Case Report: Imported Case of Lassa Fever — New Jersey, May 2015

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Abstract. We report a fatal case of Lassa fever diagnosed in the United States in a Liberian traveler. We describe infection control protocols and public health response. One contact at high risk became symptomatic, but her samples tested negative for Lassa virus; no secondary cases occurred among health care, family, and community contacts.

Lassa fever (LF) is a viral hemorrhagic fever (VHF) endemic to West Africa.¹ Clinical presentation can range from asymptomatic or mildly symptomatic infection to severe illness; symptoms can include fever, chills, malaise, headache, myalgias, nausea, vomiting, and diarrhea.^{2–5} Hemorrhagic symptoms occur among a minority of patients.⁵ The overall case-fatality rate (CFR) was previously estimated to be 1–3%, with a higher rate for hospitalized patients (~16%).^{2,4,5} Recent studies, however, have suggested CFR of almost 70% among patients with LF who were antigenemic at time of diagnosis.⁶ No LF vaccine exists.⁷ Treatment includes supportive care and the antiviral agent ribavirin.⁸ The LF reservoir host is *Mastomys* spp. rodents^{2,9}; infection occurs primarily through contact with infectious rodent excreta.⁵ Secondary person-to-person transmission of LF, including nosocomial transmission, can occur through contact with infectious blood or body fluids.⁵ The LF incubation period lasts up to 3 weeks.⁴

Since the discovery of Lassa virus (LASV) in 1969,¹⁰ a total of seven LF cases diagnosed in the United States have been reported among travelers from West Africa.^{11–13} We describe here the clinical presentation of the eighth case, laboratory methods used for diagnosis, infection control protocols used, and public health response.

CASE PRESENTATION AND DIAGNOSIS

In May 2015, a man aged 55 years who resided in the United States returned from a trip to Liberia. While working in diamond mines there, he had come into direct contact with rodents and rodent excreta; there was no report of rodents present in the home environment. As per the U.S. government policy at the time, he underwent enhanced entry screening at the U.S. arrival airport because he was returning from a country that experienced widespread Ebola virus disease (Ebola) transmission during the 2014–2015 epidemic. His temperature was within normal range. Plans for routine active monitoring via daily phone contact by public health authorities (PHAs) were implemented as per routine policy because the patient was returning from Liberia.

On the day following his return to the United States, the patient presented to a New Jersey hospital (hospital A) with fever, chills, myalgias, and sore throat. He had been feeling slightly unwell for a few days prior, but symptoms acutely worsened on the day of presentation. Travel to West Africa was denied. Temperature (T) was 103.1°F, blood pressure (BP) 159/79 mm of Hg, heart rate (HR) 101 beats/minute, and respiratory rate (RR) 20 breaths/minute. Physical examination revealed pharyngeal erythema with exudates and tender cervical lymphadenopathy. Abnormal initial laboratory results were as follows: hemoglobin 13.2 g/dL (normal: 13.5–17.0 g/dL), alanine aminotransferase (ALT) 88 U/L (normal: 0–45 U/L), and aspartate aminotransferase (AST) 219 U/L (normal: 0–41 U/L). The total white blood cell count and platelet count were normal. A rapid test for tonsillopharyngitis caused by *Streptococcus pyogenes* and a mononuclear spot test were negative. The patient was diagnosed with a nonspecific viral syndrome, treated with antipyretics and intravenous fluids (IVF), and discharged home the same day. On the following day, the patient was evaluated by his primary care physician and prescribed oral amoxicillin and ciprofloxacin.

Two days later, the patient returned to hospital A with persistent fever and sore throat and additionally, chest pain and anorexia. Vital signs were T 102.6°F, BP 135/81 mm of Hg, HR 129 beats/minute, and RR 20 breaths/minute; physical examination was unchanged. Laboratory findings were also similar except for ALT (600 U/L) and AST (1,347 U/L); total bilirubin was 0.4 mg/dL (normal: 0–1.0 mg/dL). A history of remote splenectomy after splenic infarction was obtained. The patient was admitted and supportive care including empirical ceftriaxone was initiated. His recent travel to Liberia and rodent exposure were disclosed to the medical personnel only after admission, which prompted transfer to a New Jersey Ebola assessment hospital (EAH) (hospital B) on hospital day 3.

Over the course of his hospitalization, the patient's fever continued and he developed lethargy and confusion. Diagnostic tests for malaria, human immunodeficiency virus, Epstein-Barr virus, cytomegalovirus, and hepatitis viruses (including hepatitis E virus) were negative; blood cultures did not identify any bacterial pathogens. On day 4 of hospitalization, the patient was intubated because of worsening hypoxemic respiratory failure thought to be due to the acute respiratory distress syndrome, although diffuse alveolar

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hemorrhage was also considered as a diagnostic possibility. By day 4 of hospitalization, AST had risen to 6,620 U/L, ALT to 2,154 U/L, the international normalized ratio to 2.2, and serum creatinine to 2.3 mg/dL (normal: 0.5–1.0 mg/dL). Detailed information about the patient's temperature and laboratory values over time is given in Table 1. The patient also developed mucosal bleeding and shock during the hospitalization. Mucosal bleeding consisted of nasal and oral oozing and passage of melanotic stool.

Viral hemorrhagic fever testing was initiated on hospital day 3 and initial results were available on hospital day 4. The diagnosis of LF was confirmed by reverse transcription-polymerase chain reaction (RT-PCR) performed at the Centers for Disease Control and Prevention (CDC). Two different RT-PCR assays were used for molecular identification of LASV in the patient's blood specimens. The first assay detects the L gene of LASV and related Old World arenaviruses¹⁴; the second assay was designed to detect the genomic S RNA of LASV.¹⁵ Additional details regarding these diagnostic assays are available in their original descriptions. After confirming the correct size of the amplified products by gel electrophoresis, the amplicons (397 and 306 base pairs in size) were purified and sequenced using traditional Sanger technology. The sequence analysis of these products was performed using the Basic Local Alignment Search Tool (<https://blast.ncbi.nlm.nih.gov>) and revealed a high degree of homology with a large variety of recent LASV isolates from Liberia. Reverse transcription-polymerase chain reaction assays for Ebola virus, Marburg virus, and Crimean–Congo hemorrhagic fever virus were also negative with results available on hospital day 4.

Lassa virus was also isolated from the patient's blood specimen. For this procedure, a 200- μ L aliquot of the patient's blood was inoculated onto a fresh monolayer of Vero-E6 cells seeded into a T25 flask. The virus was allowed to adsorb for 1 hour and was then replenished with fresh MEM medium. The monolayer was checked for cytopathic effect, and after 7 days postinfection, the cells were scraped from the flask and transferred to a glass slide. Virus antigen was detected by immunofluorescence using anti-LASV-specific antibodies.

Throughout his hospitalization, the patient received comprehensive supportive care with IVF, antibiotics (vancomycin, ceftriaxone, metronidazole, and azithromycin), blood products, and ventilatory and circulatory support. Despite these treatment measures, the patient expired on hospital day 5 from multiorgan system failure. Arrangements had been made to obtain intravenous ribavirin for LF treatment from out of state, but the patient expired before it could be administered.

INFECTION CONTROL

During the patient's initial visit to hospital A, standard precautions were used. After admission to hospital A during the patient's second evaluation there, VHF was suspected as a possible cause of the patient's illness, and strict infection control protocols were implemented. These included placement in an airborne infection isolation room and application of standard, contact, and airborne precautions. All health-care personnel used gloves, fluid-impermeable gowns, fit-tested N95 respirators, and face shields. At hospital B, the patient was placed in the hospital's biocontainment unit. Personal protective equipment used by staff included two pairs of gloves with extended cuffs, a one-piece full-body Tyvek[®] suit (DuPont, Wilmington, DE), and a powered air-purifying respirator with a self-contained filter and blower unit. Staff had received extensive prior training on proper donning and doffing procedures. Dedicated or single-use, disposable medical equipment was used for all patient-care activities at both facilities. After the patient's death, the body was kept in a refrigerated area after first being placed in a three-bag, fluid-impermeable ensemble. The second-layer bag incorporated a permanent, double heat-sealed closure. In accordance with the family's wishes, the body was buried. All procedures were performed following CDC guidance for handling human remains of VHF patients.¹⁶

PUBLIC HEALTH RESPONSE

Contact tracing was conducted for health care, family, and community contacts. All contacts were classified as high risk or low risk, according to criteria listed in Table 2. In total, 177 contacts were identified; Table 3 shows contacts stratified by type and risk level. Active monitoring was performed for 21 days (upper limit of incubation period) from the last possible exposure date for contacts at low risk and consisted of all contacts' reporting symptoms and temperature twice daily either to PHAs or to occupational health clinic or infection control staff. In addition to specified reporting times, contacts could also relay additional information about their clinical status at any time as needed. Contacts at high risk underwent direct active monitoring (similar to active monitoring with the addition of at least one report of temperature and symptoms being directly observed daily) for 21 days from the last possible exposure date; contacts at high risk were also not permitted to travel by commercial conveyance during the monitoring period. All 15 contacts at high risk were also offered postexposure prophylaxis (PEP) with oral ribavirin, an approach used previously¹⁷; PEP was declined by all eligible persons.

TABLE 1
Temperature and laboratory values for Lassa fever case-patient — New Jersey, May 2015

Day after initial medical evaluation	Max temp (°F)	WBC count (cells/mm ³)	Platelet count (cells/mm ³)	Potassium (mEq/L)	BUN (mg/dL)	Creatinine (mg/dL)	ALT (U/L)	AST (U/L)	INR
0	103.1	9,100	153,000	3.8	14	1.1	88	219	—
3	102.6	5,100	189,000	3.5	9	1.0	600	1,347	—
4	100.6	8,700	198,000	3.9	9	0.7	822	1,956	—
5	102.5	11,800	247,000	3.7	9	0.7	1,998	4,952	1.3
6	104.7	26,700	224,000	3.9	22	2.3	2,154	6,620	2.2
7	102.8	41,300	95,000	2.9	71	6.0	—	—	—

ALT = alanine aminotransferase; AST = aspartate aminotransferase; BUN = blood urea nitrogen; date of patient expiration = day 7 after initial medical evaluation; INR = international normalized ratio; Max temp = maximum temperature; WBC = white blood cell.

TABLE 2
Criteria for risk level determination for contacts of Lassa fever case-patient — New Jersey, May 2015 (adapted from CDC guidelines*)

High-risk exposures
Percutaneous exposure to potentially infectious material,† including needle-stick injuries and exposure through broken skin
Direct, unprotected contact with potentially infectious material†
Mucosal surface exposure to potentially infectious material†
Low-risk exposures
Sharing a room or vehicle within 3 feet of a potentially infectious patient without direct contact with potentially infectious material†
Providing routine medical care while using correct PPE correctly
Routine cleaning and laundering of contaminated linens and surfaces while using PPE correctly
Transport of a potentially infectious patient without direct contact with potentially infectious material† while using PPE correctly
Handling of clinical specimens while using PPE correctly
Casual skin-to-skin contact without contact with potentially infectious material†

CDC = Centers for Disease Control and Prevention; PPE = personal protective equipment.

* CDC. Epidemiologic risk factors to consider when evaluating a person for exposure to Ebola virus (www.cdc.gov/vhf/ebola/exposure/risk-factors-when-evaluating-person-for-exposure.html) [accessed January 9, 2017].

† Blood, vomitus, urine, feces, saliva, respiratory secretions, or semen.

One family contact at high risk, a woman aged 31 years, developed elevated temperature, sore throat, and myalgias on two separate occasions. Lassa fever testing by the two RT-PCR methods described earlier was negative both times. During the second evaluation, tonsillopharyngitis due to *S. pyogenes* was diagnosed with a rapid test. Each clinical evaluation took place in the biocontainment unit of another New Jersey EAH. Follow-up LASV serological testing was not performed. Because of multiple negative LF RT-PCR assays and an alternative clinical diagnosis confirmed by laboratory testing, the possibility of LF viremia below the level of RT-PCR detection was considered highly improbable.

Educational outreach was conducted for contacts about LF, modes of transmission, and risk for disease development. In addition, a wider risk communication campaign using public health forums for local communities was also conducted.

CONCLUSIONS

We have reported the eighth known travel-associated LF case diagnosed in the United States and associated infection control protocols and public health response. One challenge with diagnosing LF is its wide spectrum of clinical presentation. Initial symptoms are typically nonspecific, and a number of other illnesses, including malaria, are common causes of febrile illnesses among travelers returning from Africa. If initial evaluation is unrevealing, LF should be considered, particularly if a person has recently traveled to LF-endemic areas, especially during epidemic months (February–May) and had potential contact with animal reservoirs.⁵ In this case, travel to West Africa was not disclosed to the medical personnel until after hospital admission, causing a delay in effective diagnosis and treatment. Also, although active monitoring of the case-patient by PHAs had been

ongoing after his arrival to the United States, symptoms were also not disclosed to PHAs until after hospital admission. This case highlights the constant need for ongoing surveillance and vigilance for all types of serious pathogens, having occurred during the midst of an epidemic of a different disease, Ebola.

Proper infection control is essential to limiting secondary LF transmission. No secondary LF cases occurred among 151 health-care contacts, suggesting that infection control measures prevented nosocomial transmission. Prompt institution of comprehensive infection control measures in accordance with CDC guidance¹⁸ and immediate PHA notification are recommended for suspected VHF. Public health authorities can assist with conducting contact tracing, facilitating diagnostic testing, and arranging prompt antiviral treatment and/or PEP as indicated, both ideally offered as quickly as possible.^{8,17}

In our global, highly interconnected world, endemic diseases or outbreaks in one area can result in isolated cases or outbreaks in other areas, as the recent public health emergencies of Ebola and Zika virus disease have shown. Through close collaboration and careful elicitation of patients' travel and exposure histories, clinicians and PHAs should remain vigilant in detecting public health threats.

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TABLE 3
Description of contacts of Lassa fever case-patient by type and risk level — New Jersey, May 2015

	High risk	Low risk	Total
Type of contact			
Family or community members	13	13	26
Health-care personnel	2	149	151
Total	15	162	177

Risk level determination described in Table 2.

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