HOT TOPIC / Zika Virus Update

Presenter:
D. Jane Hata, Ph.D.
Assistant Professor of Laboratory Medicine and Pathology

Department of Laboratory Medicine and Pathology
at Mayo Clinic, Jacksonville, Florida
Disclosures

- Microbiology Resource Committee

Utilization Message

- As you view this presentation, consider the following important points regarding testing:
  - How is the test going to be used in your practice?
  - When should the tests be used?
  - How will results impact patient management?
Overview

- Characteristics and pathogenesis of Zika Virus
  - Zika and pregnancy
- Epidemiology
- Symptoms and treatment
- Diagnostic methods
- Prevention and infection

Zika Virus$^{1,2,12}$

- SS RNA virus; family Flaviviridae
  - 11 kb; 3 structural, 7 nonstructural proteins
- Arbovirus transmitted by a mosquito vector
  - Aedes aegypti
  - Aedes albopictus
  - Aedes hensilli
  - Other Aedes species

Photo: Aedes aegypti

Photo: James Gathany
http://phil.cdc.gov/phil/details.asp
Non-Vector Borne Transmission of Zika Virus\textsuperscript{12,13}

- Laboratory Transmission
  - Needlestick injuries
- Maternofetal transmission
- Transfusion-transmitted infection
  - Confirmed in Brazil – 2016
  - Asymptomatic donors – FL and TX 2016
  - FDA and AABB recommendations to prevent infection
    - NAA screening of blood donations/pathogen inactivation

Sexual Transmission of Zika Virus

- Multiple reports in U.S. since 2008
- Zika RNA detected in blood and semen for 6 months
  - Wait until 6 months after last Zika exposure to attempt conception (if asymptomatic)
- Women with results that indicate recent Zika virus should wait at least 8 weeks from symptom onset to attempt conception.
- Zika virus testing of nonpregnant persons with possible exposure who do not have symptoms of Zika virus disease, including persons who are planning to attempt conception, or to assess the risk for sexual transmission of Zika virus is not recommended.
History and Epidemiology

- Initial isolation in 1947 in rhesus monkey in Uganda
- First human infections reported in 1952 in Uganda and Tanzania
- Reservoir unknown
- Island of Yap – 2007
  - 185 cases; 2% of population
- French Polynesia – 2013
  - 29,000 cases; 11% of population
- Travelers to Japan, France, Easter Island, New Caledonia

South America 2014–2015

- Brazil
  - Clusters of acute erythematous rash illnesses in 2014
  - Zika virus identified in April 2015
  - All age groups affected
- El Salvador, Guatemala, Colombia, Mexico, Panama, Paraguay, Venezuela
- Concern over 2016 Olympic Games (Rio de Janeiro)
  - No confirmed cases
- 2015 Re-emergence in Africa - Cape Verde
Geographic Distribution of Zika Virus

Pathogenesis Due to Zika Virus\textsuperscript{5-7,13}

- BSL-2 pathogen
- Replication in dendritic cells near site of inoculation, then spread to lymph nodes and bloodstream
- Infects human embryonic cortical neural progenitor cells
- Viral recovery from blood, saliva, urine, CSF, genital fluids, lymph nodes, tissue
Zika Virus and Guillain-Barré Syndrome\textsuperscript{8,9}

- Autoimmune mediated
- Acute/subacute flaccid paralysis after viral symptoms
- First case noted during outbreak in French Polynesia
  - 20-Fold higher incidence, temporal relationship to Zika epidemic
- Temporal association between Zika outbreak and increase in GBS
  - French Polynesia, Brazil, El Salvador, Venezuela
- Eventual recovery with supportive care in some cases

Zika Virus and Pregnancy\textsuperscript{3,10,13,14}

- 20-Fold increase of reports of microcephaly in Brazilian infants
  - Noted in French Polynesia epidemic
- Greatest risk of fetal brain anomalies if infection during the first trimester
  - Overall risk 1 – 13%
- Virus found in amniotic fluid, placenta, brain tissue
  - May be RNA negative in maternal blood
- Reduced head circumference (microcephaly) and gestational weight
- Brain atrophy with calcifications
- Ocular cataracts, auditory impairments
Zika Virus and Pregnancy\textsuperscript{7,11}

- All pregnant women should be asked about Zika virus exposure and symptoms at each prenatal care visit
  - Recent travel or residence in Zika affected area within 8 weeks before conception
  - Sexual contact with a person who traveled to or lives in an area with risk of Zika
- Pregnant, symptomatic, ongoing exposure – Serologic and NAT test of serum and urine
  - Positive NAT is confirmatory of maternal infection

Zika Virus and Pregnancy\textsuperscript{7,11}

- Pregnant, asymptomatic, ongoing exposure
  - NAT testing (serum and urine) 3 times during pregnancy
  - IgM testing no longer recommended
    - IgM persistence may confound test interpretation
- Pregnant, asymptomatic, recent but not ongoing exposure (e.g. travel)
  - Routine testing not recommended; discuss risk with provider
- Fetal ultrasound every 3-4 weeks to detect microcephaly
- Infant serum/urine may be used for IgM and RNA studies
Symptoms of Zika Virus Infection\textsuperscript{12}

- Incubation period 2-10 days after bite
- Mild or asymptomatic presentations frequent
- 1 in 5 will be symptomatic
  - Duration of illness 3-12 days
- “Dengue-like” syndrome
  - Arthralgia, mild fever, headache, edema of extremities, retro-orbital pain, maculopapular rash, conjunctivitis
- Severe disease, death rare

Overlapping Symptoms

<table>
<thead>
<tr>
<th>Symptom</th>
<th>Zika Virus</th>
<th>Dengue</th>
<th>Chikungunya</th>
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</thead>
<tbody>
<tr>
<td>Fever</td>
<td>+++</td>
<td>++++</td>
<td>+++</td>
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<tr>
<td>Edema of extremities</td>
<td>++</td>
<td>=</td>
<td>=</td>
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<tr>
<td>Arthralgia/myalgia</td>
<td>++</td>
<td>+++</td>
<td>++++</td>
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<tr>
<td>Retro-Orbital Pain</td>
<td>++</td>
<td>++</td>
<td>+</td>
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<tr>
<td>Conjunctivitis</td>
<td>+++</td>
<td>=</td>
<td>+</td>
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<tr>
<td>Maculopapular rash</td>
<td>+++</td>
<td>++</td>
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<tr>
<td>Hemorrhage</td>
<td>=</td>
<td>+</td>
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<tr>
<td>Leukopenia/thrombocytopenia</td>
<td>=</td>
<td>+++</td>
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Adapted from Ioos, S. et al 2014. Médecine et maladies infectieuses 44:302–307
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Diagnosis of Zika Virus Infection

- Testing recommended only in cases with symptoms, significant travel history, or residence in an affected area
  - Pregnant women should be tested based on symptoms and exposure risk
  - Sexual partners with travel/residence to a Zika risk area
- Detection of IgM
- Detection of viral RNA
- Symptomatic?
  - Test for dengue, chikungunya

Serologic Testing for Zika Virus

- Qualitative IgM antibody may not be detectable until 4 days after onset of symptoms up to 12 weeks later
- Perform IgM testing if NAT negative or >14 days after symptom onset
- CDC Zika IgM Antibody Capture Enzyme-Linked Immunosorbent Assay (Zika MAC-ELISA)
  - Serum, CSF
Serologic Testing for Zika Virus

- Confirmatory assay with plaque reduction neutralization (PRNT) necessary
- IgM and confirmatory assays may cross-react with other flaviviruses
  - Previous infection with St. Louis encephalitis or West Nile virus
  - Yellow fever or Japanese encephalitis vaccination

RT-PCR (NAT) Testing for Zika Virus

- Serum and urine samples must be collected within 14 days of onset of symptoms
  - Matched samples preferred
- RNA not detectable after 14 days after onset of symptoms
- Positive RT-PCR results are confirmatory
  - Negative results do not exclude Zika infection; perform serologic testing
- Multiple PCR assays available
  - Check with performing laboratory for acceptable sample type
Testing Considerations

- Serologic and molecular testing for Zika available from commercial reference laboratories and state Departments of Health
- IMPORTANT: Check with your laboratory prior to specimen submission to determine availability of testing
- Essential to know when samples collected in relationship to symptoms
- Travel, residence and medical history

Treatment of Zika Virus Infections$^7,12$

- Supportive only; no antiviral treatment
- Aspirin/Acetaminophen/NSAIDs' 
  - Rule out Dengue
- Antihistamines
- Avoid mosquito bites to prevent local transmission
- Consider sexual transmission
Will We See A Zika Vaccine?¹⁵

- Focus on development of neutralizing antibody response
  - DNA vaccine expressing Zika pre-membrane and envelope protein sequences
  - Adenovirus vectors expressing protein sequences
  - Purified inactivated Zika virus
  - Phase 1 clinical trials in progress

- Challenges
  - Acceptable safety profile with limited side effects
  - Safety in pregnant women

Zika Transmission and Travel

- Local transmission has occurred in the US
- Vast majority of cases are travel-related
- Consult CDC website for most up to date information on areas at risk and travel recommendations
- If pregnant, consider postponing travel to areas with Zika virus transmission
- If ill after travel, provide travel history
- Protect yourself from mosquito bites!
Summary

- Zika virus has emerged around the world, with multiple areas of ongoing, active transmission
  - Sexual, laboratory, transfusion associated transmission
  - Maternal transmission
- Most infections asymptomatic or mild
- Fever, arthralgia, headache, rash
  - Symptoms can be confused with dengue or chikungunya
  - Conjunctivitis, extremity edema, rash more likely with Zika virus
- Supportive treatment only

Summary

- Unusual manifestations of Zika
  - Guillain-Barré syndrome
  - Microcephaly secondary to prenatal infection
    - Greatest risk in first trimester (1-13%)
- Prevention of exposure
  - Prevent mosquito bites
- Travel considerations
  - Be aware of epidemic areas
  - May postpone travel if pregnant
References

Questions or requests…
Email to: MMLHotTopics@mayo.edu
For more information…

Visit MayoMedicalLaboratories.com
or call Mayo Laboratory Inquiry at 800-533-1710