You're the Flight Surgeon

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You're the flight surgeon on duty when a 26-yr-old man presents first thing Monday morning for an acute appointment. The C-130 flight engineer complains of mild nausea and diffuse joint pain without respiratory symptoms. His symptoms began over the weekend with a rash, headache, and subjective fever, and all symptoms improved during the previous day with rest and acetaminophen. An active duty aircrew member previously in excellent health, he is most concerned about passing this "bug" to his two school-age children and spouse, who is 4 mo pregnant.

He returned about 5 d ago from a weekend trip to his childhood home in Puerto Rico to celebrate his father's 50th birthday. No other party guests were known to be ill and no one in attendance has fallen similarly ill. Several of his parents' neighbors have had mild febrile illnesses during the past 6 mo, including one who was hospitalized for several days.

Your airman has no significant past medical, surgical, or family history, denies smoking and sexual contact other than his spouse, and occasionally consumes alcoholic beverages. He did not seek travel medicine advice before his trip. Physical examination reveals an oral temperature of 37.2°C (99°F), mild conjunctivitis, a faint maculopapular rash of the trunk and thighs, and the absence of meningismus or lymphadenopathy. You elicit mild discomfort with passive range of motion of the bilateral upper and lower extremity joints, both small and large, without arthritis or tenosynovitis. His muscles are nontender and exhibit normal strength, his reflexes and direct funduscopic examinations are normal, and his uncorrected visual acuity is 20/20 by Snellen.

1. What recent travel exposure most likely led to this clinical picture?

A. Unprotected sexual activity.
B. Walking barefoot on soil or sand.
C. Being bitten by an insect.
D. Swimming in fresh water.
E. Ingesting contaminated food or beverage.

ANSWER/DISCUSSION

1. C. Fleas, ticks, and mosquitoes may transmit a number of diseases that are characterized by fever, headache, and rash. Dengue has long circulated in the region, and recent years have seen chikungunya and Zika epidemics. *Aedes aegypti* and *A. albopictus*, both present on Puerto Rico, are efficient mosquito vectors for these viruses and many others that circulate elsewhere such as yellow fever, West Nile, and encephalitis viruses. Unlike anophelene mosquitoes that carry malaria and bite from dusk to dawn, *Aedes* species primarily feed during the day.[12] Malaria is not present on Puerto Rico.

Disseminated gonococcal infection, which is uncommon in males, may present with similar signs and symptoms, is typically preceded by urethritis, and has a longer incubation period,[18] but our airman has no known risk factors. Cutaneous larva migrans is a self-limited, parasitic dermatitis that usually occurs a week or two after bare skin exposure to hookworm-contaminated sand or soil. *Ancylostoma* larvae incompletely penetrate the skin, where the immune response to their movements is marked by intensely pruritic serpiginous lesions that may continue for several weeks.[23] Fresh water in Puerto Rico rarely may be contaminated with leptospires shed in animal urine, but schistosomiasis has not been reported on the island for several decades.[16] Your airman denies sand, soil, or water exposure during his brief visit. Food- or water-borne illness is inconsistent with this presentation, and your airman has received oral immunization against typhoid.

Given your airman's clinical presentation, your primary differential diagnoses at this point include mosquito-borne viral infections such as chikungunya, dengue, and Zika. Maculopapular rash, conjunctivitis, and diffuse arthralgias may be observed in any of these infections. Dengue virus infections may manifest with petechial lesions, particularly in areas of skin compression such as under blood pressure cuffs. Chikungunya may cause a frank viral arthritis. Zika virus has been implicated in meningoencephalitis in adults and children, but your airman clinically is improving.

You discuss your concerns with your airman, including instructions to prevent exposing others to potential illness.

2. Which mechanism has not been demonstrated in human Zika, dengue, or chikungunya transmission?

A. Mosquito bites.
B. Respiratory droplets.

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C. Blood or tissue donation.
D. Unprotected sexual activity.

ANSWER/DISCUSSION

2. B. These infections do not exhibit significant tropism for the respiratory tract and are not transmitted by contact or inhalation of respiratory secretions. Zika virus has been demonstrated in saliva, which may aid in future diagnostic testing. However, monkeys whose tonsils were challenged with the saliva of infected subjects did not develop infection.[27]

Person-to-person spread of these and most other vector-borne infections may occur through secondary vector transmission. Zika virus transmission from an infected traveler, for instance, has been presumed to have occurred via mosquito vector in both Florida and Texas during the recent regional epidemic.[8] Dengue, but not Zika or chikungunya, transmission via blood donation has been reported.[9] Sexual transmission of Zika virus has been described and chikungunya has been detected in semen.[3] Fomites are not a vehicle for transmission of these viruses.

You specifically instruct your patient to avoid blood donation, use barrier protection during sexual activity, and avoid being bitten by insects. You recommend rest, hydration, and acetaminophen as needed and order several tests, including urine and serum reverse-transcription polymerase chain reaction testing for Zika virus RNA, which are reported positive. Your airman is relieved that he cannot casually transmit Zika to his family and is anxious to protect his wife against sexual transmission.

3. How long should your airman refrain from unprotected sexual activity?

A. 2 wk.
B. 8 wk.
C. 6 mo.
D. At least the duration of his spouse's pregnancy.

ANSWER/DISCUSSION

3. C. Men infected with Zika may experience prolonged viral shedding in seminal fluid, and currently the Centers for Disease Control and Prevention recommends that men use barrier protection during sexual activity for 6 mo after onset of symptoms.[28] Prior exposure to Zika virus is presumed to result in protective immunity against future infections. Your airman's spouse has never traveled to an area with Zika transmission, so she is presumed to be at risk for infection. Women with symptomatic Zika infection may transmit to male sexual partners for up to 8 wk. Men and women who are symptomatic are more likely to transmit the virus to partners than if they are asymptomatic.[6]

Zika infection during pregnancy can result in fetal infection, although babies exposed to Zika before birth may or may not manifest signs or developmental issues. Earlier fetal infection carries a higher risk of Zika-related disease than later infection.[7] No cases of transmission by breastfeeding have been observed to date; however, detection of viable virus in breast milk has been demonstrated.[11,32] At the time of this writing, both the World Health Organization and the Centers for Disease Control and Prevention recommend women with Zika virus infection breastfeed their babies.[10]

4. Which of the following aeromedically important complications is least likely to result from Zika virus infection?

A. Transient hearing loss.
B. Hemorrhagic manifestations.
C. Transverse myelitis.
D. Chronic arthritis.

ANSWER/DISCUSSION

4. D. Of the mosquito-borne diseases discussed, only chikungunya commonly is associated with frank arthritis that may become chronic in nature.[12] Infections with the flaviviruses dengue and Zika range from subclinical to life-threatening. Four dengue virus serotypes circulate together and antibodies are protective against future type-specific infection. The risk of severe dengue in initial infection is very low, but increases with each additional infection. Unfortunately, antibodies against one serotype may inappropriately enhance the inflammatory response to subsequent challenge with any of the other serotypes.[34] Similarly, Zika infection may result in cross-reactive antibody-dependent immune enhancement, resulting in severe disease.[17] Your airman spent much of his childhood in Puerto Rico and may have had prior dengue exposure.

It remains unclear whether neurological disease directly results from Zika virus, from an aggressive immune response, or through another mechanism.[31] Transverse myelitis and encephalomyelitis have been described among adults with Zika infection.[13,15,21] Up to one-third of Brazilian babies with congenital Zika syndrome exhibited ophthalmological manifestations, while bilateral anterior uveitis has been observed only rarely in adults.[22] Additional adult neurological Zika sequelae include meningitis, encephalitis,[30] central nervous system vasculitis, and Guillain-Barré syndrome (GBS).[1,25] Transient hearing loss (threshold shifts of > 20 dB) has been described in adults with Zika virus infection.[35]

Chikungunya is not known to cause hemorrhagic manifestations, but neurological sequelae occasionally have been described.[4] Malaria is not endemic on Puerto Rico, and your airman has not traveled to a malarious region within the past year.

Aircrew with Zika, dengue, and chikungunya virus infections often are asymptomatic, yet pose a risk of vector-borne transmission to others. Those with symptomatic Zika typically experience a mild, self-limited febrile syndrome that may include rash, conjunctivitis, arthralgias, myalgias, headache, and nausea.[5] Severe manifestations observed in adults include meningitis or encephalitis, myelitis, uveitis, and unilateral or bilateral tinnitus or hearing loss.[29] GBS (acute inflammatory demyelinating polyradiculoneuropathy) can occur after any infection. Although rates have been elevated during the present Zika epidemic, GBS remains rare even among case series of Zika virus infections.[24,25]

Neither the Federal Aviation Administration, U.S. military services, nor the International Civil Aviation Organization specifically mention Zika, dengue, or chikungunya in published medical standards.[14,19,26,33,36] Disease categories such as arthritis, conjunctivitis,

and meningitis, however, are addressed more specifically given their potential impact on aviation safety. Medical standards regarding meningitis, for example, are not differentiated by causative agent and would be disqualifying from flight duties.[14,19,36] Complications such as myelitis, uveitis, hearing threshold shift, and GBS all may be disqualifying during acute illness and require a waiver for consideration for return to flying duties.[19,26,33]

You remove your airman from flying duties and monitor him for complete resolution of his Zika syndrome, including arthralgias, eye irritation, headache, rash, and constitutional symptoms such as fever and fatigue. You judge his syndrome to be mild and do not plan more invasive testing unless he worsens or relapses.

5. Which of the following is least likely to prevent Zika virus infection?

A. Zika virus vaccine series completed at least 14 d prior to travel.
B. DEET (N,N-dimethyl-m-toluamide) repellant applied to skin.
C. Permethrin repellant/insecticide applied to clothing.
D. Condoms used correctly and consistently.
E. Picaridin repellant applied to skin.

ANSWER/DISCUSSION

5. A. No vaccine against Zika virus currently is available, although vaccine development is ongoing.[20] The Armed Forces Pest Management Board recommends repellants that contain DEET or picaridin for protection from the bites of ticks, fleas, and mosquitoes.[2] Permethrin is available in many forms to treat clothing and netting. Condoms are effective barriers against sexual transmission of Zika virus.

You encourage your airman to seek travel medicine advice prior to his next trip outside the continental United States.

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REFERENCES

1. Acevedo N, Waggoner JJ, Rodriguez M, Rivera L, Landivar J, et al. Zika virus, chikungunya virus, and dengue virus in cerebrospinal fluid from adults with neurological manifestations, Guayaquil, Ecuador. Front Microbiol. 2017; 8:42.
2. Armed Forces Pest Management Board. Personal protective measures against insects and other arthropods of military significance. Silver Spring (MD): Armed Forces Pest Management Board; 2015:23–29. Technical Guide No. 36.
3. Bandeira AC, Campos GS, Rocha VF, Souza BS, Soares MB, et al. Prolonged shedding of Chikungunya virus in semen and urine: a new perspective for diagnosis and implications for transmission. IDCases. 2016; 6:100–103.
4. Brizzi K. Neurologic manifestation of chikungunya virus. Curr Infect Dis Rep. 2017; 19(2):6.
5. Carteaux G, Maquart M, Bedet A, Contou D, Brugières P, et al. Zika virus associated with meningoencephalitis. N Engl J Med. 2016; 374(16):1595–1596.
6. Centers for Disease Control and Prevention. Clinical guidance for healthcare providers for prevention of sexual transmission of Zika virus. 2017. [Accessed 20 Oct. 2017]. Available from https://www.cdc.gov/zika/hc-providers/clinical-guidance/sexualtransmission.html.
7. Centers for Disease Control and Prevention. Pregnancy. 2017. [Accessed 20 Oct. 2017]. Available from https://www.cdc.gov/zika/pregnancy/index.html.
8. Centers for Disease Control and Prevention. Reporting and surveillance. 2017. [Accessed 20 Oct. 2017]. Available from https://www.cdc.gov/zika/reporting.
9. Centers for Disease Control and Prevention. Zika and blood transfusion. 2016. [Accessed 20 Oct. 2017]. Available from https://www.cdc.gov/zika/transmission/blood-transfusion.html.
10. Centers for Disease Control and Prevention. Zika in infants & children. 2017. [Accessed 20 Oct. 2017]. Available from https://www.cdc.gov/zika/hc-providers/infants-children/zika-in-infants-children.html.
11. Colt S, Garcia-Casal MN, Peña-Rosas JP, Finkelstein JL, Rayco-Solon P, et al. Transmission of Zika virus through breast milk and other breastfeeding-related bodily-fluids: a systematic review. PLoS Negl Trop Dis. 2017; 11(4):e0005528.
12. Contigiani MS, Diaz LA, Spinsanti LI. Flavivirus. In: Marcondes CB, editor. Arthropod borne diseases. Cham (Switzerland): Springer Int'l Publishing; 2017:73–88.
13. da Silva IRF, Frontera JA, Bispo de Filippis AM, Nascimento OJMD, RIO-GBS-ZIKV Research Group. Neurologic complications associated with the Zika virus in Brazilian adults. JAMA Neurol. 2017; 74(10):1190–1198.
14. Federal Aviation Administration. Item 46. Neurologic – infections of the nervous system. In: Guide for aviation medical examiners. Washington (DC): Federal Aviation Administration; 2017. [Accessed 20 Oct. 2017]. Available from www.faa.gov/about/office_org/headquarters_offices/avs/offices/aam/ame/guide.
15. Galliez RM, Spitz M, Rafful PP, Cagy M, Escosteguy C, et al. Zika virus causing encephalomyelitis associated with immunoactivation. Open Forum Infect Dis. 2016; 3(4):ofw203.
16. Galloway RL, Stoddard RA, Schafer IJ. Leptospirosis. In: CDC health information for international travel. 2017. [Accessed 20 Oct. 2017]. Available from https://wwwnc.cdc.gov/travel/yellowbook/2018/infectious-diseases-related-to-travel/leptospirosis.
17. Halstead SB. Biologic evidence required for Zika disease enhancement by dengue antibodies. Emerg Infect Dis. 2017; 23(4):569–573.
18. Holmes KK, Counts GW, Beaty HN. Disseminated gonococcal infection. Ann Intern Med. 1971; 74(6):979–993.
19. International Civil Aviation Organization. Manual of civil aviation medicine, 3rd ed. Montréal (Canada): International Civil Aviation Organization; 2012. Document 8984 AN/895. [Accessed 20 Oct. 2017]. Available from https://www.icao.int/publications/pages/publication.aspx?docnum=8984.
20. Lagunas-Rangel FA, Viveros-Sandoval ME, Reyes-Sandoval A. Current trends in Zika vaccine development. J Virus Erad. 2017; 3(3):124–127.
21. Mécharles S, Herrmann C, Poullain P, Tran TH, Deschamps N, et al. Acute myelitis due to Zika virus infection. Lancet. 2016; 387(10026):1481.
22. Merle H, Najioullah F, Chassery M, Césaire R, Hage R. Zika-related bilateral hypertensive anterior acute uveitis. JAMA Ophthalmol. 2017; 135(3):284–285.
23. Montgomery S. Cutaneous larva migrans. In: CDC health information for international travel. 2017. [Accessed 20 Oct. 2017]. Available from https://wwwnc.cdc.gov/travel/yellowbook/2018/infectious-diseases-related-to-travel/cutaneous-larva-migrans.
24. Musso D, Gubler DJ. Zika virus. Clin Microbiol Rev. 2016; 29(3):487–524.

25. Nascimento OJM, da Silva IRF. Guillain-Barré syndrome and Zika virus outbreaks. Curr Opin Neurol. 2017; 30(5):500–507.
26. Naval Aerospace Medical Institute. U.S. Navy aeromedical reference and waiver guide. Pensacola (FL): Naval Aerospace Medical Institute; 2016. [Accessed 20 Oct. 2017]. Available from http://www.med.navy.mil/sites/nmotc/nami/arwg/Pages/default.aspx.
27. Newman CM, Dudley DM, Aliota MT, Weiler AM, Barry GL, et al. Oropharyngeal mucosal transmission of Zika virus in rhesus macaques. Nat Commun. 2017; 8(1):169.
28. Oduyebo T, Polen KD, Walke HT, Reagan-Steiner S, Lathrop E, et al. Update: interim guidance for health care providers caring for pregnant women with possible Zika virus exposure – United States (including U.S. territories), July 2017. MMWR Morb Mortal Wkly Rep. 2017; 66(29):781–793.
29. Petersen LR, Jamieson DJ, Powers AM, Honein MA. Zika virus. N Engl J Med. 2016; 374(16):1552–1563.
30. Sebastián UU, Ricardo AVA, Alvarez BC, Cubides A, Luna AF, et al. Zika virus-induced neurological critical illness in Latin America: severe Guillain-Barre syndrome and encephalitis. J Crit Care. 2017; 42:275–281.
31. Shapshak P, Somboonwit C, Foley BT, Alrabaa SF, Wills T, Sinnott JT. Zika virus. In: Shapshak P, Sinnott J, Somboonwit C, Kuhn J, editors. Global virology I: identifying and investigating viral diseases. New York (NY): Springer; 2015:477–500.
32. Sotelo JR, Sotelo AB, Sotelo FJB. Persistence of Zika virus in breast milk in late stage of pregnancy. Emerg Infect Dis. 2017; 23(5):856–857.
33. U.S. Army. Standards of medical fitness. Washington (DC): Department of the Army; 2016. Army Regulation 40-501. [Accessed 20 Oct. 2017]. Available from http://www.apd.army.mil/epubs/DR_pubs/DR_a/pdf/web/AR40-501_WEB_Final.pdf.
34. Vasconcelos PF. Dengue. In: Marcondes CB, editor. Arthropod borne diseases. Cham (Switzerland): Springer Int'l Publishing; 2017:89–99.
35. Vinhaes ES, Santos LA, Dias L, Andrade NA, Bezerra VH, et al. Transient hearing loss in adults associated with Zika virus infection. Clin Infect Dis. 2017; 64(5):675–677.
36. Wolf J, Van Syoc D. Meningitis and encephalitis (June 15). In: Air Force waiver guide. Wright-Patterson AFB (OH): U.S. Air Force School of Aerospace Medicine; 2017:531–536. [Accessed 20 Oct. 2017]. Available from http://www.wpafb.af.mil/afrl/711hpw/USAFSAM/.