OBJECTIVES:

- Investigate how travel affects exposure to tropical diseases
- Develop a recognition of Malaria, Dengue, Chikungunya, and Zika
  - Symptoms
  - Signs
  - Pathophysiology
  - Diagnosis
  - Treatment
  - Prevention
OUR PATIENTS ARE ON THE MOVE!!

- International students on the rise to and from USA

**Figure 1.** International students at U.S. Colleges and Universities in 2013/2014 (Institute of International Education, 2013, para. 1)

STUDY ABROAD CONTINUES TO INCREASE AND EXPAND

- Historically, most study abroad students travel to Europe; however, recently destinations are expanding
- According to Rhodes et al. (2014) research, travel to Africa, Asia and the Middle East is increasing while travel to Europe is decreasing

OUR PATIENTS ARE ON THE MOVE!!

- Travel is steadily increasing for work, education and pleasure (US Travel Assn)
  - 73.9 MILLION international arrivals to US in 2014
  - 2.1 BILLION trips taken by Americans in 2014
- A tropical medicine zebra may need to be considered in the appropriate patient population
  - You will never know if you don’t ASK!!
  - Thorough patient history is ESSENTIAL
- “People, as well as pathogens, travel from all around the world in all directions” (Pyapahanee et al., 2012, p. 337).
WHERE HAVE YOU TRAVELLED INTERNATIONALLY IN LAST YEAR?

- What countries have you visited outside of the United States in the last year?
- Prior to travel, did you or your family have a pre-travel medicine consult?

PRE-TRAVEL CONSULT IS OFTEN OVERLOOKED

- According to Leder et al (2013) research
  - < 40% of febrile travelers going to risky destinations (such as Africa, Asia, India) sought any form of pre-travel consult.
- Keys to increase Pre-Travel Consults
  - Deliver prevention messages
  - Develop Health Communication Strategies

EXPOSURE TO TROPICAL ILLNESS IS A REAL CONCERN

A 19-year-old, previously healthy male, lay on the examination table. He was covered with a blanket and shaking uncontrollably with intense rigors that correlated with his 103 degree fever.

Although he was hesitant to answer questions due to feeling so ill, he reported having returned from India 2 weeks prior and his Sx’s (fever, rigors, ache, fatigue, HA, and nausea), began abruptly, hours before arriving to the clinic.

The waiting room was packed on this January morning…
EXPOSURE TO TROPICAL ILLNESS IS A REAL CONCERN

EXPOSURE TO TROPICAL ILLNESS IS A REAL CONCERN

High index of suspicion in appropriate patient population is paramount

PATIENT PRESENTATION, CONTINUED...

Pt was diaphoretic and taking rapid, shallow inspirations.
BP: 148/86 R: 24 T: 103 HR: 112
HEENT: Dry mucous membranes, but no other abnormality. Neck was supple with no LA and no nuchal rigidity.
Heart rate tachycardic with no murmur or rub.
Lungs clear to auscultation.
Abdomen was soft, nontender, BS x 4. No CVA tenderness.
Skin was warm, clammy, without rash.
No focal neurologic deficits.

TO SOLVE THIS MYSTERY, LET’S EXAMINE FOUR CAUSES OF TROPICAL MEDICINE MOSQUITO-BORNE ILLNESS

- MALARIA
- DENGUE
- CHIKUNGUNYA
- ZIKA
MALARIA: EPIDEMIOLOGY
- 198 million clinical episodes of malaria worldwide in 2013 (WHO)
- Caused over 500,000 deaths
- In 2011, CDC reported 1,925 cases of malaria in US
- Infection with the following protozoal parasites:
  - Plasmodium falciparum
  - Plasmodium vivax
  - Plasmodium ovale
  - Plasmodium malariae
  - Occasionally other Plasmodium species

MALARIA: PATHOPHYSIOLOGY AND DIAGNOSIS
- 7-30 days following an anopheles mosquito bite, parasites develop in patient's RBCs causing toxins to develop.
Diagnosis
- Thick and thin blood film
  - Gold Standard
- Rapid diagnostic test (RDT)
- Polymerase chain reaction (PCR)
**Consider screening for malaria in all febrile travelers who traveled to tropical destinations w/i previous 12 months**

MALARIA: SIGNS AND SYMPTOMS
- No symptoms
- Fever
- Headache, back pain, chills, sweating, myalgia, nausea, vomiting, and cough
- Atypical symptoms
  - Respiratory distress
  - Convulsions
  - Renal failure
MALARIA: TREATMENT

- Based on severity AND probability of resistance
  - Falciparum vs. non-falciparum
    - Ex. of anti-malaria drugs: sulphate, atovaquone-proguanil, artemether-lumefantrine, doxycycline, clindamycin, sulphadoxine-pyrimethamine, chloroquine, and primaquine.
- Combination regimens are often needed due to resistance
- Most common Tx of non-falciparum: Chloroquine + Primaquine
  - Primaquine covers dormant liver malaria
- Severe malaria: Quinine + Artesunate IV

MALARIA: PREVENTION

Avoid mosquito bites
- Long pants, shirts
- Close windows
- Avoid standing water
- Bed nets
- Spray for mosquitoes, mosquito repellant

Chemoprophylaxis
- Ex. Doxycycline
- Not 100% protective (even if taken perfectly)
- If taken inadequately, can delay Sx onset and cause initial blood film to be falsely negative. Repeat test if suspicious
- Resistance to chemoprophylaxis is increasing

MALARIA: WHO 1.5 MINUTE VIDEO CLIP

World Health Organization
https://www.youtube.com/watch?v=gwYIyjwYluc
WHICH OF THE FOLLOWING CAUSES OF MALARIA HAS THE WORST PROGNOSIS?

A. Plasmodium ovale
B. Plasmodium vivax
C. Plasmodium falciparum
D. Plasmodium malariae

LET'S MOVE ON TO DENGUE

DENGUE: PATHOPHYSIOLOGY

- The most common arbovirus in humans
- Mosquito-borne disease (transmitted by an infected Aedes mosquito)
- Caused by four types of Flaviviruses
- Outbreaks have increased by 30x in last 50 years.
  - Outbreaks present in over 100 countries including US
    - FL, TX, Hawaii

Tomashek & Margolis, 2014
DENGUE: SIGNS AND SYMPTOMS

- 75% of infected patients with DF are asymptomatic
- If symptoms occur, they occur 4-7 days after bite
- Shorter incubation period than malaria
- Symptoms include fever, myalgia, headache, rash, arthralgia, abdominal pain, and nausea
- Atypical symptoms include ARDS, DIC, conduction cardiac defects, renal failure

DENGUE CATEGORIES

PRIOR TO 2009
- Dengue Fever
- Dengue Hemorrhagic Fever
- Dengue Shock Syndrome

2009-PRESENT
- Dengue
- Dengue with Warning Signs
- Severe Dengue

TOURNIQUET TEST FOR DENGUE

- Marker for microvascular fragility
- Inflate BP cuff 1/2 way between systolic and diastolic BP
- Maintain pressure for 5 minutes
- + Test: >10 petechiae found in one square inch

Tomashek & Margolis, 2014
"Bone Break Pain"
WHICH OF THE FOLLOWING IS NOT A SIGN OF SEVERE WORSENING DENGUE?

A. Epistaxis
B. Bloody stool
C. Headache
D. Menorrhagia

DENGUE: DIAGNOSIS

- Often a clinical diagnosis based on signs and symptoms
- Laboratory diagnosis confirmation:
  - Detection of dengue viruses (DENV) through
    - Polymerase chain reaction (PCR)
    - Nonstructural protein 1 (NS1) antigen by immunoassay

DENGUE: TREATMENT AND PREVENTION

- Self-limiting febrile illness
- Typically resolves after 4-7 days
- Supportive care (rest, acetaminophen, fluids)
- NO NSAIDS
- If severe case, admission required

Prevention
- AVOID MOSQUITO BITES! (See next Slide)
- No available vaccine, antiviral or chemoprophylaxis
• An ill traveler can spread disease if sustains a mosquito bite while ill
• The mosquito can carry on the virus to other locals

DENGUE: 1 MINUTE VIDEO CLIP

LET'S MOVE ON TO CHIKUNGUNYA
CHIKUNGUNYA (CHIKV): PATHOPHYSIOLOGY AND EPIDEMIOLOGY

- Swahili and Makonde language
  - “The one that is folded”
- Arbovirus
- Transmitted by Aedes mosquitoes
- > One million cases of CHIKV were reported in the Americas since October 2013
  - Most cases occur in travelers, but local transmission is possible

CHIKUNGUNYA: SIGNS AND SX’S

- Abrupt development fever, HA, polyarthralgia (usually small joints: hands, ankles, wrists) and myalgia
  - Hunched over gait
  - Back pain
  - Joint involvement can become chronic
    - Continued arthralgia in 60% even after 36mos.
- Rash common (maculopapular or bullous)
- Atypical symptoms: Encephalomyelitis, Hearing loss, Guillain Barre, Meningoencephalitis

CHIKUNGUNYA: DIAGNOSIS

- Chikungunya should not be a clinical diagnosis as it is difficult to differentiate from Dengue and other viral illnesses
- Confirm Dx detection of CHIKV:
  - Reverse Transcriptase Polymerase Chain Reaction (RT-PCR)
  - Enzyme linked Immunosorbent Assay (ELISA)
- Access to testing is limited
  - CDC, 1 commercial lab, few health departments
  - CHIKV only recently has become issue in US
CHIKUNGUNYA TREATMENT AND PREVENTION

- Supportive care
  - Rest, hydration, acetaminophen, ice packs
- Prevention
  - No available vaccine, antiviral, or chemoprophylaxis
  - AVOID MOSQUITO BITES
    - Let’s touch on mosquito avoidance with the following question...

A 50-YEAR-OLD MALE PRESENTS FOR A PRE-TRAVEL CONSULT BEFORE HIS TRIP TO INDIA. HE INQUIRES ABOUT MOSQUITO AVOIDANCE.

Which of the following would you advise for this patient?
A. If possible, move bedding into cool, dark areas (like a bathroom or closet) as mosquitos tend to avoid these areas
B. If using insect repellent, long sleeves and long pants are unnecessary to avoid mosquito bites
C. Avoid standing water (such as flower pots), which can encourage mosquito breeding
D. Open windows during cool evenings to allow for adequate ventilation
MOVING ON TO OUR LAST TOPIC... ZIKA

ZIKA: PATHOPHYSIOLOGY

- Flavivirus transmitted *primarily* by the bite of an infected *Aedes* mosquito (similar to Dengue and Chikungunya)
- Has been detected in:
  - Blood (10 wks), urine (91 days), semen (188 days), vaginal secretions (11 days), saliva (91 days), CSF, amniotic fluid, and breast milk
- Viral load in semen is 100,000 x stronger than in urine or serum
- Other modes of Transmission:
  - Maternal-fetal
  - Sexual transmission (vaginal, anal, oral)
  - Blood/Tissue Donation
  - Occupational Exposure (1 documented lab exposure)

ZIKA: EPIDEMIOLOGY

- 1947: First isolated in Rhesus monkey from Zika Forest in Uganda
- 1st major outbreak in Yap Islands of Micronesia in 2007 (70% of population age 3+ infected)
- Outbreak in Brazil May 2015 (1.5 million cases and 4,000 cases of microcephaly)
- 1st case of Zika related microcephaly in US was in Hawaii Jan. 2016 (Mom lived in Brazil during pregnancy)
  - Territories with Active Zika Transmission:
    - Anguilla, Antigua, Argentina, Barbados, Barbuda, Belice, Bolívia, Boracay, Brazil, Cape Verde, Cayman Islands, Colombia, Commonwealth of the Northern Mariana Islands, Costa Rica, Cuba, Curacao, Dominica, Dominican Republic, Ecuador, El Salvador, Fiji, French Guiana, Grenada, Guadeloupe, Guatemala, Guyana, Haiti, Hong Kong, Indonesia, Marshall Islands, Martinique, Meshi, Micronesia, New Zealand, Nicaragua, Niue, Oceania, Panama, Paraguay, Peru, Portugal, Puerto Rico, Qatar, Reunion, Samoa, Saint Lucia, Saint Martin, Saint Vincent and the Grenadines, Samoa, South Africa, South Korea, Suriname, Trinidad and Tobago, Tonga, Turks and Caicos, US Virgin Islands, United States, Vanuatu, Vatican City, Vieques, Virgin Islands American Samoa
- Feb. 2016: WHO declared ZIKA an international health emergency

[Image of Zika virus with text: “ZIKA: PATHOPHYSIOLOGY”]

[Image of Zika virus with text: “ZIKA: EPIDEMIOLOGY”]
ZIKA CASES REPORTED IN THE US  
(CDC SEPT. 2016)


ZIKA: EPIDEMIOLOGY

- Imported Zika in travelers returning to US (3,132)
- Sexually transmitted cases of Zika (26 cases in US)
- Locally acquired Zika 1st identified in Florida
  - 43 locally acquired Zika infections in FL (CDC, late Sept)
- Just to give a comparison…Puerto Rico: 7855 locally acquired infections

ACTIVE ZIKA VIRUS LOCAL  
TRANSMISSION IN FLORIDA (CDC)

WYNWOOD NEIGHBORHOOD AND SECTION OF MIAMI BEACH

Pregnant Women advised to avoid travel to Wynwood neighborhood and an area of Miami Beach
ZIKA: SIGNS/SX’S

- No Sx’s (80%)
- Sx start 2-14 days after bite (20%):
  - 2 or more of the following:
    - Low-grade fever (100-101.3)
    - Maculopapular rash
    - Arthralgia
    - Conjunctivitis
- Other Sx’s: Myalgia, HA, pain behind eyes common
  - Occasionally, adb pain, nausea, diarrhea, itching
- Sx’s resolve within 2-7 days
- Complications: Congenital microcephaly, fetal loss, Guillain-Barre (8 cases of Zika assoc. GB in US)

ZIKA: WHEN SHOULD WE SUSPECT IN NON-PREGNANT PT?

- If relevant exposure
  - Travel to or residence in endemic area within 2 weeks
  - Unprotected intercourse with person who meets above criteria
  - AND
- 2 or More of the Following Sx’s:
  - LG fever
  - Rash
  - Arthralgia
  - Conjunctivitis

ZIKA: DIAGNOSTIC TESTS

- Preferred test for dx of acute Zika: Real-Time Reverse-transcription polymerase chain reaction (rRT-PCR) for Zika RNA in serum and urine
  - Test when viral load is highest (serum w/i 7 days Sx’s, urine may be + for 14d)
  - Neg test does not exclude infection
- Zika virus serology
  - Draw lab 4 or more days after Sx onset
  - Caution: Cross-reactivity with other flavivirus (West Nile, Dengue) limits specificity
  - If + IgM, check Zika Virus Plaque-Reduction Neutralization test (PRNT)
    - PRNT is used to rule out false positive IgM
- Commercial assays recently developed: PCR-based assay and a serologic assay
- Contact state health departments/CDC if testing needed

*When testing for Zika, also test for Dengue and Chikungunya*
ZIKA: TREATMENT IN NONPREGNANT PT

- No FDA approved treatment
- Rest, Fluids, Acetaminophen
- No ASA or NSAIDS until Dengue ruled out
- Avoid mosquito bites while ill to decrease local spread
- How long to wait before unprotected sexual activity (CDC)?
  - Symptomatic men with Zika: Wait > 6 mos
  - Symptomatic women with Zika: Wait > 8 weeks
  - Asymptomatic men or women with Zika exposure: Wait > 8 weeks
  - WHO: Recommends waiting > 6 mos for both men and women who travel to areas with active transmission regardless of Sx's

ZIKA: PREVENTION

- No vaccine...Yet... (Presently under development)
- Avoid mosquito bites
  - Both in Zika area and upon return to non-Zika area
  - Personal protective Measures: Long sleeves and pants, insect repellent, staying indoors
  - Avoid standing water
- Universal testing of donated blood products in the U.S. and its territories (Aug 2016)

ZIKA: PREVENTION IN PREGNANCY

- In Jan. 2016, CDC advised that pregnant women postpone travel to endemic area
- Men with Zika who have pregnant partner
  - Abstain from intercourse (vaginal, anal, oral) for duration of pregnancy or use barrier protection
- In areas with active Zika transmission, CDC recommends abstinence or barrier method for all individuals while transmission persists
- Breast feeding: CDC encourages continued breast feeding
**ZIKA: WORKUP IN PREGNANCY**

- Ask about relevant exposure in patient and partner at EACH prenatal visit
  - Exposure: Residence or recent travel to Zika area or unprotected intercourse with partner who traveled to or lived in Zika area

- Workup for Pregnant Pt (see algorithm next slide)
  - No exposure: Zika labs NOT indicated
  - Exposure (w/i 2 wks) WITH OR WITHOUT Sx's: Lab indicated (rRT-PCR, serum and urine). If neg, serum testing
  - Exposure (2 wks -12 weeks) WITH OR WITHOUT: Zika IgM and Dengue IgM, rRT-PCR, PRNT

- If + Zika labs, get US
  - US is the major tool used to screen for congenital Zika

- If negative Zika labs in pt with exposure, get Ultrasound (US)
  - If normal US, consider one or more f/u US
  - Abnormal US
    - Fetal Microcephaly (difficult to dx before 3rd trimester)
    - Intracranial Calcifications (seen in 2nd or 3rd trimester)
      - If + US, recheck maternal serology/rRT-PCR and consider amniocentesis

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[Algorithm for Zika Workup in Pregnancy] (http://www.uptodate.com/contents/image?imageKey=OBGYN%2F109190&topicKey=ID%2F107211&rank=2%7E59&source=see_link&search=zika+virus&utdPopup=true)
ZIKA: WORKUP IN PREGNANCY, CONT.

- If positive/inconclusive labs in mother
  - Consider Amniocentesis and Serial US (q 3-4 weeks)
  - Zika rRT-PCR in Amniotic fluid is diagnostic of exposure (sensitivity and specificity unknown)
  - + Amnio does not mean fetal abnormality is present
  - If negative Amnio and abnormal US, consider other cause of microcephaly
  - All infants with possible Zika exposure obtain thorough evaluation w/i 24 hours after delivery
    - Thorough Physical Exam and Head circumference
    - Zika labs
      - Consider histopathology of placenta and umbilical cord
FUTURE ZIKA IMPLICATIONS...

- Zika Funding
- CDC estimates that 41 states are in the potential range of *Aedes aegypti* or *Aedes albopictus* mosquitoes
  - Aug 24, 2016: Director at NIH states that Zika virus could extend its reach across the U.S. Gulf Coast (Louisiana and Texas)
  - Record flooding in Louisiana in Aug. 2016 increases risk of Zika
  - “Diffuse, broad outbreak” unlikely but CDC recommends preparation for that possibility
  - State-level strategies for improving access to contraceptives to decrease unintended pregnancies

REMEMBER OUR PREVIOUS PATIENT?

OUR FEBRILE PATIENT, CONT.

Laboratory Workup

- CBC, CMP, and UA were without abnormality.
- Thick and thin blood smear revealed multiple infected red blood cells and the appearance of the classic head phone form within the red blood cell.

WHAT DID OUR PATIENT HAVE?

- And how did we treat him?

THAT IS RIGHT!! OUR PATIENT HAD MALARIA (CAUSED BY PLASMODIUM VIVAX)

- The 19-year-old febrile traveler was diagnosed with malaria very quickly based on the in-office laboratory results of the thick and thin blood smear.
- He did not take malaria chemoprophylaxis prior to his trip.
- No pre-travel consult prior to travel.
- Consider Leder et al's research: Talk to your patients and encourage pre-travel consults.
- Short hospital admission for hydration, observation, treatment, and consultation with ID yielded rapid improvement.
- Pt. back to the rigorous demands of college life.
TAKE HOME MESSAGE

- Early detection and appropriate supportive care of patients with Malaria, dengue, Chikungunya and Zika can make the difference between life and death.
- Remember to consider these conditions in the febrile returning traveler.
- Encourage patients to consider pre-travel medical consults.

THANK YOU ALL!
Wishing you all safe travels!

REFERENCES

[References list]
REFERENCES, CONT.