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MAJOR ARTICLE

A Case of Lassa Fever Diagnosed at a Community Hospital—Minnesota 2014

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Background. In April 2014, a 46-year-old returning traveler from Liberia was transported by emergency medical services to a community hospital in Minnesota with fever and altered mental status. Twenty-four hours later, he developed gingival bleeding. Blood samples tested positive for Lassa fever RNA by reverse transcriptase polymerase chain reaction.

Methods. Blood and urine samples were obtained from the patient and tested for evidence of Lassa fever virus infection. Hospital infection control personnel and health department personnel reviewed infection control practices with health care personnel. In addition to standard precautions, infection control measures were upgraded to include contact, droplet, and airborne precautions. State and federal public health officials conducted contract tracing activities among family contacts, health care personnel, and fellow airline travelers.

Results. The patient was discharged from the hospital after 14 days. However, his recovery was complicated by the development of near complete bilateral sensorineural hearing loss. Lassa virus RNA continued to be detected in his urine for several weeks after hospital discharge. State and federal public health authorities identified and monitored individuals who had contact with the patient while he was ill. No secondary cases of Lassa fever were identified among 75 contacts.

Conclusions. Given the nonspecific presentation of viral hemorrhagic fevers, isolation of ill travelers and consistent implementation of basic infection control measures are key to preventing secondary transmission. When consistently applied, these measures can prevent secondary transmission even if travel history information is not obtained, not immediately available, or the diagnosis of a viral hemorrhagic fever is delayed.

Keywords. contact tracing; infection control; Lassa fever; sensorineural hearing loss.

Lassa fever (LF) is a viral hemorrhagic fever caused by Lassa virus (genus *Arenavirus*). Endemic in West Africa, LF is characterized by fever, sore throat, nausea, vomiting, diarrhea, and mucosal bleeding. Eighty percent of those infected with Lassa virus experience mild or no symptoms, and 20% develop severe multisystem organ disease. The case fatality rate among hospitalized patients is 15%–20% [1]. Complications from LF include hemorrhage, disseminated intravascular coagulation, miscarriage, aseptic meningitis, encephalitis, and seizures. Temporary or permanent sensorineural hearing loss has been reported in 29% of LF patients [2].

The natural reservoir of Lassa virus is the "multimammate" rat (genus *Mastomys*). Indigenous to West Africa, infected rodents can transmit the virus to humans through contact with urine or feces. The incubation period for Lassa fever is 2–21 days. Patients infected with Lassa virus can continue to excrete the virus in their urine and semen for several weeks after recovery [3]. Secondary human-to-human transmission of Lassa virus can occur through direct contact with infected body fluids [2].

Although LF is rare, from 1969-2017, 8 imported cases of LF were reported in the United States (Table 1) [1, 4, 5]. Of these, LF was not suspected in 5 patients until health care was sought in the United States [1, 5, 6]. On April 1, 2014, a case of LF was diagnosed at a community hospital in Minnesota. We describe the patient's clinical course and the public health response.

CLINICAL CASE DESCRIPTION

A 46-year-old Liberian American traveled from Minnesota to Liberia on December 12, 2013, to visit family. On March 24, 2014, he developed fever, nausea, vomiting, and diarrhea. He was hospitalized for 2 days in Monrovia and discharged home. On March 26, he was re-admitted to the hospital with worsening symptoms. At this visit, he was noted to be in acute renal failure with serum

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Table 1. Imported Cases of Lassa Fever to the United States

Year of Import	From	To	Medical Evacuation	Clinical Outcome
1969 [19]	Nigeria	New York, NY	Yes	Survived
1976 [20]	Sierra Leone	Washington, DC	Yes	Survived
1989 [6]	Nigeria	Chicago, IL	No	Died
2004 [5]	Liberia, Sierra Leone	Trenton, NJ	No	Died
2010 [1]	Liberia	PA	No	Survived
2014	Liberia	Minneapolis/St. Paul, MN	No	Survived
2015 [5]	Liberia	Trenton, NJ	No	Died
2016 [21]	Togo	Atlanta, GA	Yes	Survived

creatinine values up to 10 and was advised to return to the United States for care. On March 30, 2014, the patient traveled unaccompanied via commercial aircraft from Liberia to Accra, Ghana. In Ghana, he boarded a commercial flight for New York and arrived at John F. Kennedy International Airport (JFK) on March 31. His next flight from JFK to Minneapolis–St. Paul International Airport (MSP) arrived that same day. The flight crew and several passengers seated near the patient on the New York to Minneapolis flight noted that he appeared disoriented and required assistance finding his seat and fastening his seatbelt. When the patient failed to meet his family at the arrivals terminal at MSP, his family contacted security. Airport security found the patient sitting on a chair in the terminal hallway, confused. He was transferred by ambulance to a community hospital for evaluation.

On examination in the emergency department, the patient had a temperature of 99.1°F, pulse of 172 beats/min, blood pressure of 141/87 mmHg, and oxygen saturation of 98% on room air. His physical examination was notable for confusion and generalized abdominal pain without hepatosplenomegaly. He had no evidence of skin rashes, petechiae, or hemorrhage. Initial laboratory data showed leukocytosis, thrombocytopenia, elevated transaminases, and renal failure (Table 2). Urinalysis revealed occult blood and elevated protein. Lumbar puncture revealed a white blood cell count of 32 mm^3, (96% monocytes, 1% lymphocytes), protein level of 50 mg/L, and glucose level of 114 mg/dl. No organisms were seen on cerebrospinal fluid gram stain. A blood smear was negative for malaria and babesia.

The patient was admitted to the intensive care unit (ICU) on March 31, 2014, for emergent hemodialysis and was empirically started on intravenous methylprednisolone for rapidly progressive glomerulonephritis [1]. The following morning, he developed bleeding from the nose and mouth, and his platelet count dropped to $53 \times 10^3/mm^3$. Due to a report of 2 confirmed cases of Ebola virus disease in Liberia [7], a diagnosis of viral hemorrhagic fever was considered, and the patient was placed on contact, droplet, and airborne precautions; the Minnesota Department of Health (MDH) was notified.

Blood samples collected on hospital day (HD) 2 were sent to the Centers for Disease Control and Prevention (CDC) and tested positive for Lassa virus RNA by reverse transcriptase polymerase chain reaction (RT-PCR) 9 days after illness onset [8]. Based on the sequence of the diagnostic RT-PCR fragment, a real-time RT-PCR (qRT-PCR) was designed. This was done to improve sensitivity and to allow the semi quantitative monitoring of viral RNA level's in the patient's blood and urine specimens [8].

Lassa IgM and IgG titers were measured by enzyme-linked immunosorbent assay (ELISA). Viral RNA levels in the blood remained relatively stable for the first 10 days of hospitalization and started declining rapidly once Lassa IgG antibodies were

Table 2. Clinical Laboratory Testing

Hospital day	1	2	5	11	15	17
White blood cell count, per mm^3	11.7	7.1	13	7.1	ND	7.1
Hemoglobin, %	15.6	11.8	12.6	ND	ND	ND
Platelet count, per mm^3	107	53	141	160	ND	ND
Sodium, mmol/L	133	136	140	135	129	131
Potassium, mmol/L	5.8	5	4.2	4.1	4.7	4.3
Urea nitrogen, mg/dl	164	120	87	69	77	68
Creatinine, mg/dl	23.33	15.34	6.71	3.43	3.41	2.87
Glucose, mg/dl	172	NA	NA	NA	NA	NA
Alanine aminotransferase, U/L	119	119	60	91	60	ND
Aspartate aminotransferase, U/L	349	230	163	235	128	ND
Total bilirubin, mg/dl	3	2.4		1.3	1	ND
Albumin, g/dl	3.2	2.8	3.1	3.7	3.6	3.5
Prothrombin-time international normalized ratio	1.2	1.3	1.2	ND	ND	ND

Abbreviations: NA, test result not available; ND, test not performed.

detectable. Lassa virus RNA was also detected in serial urine samples collected starting on HD 5, and urine had a higher viral load than blood samples on several consecutive days, as indicated by the lower Ct values of the qRT-PCR assay (Table 3).

With supportive care, the patient's clinical status gradually improved, and hemodialysis and methylprednisone were discontinued on HD 4. On HD 14, the patient was discharged from the hospital after 2 successive blood samples, collected 24 hours apart, tested negative for the presence of Lassa virus RNA. Viral RNA continued to be detected in the urine, but not in the blood, for several weeks after hospital discharge (Table 3).

On HD 5, the patient complained of bilateral hearing loss. Otolaryngology consultation and evaluation revealed normal external auditory canals and tympanic membranes bilaterally. In an effort to recover some of the presumed sensorineural hearing loss (SNHL), on HD 5, the patient received 60 mg of prednisone orally. On HD 6, he received bilateral intratympanic injections of methylprednisolone 40 mg/mL via 2 puncture myringotomies at the bedside. Audiometric testing on HD 8 demonstrated profound bilateral SNHL with responses to all frequencies at 90 dB or greater, and only vibro-tactile responses below this frequency. Due to a lack of clinical improvement and discomfort from the intratympanic injections, the procedure was not repeated. The patient received 3 additional doses of oral prednisone 60 mg on HDs 7, 8, and 9 without any subjective improvement in hearing. Tympanometry testing after hospital discharge revealed normal tympanograms. Computed tomography of the temporal bones was also normal. Repeat audiometric testing confirmed total SNHL with no evidence of improvement, and the patient was referred to a cochlear implant center.

INFECTION CONTROL

On admission to the ICU, the patient was placed on standard precautions. When the diagnosis of viral hemorrhagic fever was first considered, before the diagnosis was confirmed, infection control measures were upgraded to include contact, droplet, and airborne precautions in addition to standard precautions. Hospital infection control personnel and MDH personnel reviewed infection control practices with health care providers (HCPs) to include limiting the number of HCPs caring for the patient, maintaining of a log to document all persons entering the patient room, personal protective equipment (PPE) used, and PPE supply. PPE for all HCPs caring for the patient included fluid-resistant gowns, N95 respirators, face shields, and a single pair of gloves. In addition, MDH personnel and hospital infection control personnel met with laboratory personnel to review laboratory practices and laboratory testing, including point-of-care testing capabilities. Medical waste and patient linens were handled per usual hospital protocols.

At the time of discharge from the hospital, the patient continued to have detectable levels of Lassa virus RNA in his urine. MDH personnel traveled to the patient's home to discuss home care measures to minimize exposure to household members. Home care measures included identifying a separate bathroom in the home that would only be used by the patient, sitting while urinating to minimize splashing, closing the toilet lid before flushing, and frequent cleaning and disinfection of surfaces likely to become contaminated and where others might have contact (eg, toilets and bathroom surfaces) with low- or intermediate-level household disinfectants. Caregivers were provided disinfectants and disposable examination gloves and instructed to wear the gloves when cleaning or handling items that could have been soiled with the patient's blood, urine, semen, or respiratory secretions. These measures were continued until Lassa virus RNA was no longer detected by RT-PCR in the patient's urine. In addition, because of the potential presence of virus in the semen, the patient and his wife were provided condoms and instructed to avoid unprotected sexual intercourse for 3 months.

CONTACT TRACING

MDH worked to identify family members who may have had contact with the patient or his body fluids while he was ill.

Table 3. Diagnostic Testing for Lassa Virus

	HD 2	HD 5	HD 8	HD 10	HD 12	HD 14	HD 15	8 d Post	16 d Post	30 d Post	51 d Post
Blood RT-PCR Ct value[a]	30.1	32.3	32	34	37.2	Neg	Neg	Neg	Neg	Neg	Neg
Urine RT-PCR Ct value[a]	ND	26.3	25.3	25.3	25.5	26.8	25.8	31.7	35.1	35.0	Neg
IgM titer, sum OD[b]	≥1600, 4.25	≥6400, 4.85	≥1600, 4.33	≥6400, 4.48	≥1600, 4.52	≥6400, 4.53	≥6400, 4.54	≥6400, 4.55	≥1600, 4.11	≥1600, 3.82	≥1600, 3.19
IgG Titer, sum OD[c]	<100, .06	<100, .00	<100, .63	<100, .37	≥400, 1.32	≥1600, 1.41	≥1600, 1.61	≥1600, 1.38	≥1600, 1.53	≥400, 1.77	≥1600, 1.45
Urine virus isolation	ND	Pos	ND	Neg	ND	ND	ND	Neg	ND	ND	ND

Abbreviations: HD, hospital day; NA, test result not available; ND, test not performed; Neg, negative; OD, optical density; Pos, positive; RT-PCR, reverse transcriptase polymerase chain reaction.

[a]To be considered positive, the Ct value for each target should be less than 40.

[b]To be considered positive for IgM, the titer should be ≥1:400 and the sum OD should be ≥0.45.

[c]To be considered positive for IgG, the titer should be ≥1:400 and the sum OD should be ≥0.95.

Persons who reported contact with the patient were categorized into high-, low-, or no-risk exposure on the basis of several criteria (Table 4). In total, 5 family members reported contact with the patient or his body fluids while he was ill. Of these, 2 were classified as having high-risk exposure. High-risk exposures included brushing the patient's teeth, feeding the patient, and wiping sweat and blood off the patient's face without appropriate PPE. One family member was classified as having low-risk exposure to the patient; 2 family members were classified as having no risk.

MDH worked with the hospital to identify health care workers who may have had contact with the patient or his body fluids. A total of 151 health care contacts were identified. Of these, 4 were classified as having high-risk exposures to the patient. A total of 33 health care contacts were classified as having low-risk exposure to the patient (Table 5).

The CDC's Division of Global Migration and Quarantine (DGMQ) worked with MDH and other state and jurisdictional public health authorities to identify persons who had travel-related contact with the patient while he was ill. Passenger interviews were conducted by state or jurisdictional health departments, with CDC assistance as requested, based on contact locating information (such as address or phone number), and were voluntarily reported back to DGMQ. Interviews of flight crew members were conducted by the airline's occupational health department.

In total, DGMQ identified 14 passengers seated within 6 feet of the patient during his domestic and international flights. Of these, 8 reported no contact with the patient or his body fluids and were classified as low risk based on their proximity to the patient. The remaining 6 passengers could not be located. In total, 7 pilots and 18 flight attendants were interviewed. None of the flight attendants working in the main passenger cabin identified exposure to the patient or his body fluids and were classified as low risk. All 7 pilots reported being separated from the passengers during flight and were classified as no risk.

Twelve airport personnel who assisted the patient on arrival to John F. Kennedy International Airport were identified. Eleven were interviewed, and of these, 3 were classified as low risk and 8 were classified as no risk. One airport staff member, a Transportation Security Administration (TSA) agent who screened the patient on arrival to JFK, could not be identified and was not interviewed. However, as all TSA employees are required to wear gloves when screening passengers, this person was classified as no risk (Table 5). Four airport personnel who assisted the patient on arrival to the Minneapolis–St. Paul International Airport were also identified and interviewed. Of these, 3 were classified as having low-risk exposure to the patient and 1 was classified as no risk (Table 5). Additionally, 5 emergency medical service staff responded to the patient at MSP. All 5 were interviewed; 3 were classified as low risk and 2 were classified as no risk.

All persons with high- and low-risk exposures were monitored for fever (oral temperature ≥101°F) for 21 days after their last known contact with the patient. Hospital employees were instructed to take their temperatures twice a day using a digital oral thermometer and call into a designated hotline at the hospital's employee health section to report their temperatures. Contacts who were not hospital employees were instructed to take their temperature using a digital oral thermometer and record the results into a temperature log. Once a week, they were asked to e-mail/fax the log to MDH. No restriction was placed on work or movement for asymptomatic contacts. Upon completion of the 21-day follow-up, no secondary cases of LF were identified among the 75 high- and low-risk contacts.

Table 4. Level of Risk Related to Exposure to a Patient With Lassa Fever and Action, by Category

Risk Category	Description	Action
High risk	• Exposure from a percutaneous injury (eg, a needlestick or cut with a sharp object) to potentially infectious tissue or bodily fluids • Mucosal exposure (eg, eyes, nose, or mouth) to splashes or droplets of potentially infectious body fluids[a] • Intimate contact (kissing, sex) with a symptomatic patient	Informed of risk 21-day fever monitoring Given Lassa fever factsheet
Low risk	• Sitting in a vehicle/airplane within close proximity (ie, 6 ft) of a symptomatic patient • Providing routine medical care without using PPE appropriately (gloves, surgical mask, gown) in the absence of percutaneous injury or mucosal exposure to potentially infectious tissue or bodily fluids[a] • Routine cleaning and laundry of contaminated linens and surfaces without using PPE (gloves) appropriately in the absence of percutaneous injury or mucosal exposure to potentially infectious tissue or bodily fluids[a] • Processing of routine laboratory samples without using PPE (gloves) appropriately in the absence of percutaneous injury or mucosal exposure to potentially infectious tissue or bodily fluids[a]	Informed of risk 21-day fever monitoring Given Lassa fever factsheet
No risk	• No contact with a symptomatic patient • Casual contact with a symptomatic patient • Providing routine medical care while using PPE (gloves, gown, surgical mask) appropriately • Routine cleaning and laundry of contaminated linens and surfaces while using PPE (gloves) appropriately • Processing routine laboratory samples while using PPE (gloves) appropriately	Informed of absence of risk Given Lassa fever factsheet

Abbreviations: PPE, personal protective equipment.

[a]Potentially infectious bodily fluids: blood, saliva, vomitus, urine, stool, semen.

Table 5. Categorization of Contacts of a Patient With Lassa Fever

Contact Type	High Risk	Low Risk	No Risk	Unable to Contact	Total
Family	2	1	2	0	5
Hospital staff	4	33	114	0	151
Emergency medical service	0	3	2	0	5
JFK Int'l Airport staff	0	3	9[a]	0	12
MSP Int'l Airport staff	0	3	1	0	4
Kotoka Int'l Airport staff, Accra, Ghana	0	0	3	0	3
Flight crew	0	18	7	0	25
Airline passengers within 6 ft	0	8	0	6	14

[a]Transportation Security Administration agent.

DISCUSSION

This report describes a case of imported LF in a traveler returning from Liberia whose illness course was complicated by renal failure and near complete bilateral sensorineural hearing loss. Intravenous ribavirin has been shown to reduce LF mortality if it is administered within 6 days of illness onset [9]. As LF was not suspected in this patient until 9 days after illness onset and he was clinically improving at the time of laboratory confirmation, intravenous ribavirin was not initiated.

Oral ribavirin has also been studied as a postexposure measure for LF. There are no published reports on the efficacy of ribavirin postexposure prophylaxis (PEP) in humans. However, animal data have shown efficacy when administered early [10, 11]. A review of the literature advised against liberal use of ribavirin for PEP due to the low secondary attack rate of LF; concerns about reaching the minimum inhibitory concentration at tolerable doses; and the frequency of adverse side effects following ribavirin administration. Instead, it was recommended that ribavirin PEP be restricted to those with high-risk exposures [12]. Contacts of the patient presented here with high-risk exposures were offered oral ribavirin PEP, and all refused.

International tourist arrivals to the United States have shown continued growth—from 25 million in 1950 to 75.6 million in 2016 [13]. The number of US citizens traveling internationally is also growing; between 1996 and 2015, the number of US citizens traveling to Africa alone has more than doubled [14].

The ease and frequency of international travel have also resulted in the unintentional importation of disease. Since 1989, 3 viral hemorrhagic fevers transmissible person-to-person have been unintentionally imported to the United States: Lassa [1, 5], Marburg [15], and Ebola [16]. Given the nonspecific presentation of viral hemorrhagic fevers, early identification and isolation of ill travelers, consistent implementation of basic infection control measures, and prompt notification of public health authorities are the keys to preventing secondary transmission.

Early identification strategies include eliciting a travel history from all patients who present for care and posting signs and placards asking patients with recent international travel to self-identify. Those patients with recent international travel who present in a health care facility with symptoms concerning for a viral hemorrhagic fever should be promptly isolated by placing them in a private room or a separate enclosed area with a private bathroom or covered bedside commode. To minimize disease transmission risk, only essential HCPs wearing appropriate PPE should evaluate the patient and provide care. Prompt notification of the health care facility's infection control program and state and local health departments is also key. Finally, consideration of a viral hemorrhagic fever should not delay diagnostic assessments or therapeutic interventions as other medical conditions may be more likely. Between July 9 and November 15, 2014, during the height of the EVD outbreak in West Africa, 61 returning international travelers were tested for Ebola virus at the CDC's recommendation or by health department request. One tested positive for Ebola virus [17,18].

Regardless of travel history, HCPs should adhere to basic infection control measures such as hand hygiene and the appropriate selection and utilization of PPE, specifically appropriate donning and doffing of equipment. When consistently applied, these basic infection control measures can prevent secondary transmission even if travel history information is not obtained, not immediately available, or the diagnosis of a viral hemorrhagic fever is delayed.

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