You're the Flight Surgeon

This article was prepared by David M. Navel, M.D., M.P.H.

You are the flight surgeon at your home station in clinic on a Monday morning. Your first patient is a walk-in reporting fever. He is a 27-yr-old loadmaster who just returned from a 3-wk humanitarian assistance mission to Guyana on Saturday. He reports going to bed feeling well last night and waking up with a subjective fever, headache, and joint pains. He denies any issues during his mission. He has been appropriately taking his atovaquone and proguanil hydrochloride (Malarone) malaria prophylaxis and took his dose this morning without issue. He states that he did not travel outside of Georgetown and that he did not eat anything raw or undercooked. He denies taking any supplements or medications other than his chemoprophylaxis for malaria. He has had no sexual contacts in the last 3 mo. He had been seen in clinic prior to leaving to ensure that all of his immunizations were updated.

His intake vitals are remarkable for an oral temperature of 103.1°F. On physical examination, the patient appears mildly ill and in obvious discomfort, but he is well-hydrated and appropriate. He states that he has been able to eat and tolerate water this morning. A thorough skin examination does not reveal any rash, but he does have occasional small excoriations and papules on his arms, which he attributes to mosquito bites. He has no conjunctival changes, normal nasal and oral mucosa, no palpable lymphedema, normal heart and lung sounds, no abdominal pain, and no joint swelling. You order a BinaxNOW® rapid diagnostic test (RDT) [Alere Inc. (Abbott), Livermore, CA, USA] for malaria through the laboratory in your treatment facility and it returns negative.

1. Which of the following should be considered in the differential?

A. Zika virus.
B. Dengue fever.
C. Chikungunya.
D. All of the above.

ANSWER/DISCUSSION

1. D. Zika, dengue, and chikungunya are all viral illnesses that can similarly present with fever and joint pain and should be considered in this febrile traveler. A quick review of pertinent resources such as the Centers for Disease Control and Prevention (CDC) travel website reveals other possible etiologies of fever, including acute human immunodeficiency virus infection, hepatitis, and typhoid fever.[3] The most common acute illnesses in Guyana remain upper respiratory infections and diarrheal illnesses.[6]

Zika virus presents with fever, joint pains, and conjunctivitis. Cases of Zika virus in many countries peaked in 2016[20] and have since declined. In Guyana, there were up to five confirmed cases per week in early 2016[11] and, although it remains on the list of potential countries, Zika virus is quite rare there now. Dengue virus is endemic in Guyana. Dengue is the leading cause of febrile illness among travelers returning from the Caribbean, South America, and South and Southeast Asia.[3] It was also ranked third in the top 40 unmitigated endemic disease threats to deployed military forces using a highly developed analytic system.[1] Chikungunya had a spike of suspected cases in Guyana in 2015, but data from 2014 and the first quarter of 2016 show that it affects approximately as many people as dengue fever in Guyana.[10] Chikungunya presents very similarly, but patients can also get frank joint swelling that persists as chronic arthritis. Other less common illnesses in travelers returning from Guyana can be found with pertinent risk factors or physical exam findings, such as water exposure with conjunctival suffusion in leptospirosis or acute human immunodeficiency virus in a sexually active individual.

When asked about his work in Guyana, the patient states that he was largely working in close quarters with others in a warm warehouse. The air conditioner there was not functioning well, so the windows and doors were kept open for ventilation. He states that the lodging room was air conditioned and that he used N,N-diethyl-meta-toluamide products at night. He doesn't know of any other sick team members, but there were two local workers who contracted fevers during his time working with them, and his team was told to report any fevers to their medical staff. A quick consultation with the medical technician who accompanied the team confirms that she was told about fevers among a few of the local workers near the end of the deployment by the local embassy liaison. On reaching back, she is able to find out that they are suspecting dengue fever in their cases.

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2. Which test should be performed at this time?

A. Complete blood count (CBC).
B. Malaria blood smear.
C. Dengue viral serology.
D. All of the above.

ANSWER/DISCUSSION

2. D. A CBC can reveal any number of abnormalities in the febrile traveler, but in dengue fever, leukopenia and thrombocytopenia help classify more severe cases. While the BinaxNOW RDT is very sensitive and specific for *Plasmodium falciparum* malaria,[7] it can miss cases where the parasite count is low and cases caused by *Plasmodium vivax* infection. Therefore, any RDT should be accompanied by a blood smear to confirm the result and to diagnose the type of malaria. RDTs can be quite beneficial in starting therapy early in austere environments and as a confirmation for *Plasmodium falciparum* malaria in laboratories where blood smears are not routinely performed. If malaria remains on the differential, testing should be repeated every few hours. Viral serology for dengue virus can provide a more definitive diagnosis and should be sought if available. Testing for viral components with polymerase chain reaction or with enzyme-linked immunosorbent assay for nonstructural protein 1 is available and can be positive immediately on presentation of fevers. Sensitivity of nonstructural protein 1 in the febrile phase of the illness can exceed 90% in patients with no prior dengue exposures.[13] Immunoglobulin M titers are also available but are often not positive until the fourth day of illness.[17] Care should be taken in interpreting serologic results, as recent immunization with another flavivirus such as yellow fever can create false positive results. An additional consideration in this case could be the tourniquet test, which has a sensitivity of 58% and a specificity of 71% for dengue fever according to one large meta-analysis.[4] It is performed by inflating a blood pressure cuff halfway between the systolic and diastolic blood pressures for 5 min. After removing the cuff, finding 10 or more petechiae per square inch is considered a positive test.

The tourniquet test returns positive. The CBC is unremarkable and his blood smear is negative. Given his testing, symptoms, and exposure history, you diagnose him with dengue fever. You notify Public Health of your diagnosis, as dengue is a reportable illness.[2]

Dengue fever is caused by any one of four dengue viruses that are single-strand ribonucleic acid viruses of the genus *Flavivirus*. It is transmitted primarily by the *Aedes aegypti* mosquito, although other *Aedes* species have been known to carry the virus in specific geographic areas. *Aedes aegypti* feeds during the day and twilight hours and can feed on multiple people in a short period of time, spreading the virus efficiently. Dengue fever, also known as break-bone fever, manifests approximately 3 to 10 d after a mosquito bite. The fever is abrupt and high, particularly in children, and it may have a biphasic course. Approximately 50 million people worldwide contract symptomatic dengue fever annually. In general, the fever subsides after 3 to 7 d and the patient recovers; however, in rare cases the illness can develop into a life-threatening syndrome of plasma leakage. This severe manifestation is more common in children.

In 1997, the World Health Organization (WHO) published guidelines on the diagnosis and management of dengue fever, dividing the illness into the categories of dengue fever and dengue hemorrhagic fever (DHF). Dengue fever is defined as fever with two or more secondary symptoms such as headache, eye pain, myalgias, arthralgias, rash, leukopenia, and hemorrhagic manifestations, including a positive tourniquet test or bleeding. Bleeding in dengue fever can be quite significant. DHF is characterized by thrombocytopenia and plasma leakage as evidenced by hemoconcentration with a 20% shift in hematocrit or by clinical signs such as pleural effusions or ascites. DHF is graded from 1 to 4, with grades 3 and 4 being characterized by some degree of circulatory failure and dengue septic shock.[18]

In 2009, WHO released a new publication and revised its definitions to alleviate misclassification of patients with significant dengue fever who did not meet the required numerical diagnosis of hemoconcentration in DHF.[13] The 2009 system classifies the illness as dengue fever, characterized as either without or with warning signs, and severe dengue fever. Warning signs include frank bleeding other than a tourniquet test, abdominal pain, persistent vomiting, clinical signs of fluid accumulation, lethargy or restlessness, hepatomegaly, or increased hematocrit with decreasing platelet counts. Severe dengue is classified as plasma leakage leading to shock, severe bleeding as determined by the clinician, or organ involvement as manifested by marked liver enzyme elevations, organ failure, or impaired consciousness.[17]

While there are nuances between the two publications, both can be used to help characterize and triage patients. In this instance, the patient meets the criteria for dengue fever by the 1997 publication or dengue without warning signs by the 2009 publication. The CDC website uses the 1997 categories when advising clinicians on the care of dengue patients.[2]

3. Appropriate management of this patient includes which of the following?

A. Intravenous fluid resuscitation.
B. Close observation.
C. Nonsteroidal anti-inflammatories.
D. Stopping the antimalarial medication.

ANSWER/DISCUSSION

3. B. The patient presented as well-hydrated, so intravenous fluids are not needed. Although caution should be used in patients with significant plasma leakage, intravenous fluids can be very beneficial to patients who are not tolerating oral fluids or those with warning signs. Nonsteroidal anti-inflammatories can worsen bleeding, so acetaminophen is preferred for fever and pains. Although the patient has had a negative blood smear, he should continue his prophylactic medication until his course is complete.

Treatment recommendations according to WHO vary depending on the patient's presentation.[19] If patients are able to tolerate oral fluids, urinating every 6 h, and do not have any warning signs, they can be managed as outpatient ambulatory patients with daily assessments. If they have warning signs, have a preexisting condition that may complicate their care such as pregnancy or renal failure, or have social conditions that may prevent them from being able to routinely return to

your clinic, then they can be referred for in-hospital management. Patients with warning signs should have their CBC measured and routinely monitored for changes. Leukopenia often precedes plasma leakage and the earliest signs of this stage of illness are typically an abrupt drop in platelets and a rise in hematocrit.

At his Friday follow-up appointment, the patient reports that his fever is going away. His temperature is 99.6°F. He states that he still feels ill.

4. Which of the following are correct for the patient at this time?

A. The time of transition from febrile to afebrile is typically the most critical and potentially dangerous time.
B. The sharp decline in fever means that the patient warrants no further medical care.
C. The patient should avoid sexual contact with others as this may spread dengue.
D. The patient should avoid donating blood for a period of time.
E. A and D.
F. A and C.

ANSWER/DISCUSSION

4. E. The patient is still at risk of significant illness. The plasma leakage that characterizes severe disease occurs typically in the first 2 d after the fever subsides. This time of illness is known as the critical phase, although the majority of patients will not have DHF and will progress into the recovery or convalescent phase following defervescence. Nevertheless, all patients during the febrile phase and immediately after should be warned to return for signs of worsening bleeding or plasma leakage such as petechia, severe abdominal pain, persistent vomiting, difficulty breathing, drowsiness, or pale clammy skin. Zika virus can be spread through sexual intercourse for up to 6 mo after infection, but not dengue. Dengue, as evidenced by only a handful of total cases, can be spread through needle sticks, organ donation, and blood donation. While endemic countries can require up to 6 mo before donating blood, most nonendemic countries like the United States require only a 4-wk deferral.[14]

Over the next couple of weeks, the patient does well and slowly returns to work. His serology returns positive for dengue virus, confirming your diagnosis.

5. The patient returns to your clinic 1 yr later to ask about his upcoming honeymoon to the Caribbean and wonders what he might do to reduce his risk of contracting dengue. What do you advise?

A. He should have immunity to all dengue viruses at this time and should not have any issues.
B. Secondary infections with dengue viruses are more likely to present with worse symptoms.
C. He should purchase a bednet with smaller 0.6-mm holes to be more effective against mosquitoes.
D. He should wear short sleeves to avoid heat exhaustion.

ANSWER/DISCUSSION

5. B. The patient may have immunity to the serotype he contracted for a year and may have heterotype immunity to other serotypes for a few months, but he will be vulnerable to a secondary infection. Subsequent infections can greatly increase the risk of DHF and severe illness. In a review of military cases of dengue fever, primary infection did not result in any cases of DHF.[8] In studies of endemic populations with similar primary DHF rates, the risk of DHF with secondary infection ranges from approximately 2–4%.[5] These overall rates are still quite low, however, and should not preclude travel to an area with the dengue virus. Bednets typically have 1.2-mm holes, which are sufficient to prevent mosquito bites if the nets are intact and used appropriately. Bednets with 0.6-mm holes are primarily used to prevent bites from sandflies or midges in areas where they are known to spread diseases such as leishmaniasis. Standard precautions like treating clothes with permethrin, using N,N-diethyl-meta-toluamide or similar products during the day, wearing long sleeves and pants, and having effective air conditioning can reduce the risk of mosquito bites.

An additional avenue of potential protection now exists through the dengue vaccine. This vaccine has been successfully tested in endemic areas but is still not recommended for travelers or military members, as they are at lower risk of contracting the illness. Updates on the availability and use of the vaccine can be found through the CDC travel websites.

AEROMEDICAL DISPOSITION

As dengue is an acute illness, there is no formal guidance either through the Federal Aviation Administration or the military services from an aeromedical perspective. Given the significant symptoms of dengue fever, however, Federal Air Regulation 14 CFR 61.53 would apply and restrict flying as long as the pilot "knows or has reason to know of any medical condition that would make the person unable to meet the requirements for the medical certificate necessary for the pilot operation."[12] Dengue fever or similar conditions are not specifically mentioned in the U.S. Navy Aeromedical Reference and Waiver Guide[9] or the Air Force Waiver Guide.[15] U.S. Army Regulation 40-501 section 2-30 (k) states that having "current residual of tropical fevers, including, but not limited to fevers, … does not meet the standard."[16] Fortunately, although the fatigue following dengue fever can last weeks, there are no long-term sequelae that should warrant application of that standard.

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Erratum

Goffeng EM, Wagstaff A, Nordby K-C, Meland A, Goffeng LO, Skare Ø, Lilja D, Lie J-AS. *Risk of fatigue among airline crew during 4 consecutive days of flight duty*. Aerosp Med Hum Perform. 2019; 90(5):466–474; DOI: https://doi.org/10.3357/AMHP.5236.2019.

There was an error in the text of the paper on p. 468 in the Methods section, Procedure subsection. The sentence "We regarded RT > 100 ms to frequent go stimuli as anticipation, and these were omitted from the analysis." should be corrected to "We regarded RT < 100 ms to frequent go stimuli as anticipation, and these were omitted from the analysis."

We sincerely apologize for the error and any inconvenience this may cause.