



PRACTICE

CLINICAL UPDATES

Lassa fever

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Lassa fever is part of a group of conditions known as viral haemorrhagic fevers. Viral haemorrhagic fevers can be caused by viruses from several different families, all of which have the potential to cause disease with haemorrhagic features.¹

Lassa fever—caused by infection with the Lassa virus—is named after the town in Nigeria where the first identified cases occurred. The natural reservoir of the Lassa virus is the multimammate rat (*Mastomys natalensis*), a rodent found commonly in rural areas of tropical Africa that often colonises in or around human homes where food is stored.

Who gets it?

Lassa fever is endemic in parts of West Africa, including Sierra Leone, Liberia, Guinea, and Nigeria (fig 1⇓). There also is evidence of endemicity in neighbouring countries.²⁻⁴

The Centers for Disease Control and Prevention (CDC) has estimated the number of Lassa fever cases per year in West Africa to be between 100 000 and 300 000, with approximately 5000 deaths.⁵ Other studies have reported this figure to be closer to between 300 000 and 500 000 cases per year in West Africa.⁶ Unfortunately, estimates are crude as surveillance for cases is not uniformly performed. In some areas of Sierra Leone and Liberia, there is evidence that 10-16% of people admitted to hospitals every year have Lassa fever.^{4,5}

People of all ages are susceptible and the clinical disease course is variable, ranging from mild non-specific symptoms (such as fever and malaise) to haemorrhagic fever and death. The overall case fatality rate among people infected with Lassa virus is 1%,^{4,5} but the observed case fatality among hospitalised patients is reported to be up to 65-70%.^{7,8}

What causes it?

The Lassa virus is a member of the Arenaviridae family, a group of viruses generally associated with rodent-transmitted diseases in humans.⁹

Transmission of the virus from rodent to human occurs via multiple routes. These include: human ingestion of excreta from

an infected rodent; butchering and eating infected rodents (subsistence farmers routinely encounter the rodent when burning their fields ahead of planting and consider it a cheap source of protein); viral exposure to open cuts or sores; or less likely, the inhalation of air contaminated with infected rodent excretions (for example, aerosolisation of rat excreta during sweeping).⁴⁻¹⁰ Infected rodents are asymptomatic and shed the virus in urine throughout their life.

Human-to-human transmission is less common than rodent to human transmission and occurs via direct contact with blood, tissue, secretions, or excretions of an infected individual.¹⁰ This is mainly seen in hospitals where protective equipment is not available or inappropriately used by healthcare staff and transmission has been attributed to the re-use of needles between patient.⁸ Transmission to close contacts usually occurs only in symptomatic patients and is not associated with casual contact such as hugging, shaking hands, or sitting near someone.³

Can Lassa fever be prevented?

Vaccination

Currently, there are no vaccines for Lassa virus licensed for use in humans and, although some have shown promise, no vaccine candidate has shown enough efficacy in animal models to have entered phase I human studies. The World Health Organization has issued desirable criteria for candidate Lassa virus vaccines (www.who.int/blueprint/what/research-development/Lassa_Virus_Vaccine_TPP.pdf).

Preventing animal-to-human transmission

In endemic areas, avoiding contact with the multimammate rat and its excreta is the main method for primary prevention. The following measures are recommended for people in endemic areas to discourage rodents from entering the home^{4,5}:

- Store foodstuff, including water, in rodent-proof containers
- Dispose of waste far from the home
- Maintain a clean home

What you need to know

- Lassa fever is a viral haemorrhagic fever endemic in West Africa
- It is predominantly asymptomatic or results in mild febrile symptoms (about 80% of cases). Severe symptoms (such as haemorrhage, respiratory distress, repeated vomiting, facial swelling, shock) occur in around 20% of cases. Overall mortality is around 1%, but observed case fatality rate among hospitalised patients is reported to be up to 70%
- Symptoms of Lassa fever can be difficult to distinguish from malaria and typhoid; therefore, other potentially serious illnesses should be considered in an individual returning from an endemic area with an appropriate history
- Diagnosis is entirely dependent on an accurate history and an understanding of the geography of the disease, supported by laboratory investigations
- Management involves early recognition of infection, effective isolation and infection control, early initiation of the antiviral drug ribavirin, and supportive care in hospital
- Ribavirin is occasionally used as post-exposure prophylaxis for high risk exposure to Lassa virus

- Place rat traps around the home and dispose of dead rodents using a plastic bag to avoid direct contact with the carcass
- Keep cats or non-poisonous snakes
- Cook all foods thoroughly
- Avoid rodent meat as a food source.

Contact tracing of individuals and post-exposure prophylaxis

People who have travelled with, lived with, or cared for an individual with Lassa fever within the past 21 days and who are asymptomatic should be traced and assessed, and provided with post-exposure prophylaxis with ribavirin if they meet criteria for high risk exposure.¹⁰ These criteria are:

- Penetration of skin by a contaminated instrument
- Exposure of mucous membranes or broken skin with blood or bodily secretions from an infected individual
- Participation in emergency procedures (such as resuscitation) without the use of appropriate personal protective equipment
- Prolonged and continuous exposure to a patient with Lassa fever in an enclosed space without use of appropriate personal protective equipment.

These individuals should be monitored for the duration of the incubation period (21 days) in order to ensure rapid recognition of symptoms followed by immediate isolation.

The WHO has produced guidance on contact tracing for Ebola virus, and this can be followed for Lassa fever.¹¹

Exposure risk

Lassa virus has been detected in the blood, urine, throat swabs, and cerebrospinal fluid of patients,^{12,13} and sexual transmission has been suggested.⁴ Although there is little evidence, it has been suspected that patients can excrete virus in urine for between three and nine weeks after disease onset, and in semen for up to three months; thus, it has been recommended that sexual intercourse should be avoided until three months after recovery.³

If exposure to body fluids from a patient with suspected infection has occurred, the person should immediately wash affected skin surfaces with soap and water, and irrigate mucous membranes with copious amounts of water. The patient's home and any personal belongings that could have been contaminated (such as clothes, linens, eating utensils, and medical material) should be appropriately disinfected (such as sprayed with 0.5% chlorine solution in epidemic areas) or disposed of by incineration. Safe burial practices are essential but are not always culturally accepted, and this continues to be a challenge.

How is Lassa fever diagnosed?

Lassa fever is a notifiable disease in many countries. For example, in the UK suspected and confirmed cases should be reported to Public Health England (PHE), and in the US to the Centers for Disease Control and Prevention (CDC).

Diagnosis of Lassa fever is based on clinical suspicion, history, and physical examination, with laboratory testing to confirm diagnosis. Early suspicion of exposure, and rapid testing to identify cases of Lassa fever are critical to the management of the infection and prevention of onward transmission.

History

A detailed history (including a comprehensive travel history) should be taken to determine the risk of Lassa fever. This is particularly important in order to establish the level of protection required for healthcare workers and laboratory staff.

In non-endemic countries, cases are likely to be those returning from travel or work in endemic areas; therefore, up-to-date maps of areas where there is current Lassa transmission are essential. Promed is a useful resource for up-to-date notifications internationally (www.promedmail.org)

Attention should also be paid to the seasonality of transmission. In Nigeria, there are outbreaks of Lassa fever nearly every year throughout the country, with peaks between December and February (dry season). In Sierra Leone, the peak season is the height of the dry season (February to March) with a smaller peak in December.⁷

Malaria and typhoid are usually endemic in areas where Lassa fever is found, and the history should include an assessment for malaria and typhoid risk.

What are the symptoms and signs?

Lassa fever can present in multiple different ways, but is asymptomatic or offers mild symptoms (including fever, malaise, headache, and chest pain) in about 80% of cases.⁴

Fever was noted in all of 441 patients admitted with Lassa fever to one hospital in Sierra Leone.¹⁴ Over 70% of these patients also experienced chest pain, diarrhoea, vomiting, and headache. However, fever may not be continuous; therefore, being afebrile on presentation does not rule out Lassa fever. Owing to the variation and non-specific nature of signs and symptoms associated with Lassa fever, clinical diagnosis may be difficult.

Hearing loss or impairment is a unique sign that may be useful for diagnosis. It was shown to occur in around 29% of 49 acutely febrile patients with confirmed Lassa fever in Sierra Leone.¹⁵ It has also been seen as a late consequence in survivors.¹⁴

There is no classic skin rash in patients with Lassa fever, and subcutaneous bleeding (ecchymoses or petechiae) is not

commonly seen, but oedema of the face, neck, and jaw have been described.¹⁴

A reduced Glasgow Coma Scale score or seizures may indicate Lassa fever encephalopathy.¹⁶

In late presentation or deterioration, bleeding (17%) and effusions (3%) have been reported, the latter being linked to proteinuria.¹⁴

Initial investigations

Individuals admitted with fever and recent (within 21 days) travel to an endemic or epidemic area for Lassa fever should be assessed according to national protocols (see box 1).

The initial investigation in all suspected patients should be reverse transcription-polymerase chain reaction (RT-PCR) for Lassa virus. The highest viraemia occurs four to nine days after the onset of symptoms.¹⁸ Serological testing using IgM enzyme linked immunosorbent assay (ELISA) should also be carried out. IgM ELISA has 88% sensitivity and 90% specificity for acute infection.¹⁹

If the initial laboratory investigations are negative and clinical suspicion remains high, repeating the laboratory investigations after 24 hours could be considered.

RT-PCR and IgM ELISA may not be available in some endemic areas where resources are limited. To address this, the ReLASV Antigen Rapid Test has been developed as a rapid diagnostic test for Lassa fever for bedside use in resource-limited regions.⁶

Lassa fever is usually co-endemic with malaria and typhoid; therefore, a rapid diagnostic test for malaria should be carried out immediately, along with blood cultures for typhoid.

Further investigations

Other investigations to consider are listed in box 2.

How is Lassa fever managed?

Management approach

The mainstay of treatment is early recognition of infection coupled with effective isolation, early initiation of the antiviral drug ribavirin, and best available supportive care in a hospital setting (see infographic for details).

Isolation and personal protective equipment

If infection is suspected, the patient should be isolated, and all healthcare workers in contact with the patient should wear personal protective equipment. The WHO, CDC, and UK Department of Health have produced detailed guidance on personal protective equipment for viral haemorrhagic fevers, including Ebola, and these should be followed for Lassa fever.²³⁻²⁷

Antiviral treatment

In the treatment of Lassa fever, intravenous ribavirin has been shown to reduce mortality from 55% to 5% if administered within the first 6 days of illness.²¹ However, there has been only one published trial of ribavirin in treating Lassa fever in humans, which had limited testing of dose.²¹ Side effects include haemolytic anaemia and infusion-related reactions such as rigors. When used as post-exposure prophylaxis, side effects, particularly at the dose required to achieve theoretical efficacy, may be severe and often leads to poor adherence with treatment.²⁸

Box 3 lists some potential future treatments for Lassa fever.

Symptom management

Pain and fever should be managed with a simple analgesic/antipyretic such as paracetamol. An opioid analgesic can be used if pain is severe, but non-steroidal anti-inflammatory drugs including aspirin should be avoided because of their associated increased risk of bleeding.

Bleeding is seen in around 17% of hospitalised patients with Lassa fever, although in one large study Lassa fever was identified in 74% of patients who were admitted to a hospital in Sierra Leone with bleeding.¹⁴ Thrombocytopenia should be corrected with platelet transfusion if there is bleeding. Coagulation deficits are uncommon but should be corrected with blood products (such as fresh frozen plasma, cryoprecipitate) as necessary. Blood transfusion is reserved for patients who are anaemic and who have ongoing bleeding.

Intravenous fluid and electrolyte management

Diarrhoea is experienced during the course of the illness in about 50% of cases.¹⁴ Patients with significant diarrhoea should have regular assessment of their electrolytes, with replacement provided as necessary. Intravenous fluids should be commenced and titrated to maintain adequate volume status in patients requiring admission to hospital.

What is the prognosis?

The overall death rate from Lassa fever is around 1%.^{4,5} Among hospitalised patients, the case fatality rate has been quoted as between 15% and 70%, with higher numbers reported during large outbreaks (50%)⁵ or in patients presenting to a Lassa fever hospital with a positive Lassa virus antigen test (65-70%).⁷ Death usually occurs within 14 days of onset in fatal cases. The case fatality rate in children admitted to one hospital in Sierra Leone was 27%,³¹ and a higher mortality was seen in those aged <29 years compared with older patients.⁷ A higher case fatality rate has also been seen in pregnant women infected in the third trimester with maternal death or fetal loss occurring in more than 80% of cases.⁴⁻³²

Box 4 lists the main complications of Lassa fever.

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Box 1: Laboratory testing for Lassa fever

If laboratory testing is indicated, blood sample collection, packaging, and transport should be carried out according to national protocols, while the patient remains isolated and personal protective equipment is used by healthcare workers. Specimens should be sent to a laboratory that is suitably equipped to handle biosafety level 4 pathogens. Furthermore, specimens should be sent only once a full risk assessment has been carried out and after discussions with the laboratory (to alert them of potentially biohazardous material) in order to minimise risk of nosocomial transmission. In the UK, suspected cases should be discussed with the Imported fever service¹⁷

Box 2: Possible further investigations

- *Renal function and serum electrolytes*—Moderately elevated creatinine has been seen in patients with Lassa fever, probably indicating dehydration or damage from elevated creatine kinase¹⁴
- *Blood lactate or arterial blood gases*—Blood lactate, arterial or venous pH, and bicarbonate can be used to indicate tissue hypoperfusion and guide fluid management in patients with Lassa fever
- *Full blood count*—An elevated haematocrit is seen, usually indicative of dehydration. Thrombocytopenia has been described²⁰
- *Coagulation studies*—Coagulation should be measured and corrected as necessary
- *Liver function tests*—Elevated alanine transaminase levels have been noted and associated with worse outcome²¹
- *Chest x ray*—A chest x ray should be done to look for pleural or pericardial effusion
- *Urine analysis*—Urine analysis should be done to screen for proteinuria
- *Blood cultures*—Blood cultures may be helpful in the identification of other causes of sepsis (such as deep abdominal infection, upper urinary tract infection, endocarditis, or discitis)
- *Lumbar puncture*—Encephalopathy is quite common among symptomatic patients who present after more than six days of symptoms. However, detection of Lassa virus RNA in cerebrospinal fluid has been rarely reported, since lumbar puncture risks healthcare worker exposure and is unlikely to alter the management of patients with confirmed Lassa fever.¹⁶
- *Ultrasonography*—Could be considered for the investigation of intraperitoneal fluid and pericardial effusion²²

Box 3: Emerging treatments for Lassa fever

- *Monoclonal antibodies*—Monoclonal antibodies targeting the viral glycoprotein on the Lassa virus have been tested in animal models (guinea pigs), in which they have shown protective efficacy when given shortly after exposure. This requires further study²³
- *Favipiravir*—Developed as an antiviral drug for influenza, it was used experimentally to treat Ebola haemorrhagic fever during the epidemic in West Africa. It has shown synergistic activity in vitro against Lassa virus in combination with ribavirin and improved survival in mouse models³⁰

Box 4: Complications of Lassa fever?*High likelihood, short term complications*

- Spontaneous abortion and fetal mortality in pregnant women

Medium likelihood, long term complications

- Deafness (sensorineural)—Seen in approximately 25% of patients who survive the disease and can be permanent¹⁵

Low likelihood, long term complications

- Neuropsychiatric sequelae—Includes sleep disturbance, psychosis, hallucinations, and depression³³
- Transient hair loss
- Gait disturbance
- Polyserositis

Resources for healthcare professionals: Treatment guidelines*Europe*

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Sources and selection criteria

We searched PubMed using the MeSH term Lassa virus. Epidemiological information was gathered from World Health Organization (WHO), Centers for Disease Prevention and Control (CDC), and ProMed Mail. Guidelines and disease information from WHO, CDC, and Public Health England were included and updated reviews were reviewed.

Competing interests: We have read and understood BMJ policy on declaration of interests and have no relevant interests to declare.

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Figure

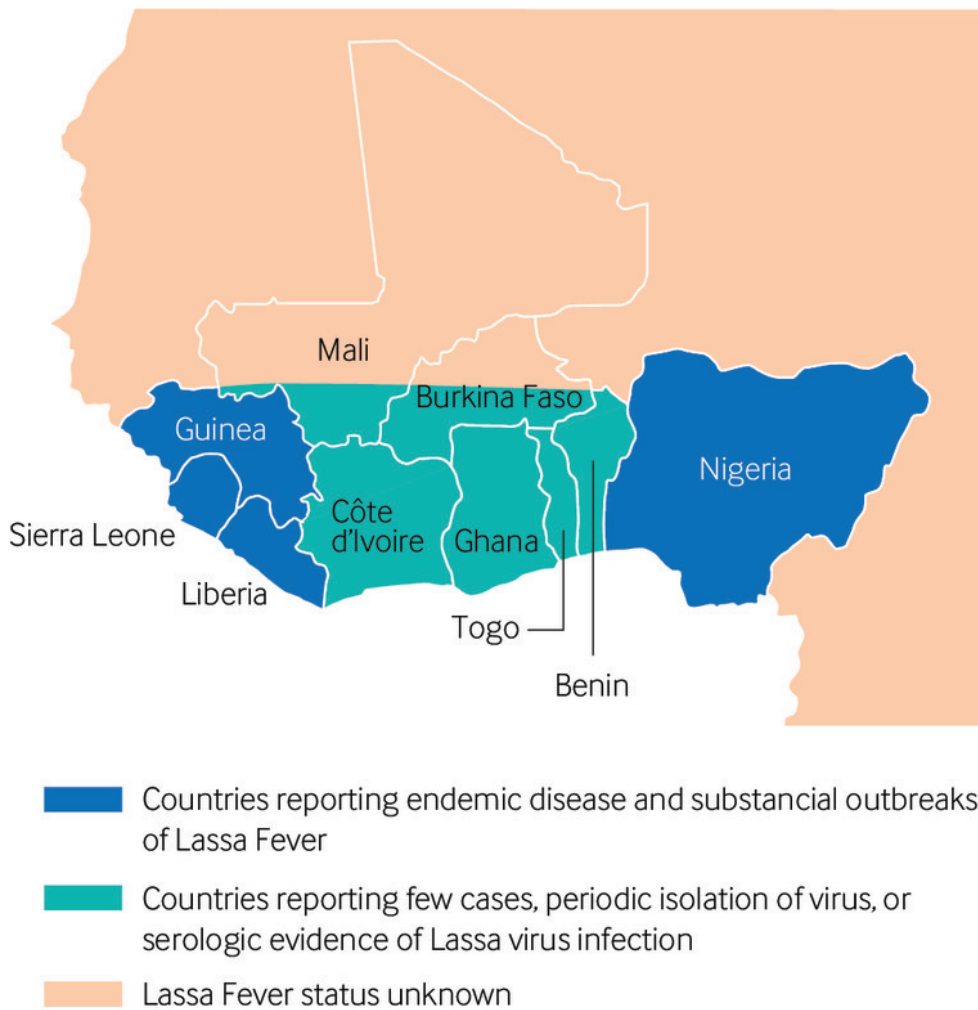


Fig 1 Distribution map of Lassa fever outbreaks (adapted from Centers for Disease Control and Prevention. Lassa fever. www.cdc.gov/vhf/lassa/index.html)