Lesson S49: Assessment of the Pregnant Patient with a Possible Zika Virus Infection

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Read this article, reflect on the information presented, then go online and complete the lesson post-test and course evaluation before the termination date below. (CME credit is not valid past this date.) You must achieve a score of 80% or better to earn CME credit.

TIME TO COMPLETE ACTIVITY: 2 hours
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Professional Gaps

According to a poll conducted in early 2016 by the Associated Press-NORC Center for Public Affairs Research at the University of Chicago, many Americans know very little about the Zika virus and express little concern. Anesthesiologists should have a working knowledge of this emerging infection and the impact on practice.

Learning Objectives

At the completion of the activity, the reader will be able to:

1. Identify means of transmission for the Zika virus
2. Describe the life cycle of Zika in the mosquito
3. List geographical locations for Zika infection
4. Describe the symptoms of Zika fever
5. Compare commonly used repellents
6. Inform patients about prevention techniques
7. Advise pregnant patients about fetal risks of Zika infection
8. Understand the importance of mosquito control
9. List innovative methods to control Zika infection
10. List means to diagnose Zika infection
Case

A 23 year old woman in her 34th week of pregnancy presented to the emergency room, complaining of general malaise. She reported that she had a headache and vague joint pains for a few days. A rash appeared on her arms and upper torso. Her pregnancy to date had been uncomplicated. Her history revealed a holiday trip to visit her family in Trinidad about 10 days prior. As part of a differential analysis, a presumptive diagnosis of Zika fever was made, and a conference was arranged between the obstetrical, pediatric, anesthesia and infectious disease departments as to how best to manage her care and pregnancy.

Introduction

The Zika virus belongs to the family Flaviviridae and the genus Flavivirus. It is spread mainly by the daytime activity of the Aedes mosquitoes, such as Ae. aegypti and Ae. albopictus.1 However, the mosquito may also bite at night, both indoors and outdoors. Only the female mosquito carries the virus which was first isolated in the Zika Forest of Uganda, in 1947, hence the name.2

Zika virus is transmitted like other arboviruses that cause diseases such as chikungunya, dengue, yellow fever, Japanese encephalitis, and West Nile infection. Like other flaviviruses, the Zika virus is enveloped and icosahedral and has a non-segmented single-stranded positive-sense RNA genome. Although the virus was first isolated in 1947, the first documented outbreak among humans occurred in 2007 in the Federated States of Micronesia.3 By early 2016, the disease was occurring in twenty regions of the Americas and also in Africa, Asia, and the Pacific. Following an outbreak in Brazil in 2015, the World Health Organization (WHO) declared a Public Health Emergency of International Concern because of clusters of microcephaly and other neurological disorders in areas affected by Zika.

As Zika infection has quickly spread internationally without any indication of being contained or slowing down, the possibility of acquiring the disease has prompted travel alert warnings from the United States and the relocation of sporting events from Puerto Rico to mainland US, as of May 2016.

As of the time of this writing (May, 2016), the virus has not been spread directly by mosquitoes in the continental United States. Lab tests have confirmed its presence in the United States in persons returning from affected areas and non-travelers who became infected with Zika through sex with a infected traveler.4 Local transmission of Zika has been reported in the Commonwealth of Puerto Rico, the US Virgin Islands, and American Samoa.

Transmission

Vertebrate hosts of the Zika virus were initially monkeys in an enzootic mosquito-monkey-mosquito cycle. Transmission to humans was rare, seldom causing infection prior to the start of the current pandemic in 2007. However, other arboviruses had already been identified as causes and transmitters of human disease and spread in a mosquito–human–mosquito cycle, such as yellow fever virus and the dengue fever virus (both flaviviruses), and the chikungunya virus (a togavirus). Transmission has also been confirmed via blood transfusion from infected humans.

Sexual transmission of the Zika virus has been documented in at least six countries as of April, 2016.5 In fact, the Zika virus has been shown to remain active in semen for at least two weeks and possibly up to
10 weeks after the onset of symptoms of Zika fever. In the United States, an American biologist returning home from Senegal suffered Zika fever. Following unprotected intercourse, his wife developed symptoms of Zika fever and Zika antibodies were later identified. As of February 2016, 14 additional cases of possible sexual transmission were under investigation. In all documented cases, the transmission of Zika virus was from men to women. It has not been established that women can transmit the virus to sexual partners.

Blood transfusion has also been shown to allow transmission of the virus. As of April 2016, two cases of transmission through blood transfusions have been reported globally. The US Food and Drug Administration recommends screening blood donors and deferring high-risk donors for 4 weeks. In one study in French Polynesia, 2.8% (42) of donors from November 2013 to February 2014 tested positive for Zika RNA but were all asymptomatic at the time of blood donation. Eleven of the positive donors reported symptoms of Zika fever after donation.

Life Cycle of the Mosquito

Standing water is essential to the life cycle of the mosquito. The insect is remarkable in that it can live in salt or fresh water, in brackish water and even in the stagnant water found in tires or in holes in trees. Mosquitoes have 4 life cycles. The female mosquito lays several hundred eggs on the surface of water, or in an area prone to flooding. Unhatched eggs are extremely resistant to adverse conditions and can adhere to the sides of any contained area. Eggs remain viable even when desiccated until the right conditions for hatching develop. The eggs of most species hatch in 2-3 days and the larvae feed on organic matter in the water for about a week before changing into pupae. The pupae continue to live in the water for another 2-3 days and then metamorphose into adult mosquitoes.

Male mosquitoes feed on flower nectar and do not bite. Females require blood to produce eggs. Feeding is approximately every three days and a female mosquito will typically consume its own weight in blood. Some insects feed only at twilight, while others bite mostly during the day.

The virus divides in the midgut epithelial cells of the mosquito and then spreads to its salivary gland cells. After 5 - 10 days, viruses are found in the mosquito’s saliva which enable transmission to humans. Inoculation of mosquito saliva into human skin results in infection of epidermal keratinocytes, skin fibroblasts and the Langerhans cells. The virus then spreads to lymph nodes and vascular spaces. Flaviviruses generally replicate in the cytoplasm, but Zika antigens have also been found in cell nuclei.

Zika Fever

Flaviviruses are human neuropathogens and can cause a wide range of clinical syndromes ranging from fever, meningitis, encephalitis, and a flaccid paralysis like that of Guillain Barre syndrome. Chikungunya is characterized by high fever, severe arthralgia, arthritis, rash, and lymphopenia. Dengue is more likely to cause neutropenia, thrombocytopenia, hemorrhage, shock, and death. Co-infection with these viruses is possible and has been reported in previous outbreaks. Acetaminophen should be used to manage pain in people suspected of having one of these illnesses since aspirin or nonsteroidal anti-inflammatory drugs can increase the risk of bleeding.

Most persons infected with Zika are asymptomatic. Symptomatic infection can resemble a milder form of dengue fever and include fever, red eyes, joint pain, headache and maculopapular rash. Symptoms generally last less than a week. Death is very rare during the initial infection, although complications can
develop later. Infection during pregnancy can result in fetal microcephaly and other neurologic abnormalities.\textsuperscript{12,13} Complications of microcephaly include mental retardation, seizures, vision and hearing problems and other morbidities. While microcephaly generally occurs in 2 out of 100,000 live births, several thousand cases have been reported recently in Brazil, the country most affected by Zika. In addition, a spike of more than 400 cases of Guillain-Barre associated with Zika infection has been reported, according to the WHO.

**Diagnosis**

During the first week after onset of symptoms, Zika virus disease can often be diagnosed by performing real-time reverse transcription-polymerase chain reaction (rRT-PCR) on serum.\textsuperscript{14} Urine testing is also recommended and samples should be collected less than 14 days after onset of symptoms for rRT-PCR testing. Virus-specific IgM and neutralizing antibodies typically develop toward the end of the first week of illness; cross-reaction with related flaviviruses (e.g., dengue and yellow fever viruses) is common and may be difficult to discern. Plaque-reduction neutralization (PRNT) testing can be performed to measure virus-specific neutralizing antibodies and discriminate between cross-reacting antibodies in primary flavivirus infections.

**Prevention**

It is important for populations at risk to take measures to avoid acquiring the infection. To this end, several guidelines have been developed including the following:

1. When outdoors, wear long sleeved shirts and pants or long skirts.
2. Wear a hat with a shade over the brow.
3. Spray skin and clothing with insect repellent.
4. Restrict outside activity at dawn, dusk and during the evening.
5. Cover babies in strollers with nets.
6. Remove pools of standing and stagnant water, including those found in wading pools and wheelbarrows.
7. Keep storm drains free of debris.
8. Drill holes in recycling garbage containers.
9. Chlorinate swimming pools.
10. Maintain the integrity of window and door screens.

Several factors have been identified that increase the attraction of mosquitoes to a host. It is known that mosquitoes use visual, thermal and olfactory stimuli, of which olfactory is probably the most important. Daytime feeding insects appear to be oriented to the host by dark colored clothing. Visual stimuli help flight orientation, especially at far distances. Up close, smell seems to be the primary stimulus. Of the 3-400 compounds that are released from the body as by-products of human metabolism, some 100 volatile substances can be detected in the breath. Mosquitoes are most attracted to carbon dioxide and lactic acid. Carbon dioxide is a long range airborne attractant and can be detected by mosquitoes at up to 100 feet. Chemoreceptors on the antennae of the insects are stimulated by lactic acid. These same chemoreceptors may be inhibited by N,N-diethyl-m-toluamide (DEET)- based insect repellents.\textsuperscript{16} Up close, skin temperature and moisture attract. Propensity to bite around the head or feet may be due to local temperature and eccrine sweat gland output. Mosquitoes are generally not attracted to anhydrotic individuals. Other chemoattractants include volatile compounds derived from sebum, eccrine and apocrine sweat and the cutaneous microfloral actions on these secretions. Floral fragrances, perfumes,
soaps, lotions and shampoos also can increase the likelihood of being bitten.

There seems also to be a gender and age preference as men are bitten more frequently than women, adults more than children (except for the very old), and larger people more often than thinner ones (perhaps because of greater relative heat and carbon dioxide production). 17

**Insect Repellents**

As noted above, the attraction of mosquitoes for humans can be chemically decreased, although there is variation in effectiveness by species. There is no repellent effective against several arthropods that could be taken orally. Topical preparations are recommended and somewhat effective but are capable of causing skin irritation and systemic adverse actions. They can also rub off. Effective repellants must have appropriate volatility to maintain a vapor concentration on the skin without evaporating too quickly. Factors that contribute to the effectiveness of repellents include the frequency and uniformity of application, the types of susceptible organisms, the user’s attractiveness to the biting insect and the activity of the host. Repellents all become less effective in the rain, as the individual sweats, as the temperature rises (10°C rise in temperature causes 50% decrease in effectiveness), and as wind increases. 18-20

**Chemical Repellents**

The gold standard in chemical repellents is DEET which was discovered and developed by scientists at the US Department of Agriculture and patented by the US Army in 1946. Registration for use by the public occurred in 1957. 16 Although more than 20,000 compounds have subsequently been tested, none have proven as effective. It is a broad spectrum repellent with a long duration of action. The US Environmental Protection Agency (EPA) estimates that one-third of the US population uses this preparation every year and, annually, it is used by over 200 million worldwide.

DEET was historically believed to work by blocking insect olfactory receptors for 1-octen-3-ol, a volatile substance that is contained in human sweat and breath. The prevailing theory was that DEET effectively "blinds" the insect's senses so that the biting or feeding instinct is not triggered by humans or other animals which produce these chemicals. Some evidence seems to indicate that DEET does not affect the insect's ability to smell carbon dioxide but it has been shown that it can serve as a true repellent in that mosquitoes intensely dislike the chemical. A type of olfactory receptor neuron in special antennal sensilla of mosquitoes that is activated by DEET, as well as other known insect repellents such as eucalyptol, linalool, and thujone, has been identified. Moreover, in a behavioral test, DEET had a strong repellent activity in the absence of body odor attractants such as 1-octen-3-ol, lactic acid, or carbon dioxide. Both female and male mosquitoes showed the same response.

DEET is available in many formulations and concentrations ranging from 5% to 100%. Over the past 40 years, it has been shown to have a remarkable safety profile. Skin irritation is very rare, although contact urticaria in the antecubital fossa has been described. Eye irritation from direct spraying has also been reported. Currently a slow release, polymer-based product containing 35% DEET, which is the formulation provided to US military personnel, is marketed under the brand name of Hour Guard® (Amway Corp, New York). Lower strengths of extended release DEET (6.5% and 10%) are marketed by Minnetonka Brands (Eden Prairie, MN).

Unfortunately, there is not an “insect repellent factor” that can be appended to drug labels, so the
appropriate concentration and times of application are unknown, particularly as mosquitoes vary greatly in their susceptibility to the compound. However, the polymer formulation appears to increase the effectiveness to about 12 hours. The American Academy of Pediatrics has recommended that repellents used for children contain not more than 10% DEET. While DEET does not affect natural fibers, it can damage plastics, synthetic materials, leather and painted or varnished surfaces. It should also be noted that application of DEET in conjunction with a sunscreen preparation will decrease the effectiveness of the latter.

**Plant Derived Repellents**

Although thousands of plant derived compounds have been tested for repellent activity, none have tested as effective as DEET with regard to duration and broad spectrum activity. Some essential oils that are effective include citronella, cedar, geranium, lavender, rosemary, basil, thyme, allspice, garlic and peppermint. Generally, protection lasts less than 2 hours. Citronella has been used widely in candles as an insect repellent. However, studies have shown an almost equal protective effect from plain candles, perhaps due to the action of the latter as a decoy of warmth, moisture and carbon dioxide.

Pyrethrum is a rapidly acting insecticide that is neurotoxic to the insect. It is derived from the chrysanthemum and is a synthetic pyrethroid. The agent is effective against several insects, has low toxicity and is rapidly inactivated by ester hydrolysis. It should be applied directly to clothing or to screens or nets. Potency is maintained for up to 2 weeks.

**Electronic Devices**

Ultrasonic, handheld devices that are advertised to emit sounds that repel mosquitoes are not effective. Similarly, larger devices that are hung in gardens and back yards (bug zappers) to attract and electrocute insects are ineffective against mosquitoes. Only 0.1% of the insects killed by these instruments are female mosquitoes. It has been estimated that 71 billion to 350 billion beneficial insects are killed in this manner annually.

**Controlling the Mosquito Population**

The *Aedes aegypti* mosquito transmits not only the Zika virus but also the viruses for dengue, yellow fever as well as several other tropical diseases. Oxitec, working at Oxford University in England has developed a means to genetically modify the male mosquito. These mosquitoes, known as OX513A, have been tested in field trials in Brazil and Panama and were shown to reduce target mosquito populations by more than 90%. A self-limiting gene prevents the offspring from surviving. Male modified mosquitoes, which do not bite, are released to mate with females. Their offspring inherit the gene and die before reaching adulthood.

The mosquito control effect is non-toxic and species-specific as the OX513A mosquitoes are *Aedes aegypti* and only breed with *Aedes aegypti*. A proposal is presently under review to release the altered mosquitoes in a part of Florida.

Radiation has also been proposed to sterilize male larvae so that when they mate, they will produce no progeny.

Another means to control the mosquito population that has received enthusiastic support from local
governments is the use of fat head minnows. These little fish will eat the larvae, consuming several times their own weight on a daily basis.

Management of the Case

The diagnosis of Zika fever was confirmed by both serum and urine testing. The patient was started on non-steroidal antipyretic medication. She quickly became afebrile. Ultrasound indicated that the fetus’ head and body were of normal size for the period of gestation. The mother was advised that there did not seem to be microcephaly at this point but the virus could possibly still be transmitted during delivery, although information about this type of transmission is limited. She was asked to consider the possibility of neurologic abnormalities in the baby related to the viral infection versus the hazards of a premature birth. After extensive consultation with all members of the team, the patient elected to undergo a cesarean section on the following day. The entire operating room staff and the staff of the pediatric intensive care unit were assured that the virus was not transmitted by simple contact with the patient or the baby.

Under neuraxial block, a health baby girl, weighing 3lbs 6oz was delivered. She appeared neurologically intact with a normal head size. The mother recovered within 3 days and returned home. The baby followed shortly thereafter.

Dr. Elizabeth A.M. Frost, who is the editor of this continuing medical education series, is clinical professor of anesthesiology at The Mount Sinai School of Medicine in New York City. She is the author of Clinical Anesthesia in Neurosurgery (Butterworth-Heinemann, Boston) and numerous articles. Dr. Frost is past president of the Anesthesia History Association and former editor of the journal of the New York State Society of Anesthesiologists, Sphere. She is also editor of the book series based on this CME program, Preanesthetic Assessment, Volumes 1 through 3 (Birkhäuser, Boston) and 4 through 6 (McMahon Publishing, New York City).
REFERENCES

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Post-test

1. The life cycle of the mosquito:
   a. Requires fresh flowing water
   b. Is 2 cycles because of lack of adaptation
   c. Involves four cycles
   d. Takes over a month to complete

2. Human infection with Zika in the United States:
   a. Is primarily from contact with domestic animals
   b. Is mostly acquired through blood transfusion
   c. Usually causes only mild symptoms
   d. Results in death in 75% of cases

3. The least effective deterrent to mosquito bites is:
   a. DEET spray
   b. Citronella candles
   c. Permethrin
   d. Electronic Bug Zappers

4. The mosquito population can be controlled by:
   a. Genetic modification of the male insect
   b. Radiation of larvae
   c. Fat head minnows
   d. All of the above

5. Regarding sexual transmission of Zika virus:
   a. There are no documented cases in the United States.
   b. Transmission appears only to be from men to women.
   c. The Zika virus lives only for a few hours in semen.
   d. All cases of sexual transmission have been fatal.
6. The Zika virus:
   a. Was isolated in 2007
   b. Takes its name from a forest in Uganda
   c. Contains a segmented, multi-stranded positive-sense RNA
   d. Has not as yet warranted any travel alerts

7. Which of the following statements is true?
   a. Only the female mosquito carries the Zika virus
   b. Both male and female mosquitoes can transmit the virus
   c. The male mosquito bites mainly at dusk
   d. By genetically modifying female mosquitoes, the population can be controlled

8. Chikungunya virus and Zika virus are similar in that both can be classified as a(n):
   a. Togavirus
   b. Flavivirus
   c. Arbovirus
   d. Alphavirus

9. Which is the most important stimulus that attracts mosquitoes?
   a. Bright colors
   b. Warm rooms
   c. CO2 and lactic acid
   d. Citronella candles

10. Following the onset of symptoms, Zika virus can be detected by:
    a. rRT-PCR testing on serum during the first week
    b. rRT-PCR testing on urine after 14 days
    c. IgG antibody testing within the first 2 days
    d. All of the above are suitable