNS: Seizures, encephalitis, mononeuropathies, polyneuropathies, Guillain-Barré, transverse myelitis, acute pure motor weakness
• Kidney: Acute renal failure
Treatment

- Supportive
- IV Fluids
- Acetaminophen (avoid NSAIDs for bleeding risk)
- Mosquito avoidance for 1 week (the period of viremia) to prevent further transmission
- In hemorrhagic or shock syndrome iv fluids, correct lab abnormalities if possible.
Pre-travel counselling

• Mosquito avoidance!
• Stay in places with air-conditioning or nets on the windows
• Mosquito nets
• Wear long-sleeved shirts and pants
• Wear closed toe shoes
Mosquito Repellent

• Wear mosquito repellent
• Mosquito repellent-impregnated clothing
• Mosquito repellent-impregnated nets
• Place mosquito repellent on outside of clothes, not under
• Wear sunscreen first, then mosquito repellent
• Stat consult from the surgical service!

• “My spouse is refusing to go to our conference in Hawai‘i! Dengue. We are staying at the Fairmont for Pete’s sake!”

• I did say that having your own personal ID doctor is surprising affordable!

As of April 13, 2016

Total number of confirmed cases 263

Risk levels for potential dengue infection*:

- High Risk
- Moderate Risk
- Some Risk

*Risk levels of areas where confirmed cases may have contracted dengue fever are determined by the number of confirmed cases with recent onset dates who reported visiting those areas. Individuals should always protect themselves against mosquitoes and mosquito bites island-wide; extra precaution should be taken in areas of risk. For more information on dengue fever and ways to protect yourself from mosquitoes, visit:
26 year old healthy female comes to the Post-Travel Clinic after returning from a trip to visit family in Amazonas, Brazil.

She had multiple insect bites, ate local food and drank tap water.

She is in a stable relationship and not using birth control, barrier protection

She developed fever, cough, myalgias a day after returning
Zika virus

• Flavivirus
• First described in 1947 in the Zika forest in Uganda
• Reservoir human and non-human primates
• Previous outbreaks in Africa, SE Asia, Pacific Islands
Countries with past and present Zika cases

World Map of Areas with Risk of Zika

2015-October 2018 US Zika cases

US States
- Travel-associated: 5,728
- Locally acquired: 231
- Pregnant: 2,474
- Sexually acquired: 52
- Lab acquired: 2

US Territories
- Travel-associated: 147
- Locally acquired: 37,139
- Pregnant: 4,900
US Pregnancy outcomes

US States
- Liveborn with birth defects: 116
- Pregnancy Losses with Birth defects: 9

US Territories
- Liveborn with birth defects: 167
- Pregnancy Losses with Birth defects: 8
Transmission

• Mosquitos! *Aedes aegypti, Ae. albopictus*
• Rarely blood transfusions
• Rarely Mother to fetus
• Rarely via sex
• Found in breast milk but no known transmission
Zika: Clinical Features

- 1:5 are symptomatic
- Incubation period unknown, but likely 3 days to 2 weeks
Zika: Clinical Features

- Red eyes
- Headache
- Fever
- Rash
- Joint pain
- Muscle pain

Zika: Clinical Features

- Symptoms usually last for days to a week
- Most patients do not seek care
- Rare hospitalizations
- Rare death

- Felt to be a more minor illness than Dengue of Chikungunya
Zika: Diagnosis

- RT-PCR: positive during first week, and may persist in urine
- Serology IgM, IgG: turns positive by the end of the first week and continues through at least 12 weeks
- Older (more common) serologic-tests cross react with other Flaviviruses like Dengue and West Nile. Newer more specific assays are now available
- Plaque-reduction neutralization assays can help distinguish between flaviviridae
Zika: Complications

- We don’t really know
- Guillain-Barré
- Encephalitis
- Fetal
- ITP
Ultrasound findings by week of gestation at time of infection

Week of Gestation at the Time of Infection

No. of Cases

Abnormal findings
Normal findings

Congenital Zika Syndrome

- Cognitive, Sensory, and Motor Defects

5 Unusual types of birth defects:
- Severe microcephaly resulting in a partially collapsed skull
- Decreased brain tissue with brain damage (as indicated by a specific pattern of calcium deposits)
- Damage to the back of the eye with a specific pattern of scarring and increased pigment
- Limited range of joint motion, such as clubfoot
- Too much muscle tone restricting body movement soon after birth
Fetal complications

Brain:
- Microcephaly
- Cerebral calcifications
- Choroid plexus cyst
- Cerebella atrophy
- Agenesis vermis
- Mega cisterna magna
- Ventriculomegaly
- Blake’s pouch cyst
- Brachycephaly
- Middle cerebral artery abnormality

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Placenta:
• IUGR
• Oligohydramnios
• Anhydramnios
• Placental insufficiency

**Fetal complications**

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- Microcephaly
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**Placenta:**
- IUGR
- Oligohydramnios
- Anhydramnios
- Placental insufficiency

**Other:**
- Club foot
- Fetal demise

Treatment

• Supportive
• IV Fluids
• Acetaminophen (avoid NSAIDs until dengue ruled out for bleeding risk)
• Mosquito avoidance for 1 week (the period of viremia) to prevent further transmission
Pre-travel counselling

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When to test for Zika

If your patient is...

Experiencing or has recently experienced symptoms of Zika

Does your patient meet the following criteria?

Possible Zika virus exposure through residence in or travel to an area with risk for Zika virus

OR

Possible Zika virus exposure through unprotected sex with a partner who has lived in or traveled to an area with risk for Zika virus

NO

Do Not Test for Zika

YES

Test for Zika

A pregnant woman without symptoms

Does your patient meet the following criteria?

ONGOING possible Zika virus exposure through residence in or frequent travel (e.g., daily or weekly) to an area with risk for Zika virus

OR

Possible Zika virus exposure

AND

Prenatal findings on ultrasound findings consistent with congenital Zika virus syndrome

NO

Routine Testing Not Recommended

When to test for Zika

If your patient is...

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OR

Possible Zika virus exposure

AND

Prenatal findings on ultrasound findings consistent with congenital Zika virus syndrome

NO

Routine testing not recommended

With caveat!
When to test for Zika

If your patient is...

- Red eyes
- Fever

CDC does not recommend testing for asymptomatic
- Men
- Children
- Women who are not pregnant

Possible Zika virus exposure through unprotected sex with a partner who has lived in or traveled to an area with risk for Zika virus

Possible Zika virus exposure

AND

Prenatal findings on ultrasound findings consistent with congenital Zika virus syndrome

NO

Do Not Test for Zika

YES

Test for Zika

NO

Routine Testing Not Recommended
Testing Asymptomatic Pregnant Women with possible exposure

**WHOM to test?**
Asymptomatic pregnant women with ongoing possible Zika virus exposure

**WHEN to test?**
Three times during pregnancy:
- First test at initiation of prenatal care.

**WHICH tests?**
Zika virus NAT (serum and urine)

**RESULTS**
- Positive Zika virus NAT
  - ACUTE ZIKA VIRUS INFECTION
- Negative Zika virus NAT
  - NO ZIKA VIRUS RNA DETECTED. ZIKA VIRUS INFECTION DURING PREGNANCY CANNOT BE RULED OUT.

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Caveat from before

Asymptomatic pregnant women with recent possible Zika virus exposure, without ongoing exposure:
Testing not routinely recommended, but should be considered.
If considering testing, base decisions on patient preferences and values, clinical judgment, a balanced assessment of risks and expected outcomes, and jurisdiction's recommendations.
If testing is conducted, follow algorithm for symptomatic pregnant women using timeframe from last possible exposure.

Testing Asymptomatic Pregnant Women with possible exposure: issues

- NAT is highly specific, but false positives occur.
- Positive urine and serum NAT = acute infection.
- Discordant results (+/-) lead to repeat testing of original positive specimen. If still positive = acute infection. If negative = indeterminate infection, consider IgM testing.
- Negative test does not exclude infection as viral levels decline over time and this varies from woman to woman. Can consider IgM testing.
The problem with Zika IgM results

A positive Zika IgM test result could mean...

- Zika virus infection during current pregnancy, meaning pregnancy is likely at risk from Zika
- Zika virus infection before current pregnancy, meaning pregnancy is not likely at risk from Zika
- False positive result, meaning pregnancy is not likely at risk from Zika

Testing for Symptomatic, Non-Pregnant Individuals

Specimen collected < 14 days post-symptom onset

- Zika virus NAT testing
  - Positive Zika virus NAT
    - ACUTE ZIKA VIRUS INFECTION
  - Negative Zika virus NAT
    - Zika virus IgM serology
      - Non-negative Zika virus IgM
        - Plaque reduction neutralization test (PRNT)
          - Zika virus PRNT ≥ 10 AND Dengue virus PRNT < 10
            - ZIKA VIRUS INFECTION, TIMING OF INFECTION CANNOT BE DETERMINED
          - Zika virus PRNT ≥ 10 AND Dengue virus PRNT ≥ 10
            - FLAVIVIRUS INFECTION, TIMING OF INFECTION CANNOT BE DETERMINED
          - Zika virus PRNT < 10
            - NO EVIDENCE OF ZIKA VIRUS INFECTION

Specimen collected ≥ 14 days post-symptom onset

- Negative Zika virus IgM

Recommendations for men and their pregnant partners

• Has been detected in semen for up to 188 days post infection

After travelling to or while residing in an area with active Zika transmission

• Abstain from sexual activity or consistently and correctly use condoms during sex (i.e., vaginal intercourse, anal intercourse, or fellatio) for the duration of the pregnancy

Preventing sexual transmission in couples

<table>
<thead>
<tr>
<th>Traveling Partner</th>
<th>How Long to Wait</th>
</tr>
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</table>
| If **only the male partner** travels to an area with risk of Zika | The couple should use condoms or not have sex for at least **3 months**  
- After the male partner returns, even if he doesn’t have symptoms, or  
- From the start of the male partner’s symptoms or the date he was diagnosed with Zika |
| If **only the female partner** travels to an area with risk of Zika | The couple should use condoms or not have sex for at least **2 months**  
- After the female partner returns, even if she doesn’t have symptoms, or  
- From the start of the female partner’s symptoms or the date she was diagnosed with Zika |
| If **both partners travel** to an area with risk of Zika | The couple should use condoms or not have sex for at least **3 months**  
- After returning from an area with risk of Zika, even if they don’t have symptoms, or  
- From the start of the male partner’s symptoms or the date he was diagnosed with Zika |

Just don’t go if planning a baby or if pregnant

• Consider not travelling to an area with active Zika transmission
Our Case

• Respiratory illness not a feature of Zika
• Influenza A

• Planes are cesspools!
June of 2015: 83 y/o female with a past medical history of mild chronic kidney disease, presents to the ER with lethargy, delirium, malaise, found to have acute on chronic renal failure (Cr 8), hyperkalemia (K 7), and severe anemia (Hct 16).

Was admitted to the ICU and started on dialysis. Had an EGD and colonoscopy with non-bleeding ulcers and benign appearing polyps found.

New fever on hospital day 3, cough, but was well enough to transfer to the floor.
• Fever continued and ID was consulted
• Several family members sick with febrile respiratory illness
• She had just returned from a 3 week visit to Vietnam where she was in Hanoi, not out of the city, not around sick contacts, and not around birds
• She transited through Seoul
The forgotten travel history

• CDC still advises all patients be asked about travel at each clinical encounter
MERS

• Middle East Respiratory Syndrome
• Caused by the MERS-coronavirus (CoV)
• First described in Saudi Arabia in 2012
• Reservoir is unclear (camels and bats have been implicated)
• Humans can spread the virus via inhalation of infected secretions
MERS-CoV: Case definition

- Fever AND pneumonia or acute respiratory distress syndrome AND EITHER:
  - history of travel from countries in or near the Arabian Peninsula within 14 days before symptom onset, OR
  - close contact with a symptomatic traveler who developed fever and acute respiratory illness (not necessarily pneumonia) within 14 days after traveling from countries in or near the Arabian Peninsula, OR
  - history of being in a healthcare facility (as a patient, worker, or visitor) in South Korea within 14 days before symptom onset, OR
  - a member of a cluster of patients with severe acute respiratory illness of unknown etiology in which MERS-CoV is being evaluated, in consultation with state and local health departments
  
OR

- Fever AND symptoms of respiratory illness (not necessarily pneumonia; e.g., cough, shortness of breath) AND being in a healthcare facility (as a patient, worker, or visitor) within 14 days before symptom onset in a country or territory in or near the Arabian Peninsula in which recent healthcare-associated cases of MERS have been identified.

OR

- Fever OR symptoms of respiratory illness (not necessarily pneumonia; e.g., cough, shortness of breath) AND close contact with a confirmed MERS case while the case was ill.
“In or near the Arabian Peninsula”

- Bahrain
- Iraq
- Iran
- Israel
- the West Bank and Gaza
- Jordan
- Kuwait
- Lebanon
- Oman
- Qatar
- Saudi Arabia
- Syria
- the United Arab Emirates (UAE)
- Yemen
MERS-CoV: Clinical Course

• Incubation period ~5 days (range from 2-14)
• Medium time from onset of symptom till hospitalization is 4-5 days
• Medium time from onset till death is 12 days
• Mortality 35%
MERS-CoV: Clinical Features

• Mild respiratory illness: cough, rhinorrhea, sore throat, fever, myalgias

• Severe respiratory illness with pneumonitis or respiratory failure progressing to multisystem organ failure and death

• Diarrhea, vomiting, abdominal pain (rarely can precede pneumonia)
MERS-CoV Lab abnormalities

• Leukopenia
• Lymphopenia
• Thrombocytopenia
• Elevated LDH levels
• Detectable virus from respiratory secretions, feces, serum, and urine
• Diagnosis from: upper respiratory, lower respiratory, and serum specimen (stool no longer requested)
MERS-CoV: Treatment

• Symptomatic
• No specific treatment
Respiratory Illness: Infection Prevention

• When scheduling appointment, all patients with respiratory complaints (cough, rhinorrhea, fever) should be told to mask on arrival.

• When checking in all patients with respiratory complaints should be masked. Minimize waiting room time.
MERS: Infection Prevention

• If MERS suspected, arrangements made in advance to meet patient and take them directly to a room (negative pressure if in hospital)

• Contact, Droplet, Airborne Precaution
Our Case

- Travel through Seoul, but didn’t leave the airport
- Summer is flu season in Vietnam
- Influenza A
Remember this?

What about SARS

- Also a β-group coronavirus
- Reservoir bats, although civets implicated in 2003 outbreak
- Clinical features essentially the same, although mortality appears higher for MERS
- Super-spreaders a larger feature for SARS, but they were implicated in Seoul outbreak of MERS
- Healthcare workers heavily affected by both
- No SARS cases since 2004
Virginia Mason

Each Person.
Every Moment.
Better Never Stops.