More Than Just a Fly on the Wall: Mosquito-borne Infections

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Learning Objectives:

• Understand the enemy: Mosquitos as disease carriers and how mosquito-borne infections can emerge in new regions

• Be able to recognize the important mosquito-borne infections currently present in Delaware
  - West Nile Virus infections
  - Arboviral encephalitis

• Become familiar with emerging mosquito born diseases in the Western Hemisphere and potential of spread to the US
  - How to differentiate and diagnose emerging mosquito-borne infections in the returned traveler

• Learn what’s new in the prevention of mosquito-borne infections in travelers: Malaria and Yellow Fever
Learning Objectives:
➢ Understand the enemy: Mosquitos as disease carriers and how mosquito-borne infections can emerge in new regions

Source: US Army Environmental Command


@Disney #malaria awareness video at http://t.co/SJgy5gH #TBT

Mosquito-borne Diseases in Humans: Requirements
➢ Competent Mosquito vector
➢ Reservoir of Infectious pathogens
➢ Human reservoirs
   AND/OR
➢ Non-human reservoirs
➢ Non-immune Human Hosts


How Mosquito born infections spread: Another important vector

Learning Objectives:
➢ Be able to recognize the important mosquito-borne infections currently present in Delaware
   ➢ West Nile Virus infections
   ➢ Arboviral encephalitis
Case 1

- 45 y.o. woman presents on 9/24/18 with neck pain, tremors, tingling, "numbness" in hands x 3 days; one day of fevers and "tremors" and progressive RUE weakness
- Living in Cape May for the summer, lots of "bug bites"
- MRI brain negative
- MRI spine: "elongated right cord lesion from C3-C6"
- LP: WBC 300 (40% PMN, 34% L, 8% M) 17 RBC Protein 89, Glu 60
- Started on IV acyclovir and methylprednisolone; transferred to CUH
- Exam: non toxic, 100.8 F, mental status normal, supple neck, dysphonia
- Right UE strength 1/5 prox., 3/5 distal, Left UE 3/5 prox, 5/5 distal
- Reflexes mildly decreased in RUE and RLE, normal sensory exam

What does she have? How do we prove it? How do we treat her?

Diagnosis: Neuroinvasive West Nile Virus Infection

West Nile Virus: Transmission Cycle

West Nile Virus: Transmission Cycle

The West Nile Virus Infection “Iceberg”

CDC: Average annual incidence of West Nile virus neuroinvasive disease by age group — United States, 1999–2006

Source: Quest Diagnostics

West Nile Fever: 15-20%
- Incubation 2-6 days (up to 14)
- Acute systemic febrile illness
- Headache
- Weakness
- Myalgia or arthralgia
- Gastrointestinal symptoms
- Transient maculopapular rash
- Generally complete recovery though Sx can linger

Neuroinvasive: < 1%
- Aseptic meningitis syndromes: fever, headache, nuchal rigidity
- Encephalitis: altered mental status, seizures, focal neurologic deficits, movement disorders such as tremor or parkinsonism
- Acute Flaccid paralysis (poliovirus like) with involvement of anterior horn cells
- Other: Radiculopathy, Guillain-Barré like illness

Progression of the West Nile Virus Through the Continental United States NASA Scientific Visualization Studio,2002

https://svs.gsfc.nasa.gov/2564

West Nile Virus: Transmission Cycle

Neuroinvasive Disease

Diagnosis

- CSF IgM Antibodies positive 3 to 8 days after Sx, persists 30 to 90 days
- CSF IgG Ab persists years
- Cross reactivity with other flaviviruses (Dengue, Zika…)
- Can send blood/CSF PCR for virus but viremia transient, negative predictive value low

Treatment

West Nile virus disease therapeutics
Overview: No antiviral or adjunctive Therapies are approved or recommended for the treatment of West Nile virus (WNV) disease; clinical management is supportive. There are numerous case reports and case series regarding the use of various products (e.g., standard and hyperimmune polyclonal immune globulin, monoclonal immune globulin, interferon, ribavirin, and corticosteroids) in patients with WNV disease. None have shown clear benefit.
https://www.cdc.gov/westnile/resources/pdfs/WNV-therapeutics-summary-Fpdf

West Nile Prevention

- Surveillance: Birds, Mosquito pools
- Mosquito control
- Personal Protective Measures
- Blood and organ donor screening
- Vaccination???

Endemic Arbovirus Infections in Delaware 2016-2018

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Source: https://www.cdc.gov/arbivet (accessed 1/1/19)

Learning Objectives:

➢ Become familiar with emerging mosquito born diseases in the Western Hemisphere and potential of spread to the US
➢ Zika, Chikungunya, and a few words about Dengue
➢ How to differentiate and diagnose emerging mosquito-borne infections in the returned traveler
Case 2

- A 24 year old from Middletown presents 1/12/19, one week after spending 5 days in the Dominican Republic with her fiancé.
- She was well there, but now has fever to 102, chills, mild headache, and joint aches “all over”. A rapid flu test is Negative.
- She is febrile and uncomfortable but non toxic, she has bilateral conjunctivitis without discharge and a faint, non petechial, erythematous maculopapular rash.
- She does not think that she is pregnant, but she and her fiancé had unprotected intercourse while they were there.
- She says that there weren’t any mosquitos on the resort, but she did get “a few” mosquito bites on a day trip to a nature preserve.

What are you worried about? What to you do now?

Zika virus

- Mosquito born flavivirus (ss RNA) related to Dengue, Yellow Fever, WNV…
- Carried by Aedes mosquitos, mainly Aedes aegypti
- First identified in 1947 near the Zika River in Uganda
- Sporadic cases from Africa and Asia through 2007
- 2007-2014, outbreaks in SE Asia and W. Pacific, lasting 1-2 years
- Very high attack rates but mild illness-less severe than Dengue, complications not reported*

Zika virus: Clinical Manifestations

- Onset of symptoms (if they occur) up to 14 days post exposure
- BUT ~80% of those infected are asymptomatic
- Symptom onset often abrupt onset, with any or all of these:
  - Severe Disease rare:
    - CNS Disease, Including GBS
    - Thrombocytopenia
    - Other

Source: http://www.independent.co.uk
Zika virus: Pathogenesis

- Viremia during symptomatic periods
  - But most (up to 80%) are asymptomatic
  - Viremia (rRT-PCR) for up to 7 days post Sx onset
  - Higher level of virus, prolonged shedding in urine
- Virus found in many other tissues/fluids:
  - CNS/CSF
  - Placental tissue and Fetal tissue including brain
  - Semen and vaginal secretions
  - Breast milk
  - Saliva, tears
- Zika-specific neutralizing IgM Ab day 4, but cross reactive with Ab against other flaviviruses (Dengue, West Nile...)

Zika virus: A Couple of Questions

- What is the current status in the Western Hemisphere (and elsewhere)?
- What about transmission in the US?
- What are the severe complications of Zika virus infection?
- Zika virus and pregnancy: What do we know now?

Source: Times of India

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How long do Zika virus epidemics last? And why do they stop?

![Graph showing Zika virus cases over time]

- Need enough susceptibles to sustain cycle

Reported Zika Cases in US (excl. territories) as of 12/4/18
- Symptomatic Disease: 5590
- Returned travelers: 5454
- Presumed local mosquito-born: 231
- Other: 55

Delaware: 2016: 17 Imported Cases
2017 and 2018: 0 Imported Cases

Where has Zika been locally transmitted in the US so far?

- Texas: 11 locally acquired cases, none in 2018
  [http://www.dshs.texas.gov]
- Florida: 220 locally acquired cases, but none in 2018
  [http://www.floridahealth.gov/]
- Where could it go?
Where could Zika potentially go in the US mainland?

The new estimated range maps have been updated from a variety of published and unpublished sources. These maps show CDC’s best estimate of the potential range of Aedes aegypti and Aedes albopictus in the United States. These maps include areas where mosquitoes are or have been previously found. Maps are not meant to represent risk for spread of disease. http://www.cdc.gov/zika/vector/range.html

Zika as a Sexually Transmitted Infection:

37

52 Sexually Transmitted Cases in the US

Figure 2: Estimated Proportion of Semen Samples Positive for ZIKV on RT-PCR, According to Days since Illness Onset


Zika and Gullain-Barré: What do we know?

Gullain-Barré Syndrome outbreak associated with Zika virus infection in French Polynesia: a case-control study

The Lancet, Feb 29 2016

Baseline GBS Incidence: 1.2 Cases per year
Estimated Zika attack rate: 64% of population
GBS burden: 0.25 episodes per 1000 Zika infections

What about Zika virus and Pregnancy?

MMWR / August 10, 2018 / Vol. 67 / No. 31

So why didn’t we see these complications of Zika infection before?

The ZIKA Virus Grew Dearer With a Small Mutation, Study Suggests

EBioMedicine, 2017

Chikungunya Virus in the Americas

Delaware Cases
Chikungunya: “That Which Bends”

- Primary reservoirs
  - Humans (during epidemic periods)
  - Other reservoirs (sylvan cycle)
  - Non-human primates, rodents, birds, small mammals
- Primary Vectors:
  - Ae. aegypti
  - Ae. albopictus

Chikungunya: Acute and Chronic Illness

- Acute: 1-12 days after bite: mean 3-7 days
  - Most infected have symptoms: 72-97%
  - Fever: Generally > 102 F (39 C)
    - “Saddleback” fever, bradycardia
  - Polyarthralgias, polyarthritis
    - Bilateral, symmetrical
    - Hands, feet, other prox. joints, back
    - Can be severe & debilitating
  - Headache, Myalgias, Nausea
  - Conjunctivitis
  - Maculopapular rash
  - Acute Sx: usually 7-10 Days
- Subacute: up to ~ 3 months
  - Prevalence: up to 80%
  - Polyarthritis, Tenosynovitis, joint aches
  - Transient vasc. disease, Raynaud’s
  - Fatigue, Weakness
- Chronic: Greater than 3 months
  - Up to 40-50% at 6 mo.
  - Recent study in Columbia ¼ with joint Sx persisted at 20 mo. (Chang Arth. and Rheum, 2018)
  - Mechanism of chronic arthritis unknown- not direct infection
  - Optimal Rx not defined

Clinical Features: Zika Virus Compared to Dengue and Chikungunya

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<th>Zika</th>
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<tr>
<td>Thrombocytopenia</td>
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What You Need to Know About the Zika Virus

  - Who and when to test? And how?
  - What to advise if pregnant, planning pregnancy, or a male partner of a woman pregnant or planning pregnancy?
  - What is the risk? Absolute vs relative risk?

Some comments about dengue

- WHO Guidelines (updated 2009)
  https://www.who.int/dpc/guidelines/9789241547871/en/
- Primary vector: Ae. aegypti
- Multiple Serotypes so even though long lasting type specific immunity, epidemic curves can wax and wane as serotypes spread
- Diversity of serotypes has steadily increased many Western Hemisphere countries
- Risk of severe disease highest after re-infection “Heterotopic infection”
  - Implications for who is at risk for severe disease
  - Implications for vaccine development → the CYD-TDV Experience

Source: Health Information Ministries for the Americas
Learning Objectives:
➢ Learn what’s new in the prevention of mosquito-borne infections in travelers: Malaria and Yellow Fever

Case 3
• A 34 year old woman presents to your office for travel advice
• She works for a large international NGO, and will be leaving in 2 weeks to go to Ethiopia for 2 months to work in a refugee camp
• She is otherwise healthy, but is 18 weeks pregnant
• She has history of having received yellow fever vaccination at age 16

Source: Businessdailyafrica.com

Prevention in Travelers: Yellow Fever
• Where are the current Yellow Fever outbreaks?
• Where do you need Yellow Fever Vaccine?
• Is there Yellow Fever Vaccine available?
• Where can you get it? How often do you need it?

The Yellow Fever Outbreak in Brazil: 2015-2018
End 2017 to Summer 2018
• 1,376 confirmed human cases
• 483 deaths
• Expanding areas of transmission in Brazil
• Ongoing Epizootic transmission in primates
• Shortages of vaccine and use of fractionated doses
• Higher numbers of cases in Bolivia and Peru also

Yellow Fever Vaccine: Ongoing shortages here, but you can use less if you have to
• US Yellow Fever Vaccine Shortage
• Total Depletion of YF-Vax® Supply in 2017
• Limited availability of Stamaril® in selected travel clinics through an Expanded Access Program
• Not an FDA approved US vaccine but used in 70+ countries
• Return of YF-Vax® in mid 2019

What's new in Malaria prophylaxis and Treatment?
• Malaria, including drug-resistant disease, remains a global challenge
• Considerations for traveler prophylaxis:
  • Includes a risk assessment
  • Exactly where going, and exactly when, activities while there
  • Who is the patient?
• A newly approved drug for both prophylaxis and as treatment for hepatic phase: tafenoquine
  • For treatment: Krintafel™
  • For Prophylaxis: Arakota™

Source: CDC
Prevention of Mosquito-Borne Infections:

- Avoid Travel to known high risk areas if possible
- Pay attention to high risk season and times of day
- Avoid Mosquito bites: wear long sleeves, insect repellent, mosquito nets, permethrin treated clothing
- Mosquito proofing of homes - screens, remove standing water
- New Vaccines in development


Prevention of Mosquito-borne Infections: Old and Emerging Mosquito Control Strategies

- Aerial Spraying and Indoor Spraying
- Genetically Modified (GM) Mosquitos
- Wolbachia

From: Dutra et al, Cell Host and Microbe, 2016

Summary:

- Mosquito-borne diseases pose global and local health challenges; geographic range of these diseases are evolving
- West Nile Virus is the most common endemic mosquito borne infection in Delaware; 1/150 with West Nile infection develop neuroinvasive disease
- Important emerging/reemerging mosquito born diseases in Western Hemisphere include Zika, Chikungunya and Dengue
- There is an ongoing yellow fever outbreak in Brazil, and there is a national and international shortage of yellow fever vaccine
- There is a new drug for prevention of malaria that also can be used to treat the hepatic phase of malarial infection