

DECISIONS

Fever in a returned traveller from West Africa

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A previously healthy 40-year-old man presents to his family physician's office with a 24-hour history of fever and myalgia. One week earlier, he returned to Canada from Guinea, where he was visiting family. While away, he resided in the same home as his sister and cared for her when she was experiencing fevers and a flu-like illness. He is concerned that he might have Ebola virus disease.

What causes of fever should be considered in this patient?

In addition to considering Ebola virus disease, the physician must exclude other common, life-threatening and potentially treatable causes of fever.

Ebola virus disease is a viral hemorrhagic fever caused by an RNA virus. The current outbreak, the largest to date, is active in Liberia, Sierra Leone and Guinea, with transmission to Mali. Secondary cases have occurred in Spain, Senegal, Nigeria and the United States.¹ In mid-January 2015, suspected and confirmed cases totalled 21 794, with 8683 deaths.¹

Possible causes of fever in this patient would include both travel-related infections and cosmopolitan infections that may or may not be travel-related.² It is especially important to rule out malaria, which is the most common cause of fever and severe illness in returned travellers.^{2,3} A detailed travel history should include a review of travel-related immunizations and the use of and adherence to malaria chemoprophylaxis. For a summary of common infectious diseases in sub-Saharan Africa and components of a detailed travel history, see Appendix 1 (available at www.cmaj.ca/lookup/suppl/doi:10.1503/cmaj.141146/-/DC1).

Common respiratory illnesses, including influenza (which occurs year-round in the tropics), are also a possibility.² Travellers' diarrhea and typhoid fever remain widespread. Dengue fever is uncommon though increasingly reported in this region. Meningococcal disease occurs in Guinea, a part of the "meningitis belt" of sub-Saharan Africa.³ Other infections that may pres-

ent with fever and nonspecific symptoms include viral hepatitis, arboviral infections (e.g., chikungunya), nonspecific viral syndromes such as those caused by Epstein-Barr virus and cytomegalovirus, rickettsial infections, leptospirosis, relapsing fever and other viral hemorrhagic fevers (e.g., Lassa and Marburg).⁴

Box 1 outlines the incubation period for common causes of fever in the returned traveller, an important factor in narrowing the differential diagnosis. Ebola virus disease has an incubation period of 2 to 21 days, in keeping with the timing of this patient's presentation.^{3,4}

Does this patient have risk factors for Ebola virus disease?

Ebola virus disease is contracted by humans who are in close contact with infected mammals, including other humans. The natural reservoir is unknown, although fruit bats have been implicated.⁵ Human-to-human transmission occurs through contact with infected bodily fluids (e.g., blood, saliva, stool, vomitus) or with contaminated objects.⁶ The virus enters through mucous membranes or nonintact skin. Ebola virus disease is not known to be infectious before the onset of symptoms.

This patient had travelled to an outbreak region within the past 21 days and had potential contact with bodily fluids from a person suspected of having the disease,¹ which constitutes high-risk exposure. Exposure risk stratification and approaches to the management of inadvertent exposure of health care workers are outlined in Appendix 1.

Are this patient's symptoms compatible with those of Ebola virus disease?

Compatible symptoms include fever or one of malaise, myalgia, severe headache, conjunctival injection, pharyngitis, abdominal pain, vomiting or diarrhea.¹ Unexplained hemorrhage, which occurs in less than 50% of patients with Ebola virus disease,⁵ is an independent criterion. A transient rash may develop between days 5 and 7.⁶ Ebola virus disease can rapidly progress to shock, multiorgan failure, hemorrhage and

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death, usually between days 6 and 16. The case fatality rate for the current epidemic strain, *Zaire ebolavirus*, is 55%–60%.¹ Other infections that may present with fever and hemorrhage, mimicking viral hemorrhagic fevers, include yellow fever, dengue fever, leptospirosis, meningococemia and rickettsial infections.⁴

This patient had a high-risk exposure and has symptoms consistent with Ebola virus disease,

and thus should be considered as having probable Ebola virus disease.

What tests should this patient undergo?

Returned travellers with fever should urgently undergo the initial baseline tests listed in Box 2, particularly to rule out malaria. If patients do not fulfill the risk criteria for Ebola virus disease, they can undergo all of the tests listed in Box 2.³

For this patient with probable Ebola virus disease, the physician should consult the local infection prevention and control unit or an infectious disease physician before requesting blood tests. More specifically, initial investigations should be limited, to reduce transmission risks during sample collection and laboratory testing. At this point, only methanol-fixed thin smears for malaria and rapid diagnostic tests on inactivated blood should be performed; thick smears should be avoided.³

Laboratory investigations for Ebola virus disease may show early leukopenia with late granulocytosis, thrombocytopenia, transaminitis and elevated creatinine. In the later stages, patients may develop disseminated intravascular coagulation with elevated international normalized ratio, prothrombin time and D-dimers.⁶

Testing for Ebola virus disease should be undertaken only in appropriately equipped reference laboratories. The institutional on-call hematologist, biochemist and microbiologist, as well as the infection prevention and control unit and the regional reference laboratory, should be notified to prepare for impending samples.⁷ Specimens should be placed in a leak-proof container containing an absorbent, in case of a spill.⁷ Instructions may differ depending on local procedures and should be confirmed before sample collection.

Diagnostic specimens for Ebola virus disease consist of whole blood collected in plastic tubes, stored at 4°C and submitted for viral serology, viral culture (for viral hemorrhagic fever) and polymerase chain reaction.⁷ Importantly, Filovirus is detectable by polymerase chain reaction after 72 hours of symptoms and up to 7 to 16 days thereafter.⁶ Filovirus-specific immunoglobulin M antibodies may be detectable at 48 hours after the onset of symptoms, whereas immunoglobulin G antibodies develop between days 6 and 18 of the illness.

If Ebola virus disease is suspected, what are the next steps?

This patient should be isolated. On the basis of information provided by local public health authorities, the infection prevention and control unit and/or an infectious disease consultant, the patient will likely be transferred to the nearest

Box 1: Estimated incubation period for selected causes of fever in the returned traveller^{3,4}

Cause of fever*	Incubation period, dt
Incubation < 14 d	
Malaria‡	
<i>Plasmodium falciparum</i>	6–30
<i>Plasmodium vivax</i>	8 d to 3 yr
Influenza‡	1–3
Dengue‡	3–14
Enteric fever‡	7–18
Spotted fever rickettsiae	3–21
Chikungunya	2–12
Meningococemia	2–10
Acute HIV infection	10–28
Arboviral encephalitides	3–14
Leptospirosis	7–12
Viral hemorrhagic fever	1–21§
Ebola virus disease	2–21
Incubation 14 d to 6 wk	
Malaria,‡ enteric fever,‡ spotted fever rickettsiae, acute HIV infection, arboviral encephalitides, viral hemorrhagic fever	See above
Hepatitis A	15–50
Hepatitis E	26–42
Acute schistosomiasis (Katayama fever)	4–8 wk
Amebic liver abscess	Weeks to months
Incubation > 6 wk	
Malaria,‡ hepatitis A and E, acute schistosomiasis, amebic liver abscess	See above
Tuberculosis	Primary: weeks Reactivation: years
Hepatitis B	60–150
Hepatitis C	6–10 wk
Visceral leishmaniasis	2–10 mo

*The three categories in this column are not exclusive. Some diseases appear in more than one category because of their wide range in potential incubation period (these are grouped in the first row of the second and third categories).
 †Except where indicated otherwise.
 ‡These diseases are among the most common causes of fever in the returned traveller within each category of incubation period.³
 §The incubation period varies by virus.

emergency department, which should be notified before the patient's arrival.

In hospital, the patient should be placed in standard droplet and contact isolation, with negative-pressure airborne isolation if aerosol-generating procedures, such as bronchoscopy, are anticipated.^{1,7,8} Personal protective equipment should include an N95 respirator, full face shield, single-use impermeable gown extending to overlap boot covers, double gloves and surgical hood.^{1,7,8} Alternatively, a one-piece decontamination suit may be used. An airborne isolation room should be used, if available,⁷ as these rooms generally have an ante-room in which personal protective equipment can be applied and removed. Removal of personal protective equipment should be observed by another staff member to ensure there are no breaks in protocol. Any contact with the patient should be restricted to necessary personnel, and all such contact should be logged.

If Ebola virus disease is confirmed, what treatment options are available?

There is no cure for Ebola virus disease. Treatment is supportive and includes fluids, nutritional support and antibiotics for secondary infections.⁶ Spread of the virus can be limited by use of appropriate personal protective equipment and avoidance of nonessential travel to outbreak regions. Multiple experimental therapies and recombinant vaccine candidates are in preclinical and phase 1 trials, and clinical trials will be starting within weeks. These trials will involve two experimental vaccines supported by the US National Institutes of Health, one from GlaxoSmithKline and the other from NewLink Genetics partnered with Merck. Some of the experimental therapies and vaccines have already been used emergently in health care workers.

The case revisited

The patient underwent investigations as outlined and remained isolated while awaiting results of tests for Ebola virus disease. The results of serologic and viral polymerase chain reaction tests for Ebola virus disease were negative. Malaria smears showed *Plasmodium falciparum*. The patient received atovaquone–proguanil and recovered without complication.

References

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Box 2: Initial tests for fever in the returned traveller³

Baseline tests

- Thick* and thin blood smears for malaria (two sets separated by at least six hours)
- Rapid antigen-based malaria assay (if available)
- Blood culture (two sets)
- Complete blood count (with differential)
- Serum electrolytes, creatinine and glucose
- Liver enzymes and liver function tests (with coagulation profile)
- Urinalysis

Additional tests based on symptoms and/or travel history:

- Urine culture
- Chest radiography
- Stool culture; stool ova and parasites; *Clostridium difficile* toxin
- Nasopharyngeal swab for viral polymerase chain reaction
- *Legionella* urine antigen
- Serologic tests for dengue, chikungunya, viral hepatitis

*In a suspected case of Ebola virus disease, thick smear for malaria should be avoided.

Resources for physicians: Ebola virus disease and fever in returned travellers

Centers for Disease Control and Prevention

- Update on 2014 Ebola outbreak in West Africa: www.cdc.gov/vhf/ebola/outbreaks/guinea/index.html
- *CDC Health Information for International Travel 2014* (The Yellow Book): wwwnc.cdc.gov/travel/yellowbook/2014/table-of-contents

Public Health Agency of Canada

- Fever in the returning international traveller (article in *Canada Communicable Disease Report*): www.phac-aspc.gc.ca/publicat/ccdr-rmtc/11vol37/acs-3/index-eng.php
- National case definition: Ebola virus disease (EVD): www.phac-aspc.gc.ca/id-mi/vhf-fvh/national-case-definition-nationale-cas-eng.php

Public Health Ontario

- *Ebola Virus Disease (EVD) Interim Sample Collection and Submission Guide*: [www.publichealthontario.ca/en/eRepository/Ebola_Virus_Disease_\(EVD\)_Sample_Collection_Submission_Guide.pdf](http://www.publichealthontario.ca/en/eRepository/Ebola_Virus_Disease_(EVD)_Sample_Collection_Submission_Guide.pdf)
- Screening tool for primary health care providers: www.health.gov.on.ca/en/public/programs/emu/ebola/docs/evd_primary_screening_tool.pdf

World Health Organization

- Global alert and response (GAR). Ebola in West Africa: 12-months on: www.who.int/csr/en/

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