

PUBLIC HEALTH IMPORTANCE OF LASSA FEVER EPIDEMIOLOGY, CLINICAL FEATURES AND CURRENT MANAGEMENT REVIEW OF LITERATURE

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The public health importance of Lassa fever can not be over emphasized if one considers the high infectivity and mortality rates associated with the disease. This study dealt extensively on the epidemiology, clinical features and current management of Lassa fever through literature review. The aim of this study is to sensitise the public on what it needs to know on Lassa fever as well as updating the knowledge of health workers on current management of the disease and important precautionary measures to take when handling a patient with Lassa fever. Strict barrier nursing, isolation, use of protective devices are important preventive measures when managing a patient with Lassa fever infection. As Lassa fever may have a long incubation period (Up to 20 days), it is possible that travellers from endemic areas may be incubating the disease. However, one case of Lassa fever entering a non-endemic area should not cause fear of an epidemic as long as correct infection control procedures are followed.

INTRODUCTION

Lassa fever is an acute viral illness caused by Lassa virus a member of the arena virus family of viruses. The disease was first described in the 1950's, although the virus was not isolated until 1969. Lassa fever is confined to West Africa from where it was first recognized in 1969 in Lassa, Northern Nigeria, when an American missionary died from it. Since then small outbreaks have occurred in Zaire, Liberia, Paragua Tongo in Sierra Leone and cases have occurred in various parts of Nigeria. It has been shown in Sierra Leone and cases have occurred in various parts of Nigeria. It has been shown in Sierra Leone and Nigeria that the infection occurs widely in communities as a major illness or unapparent infection. Many people in endemic areas have antibodies, for example, 35% in an area in Sierra Leone (1), and have had mild or unapparent infection.

Epidemics and deaths are particularly associated with hospitals and poor hygienic practices. Hospital personnel appear particularly vulnerable. Every year there are about 100,000 cases in West Africa and about 5,000 deaths (2). A distressing report on nosocomial Lassa fever in two hospitals in Nigeria highlights the problems that the health system in large parts of Africa is facing: poor formal education and training, unqualified personnel, lack of resources and materials as well as lack of supervision (3). This report was just a limited outbreak in two small private hospitals with 34 patients, 22 of whom died, indicating at 65% fatality rate. Among the deaths were 3 doctors, six nurses and a son of a patient. The fatality among the doctors and nurses was probably the reason while this epidemic came into light. Most patients were exposed to the disease in hospital. The staff was infected during emergency surgery and while caring for nosocomially infected patients.

EPIDEMIOLOGY

Lassa fever is transmitted to humans from wild rodents (the multimammate rat, *mastomys natalensis*). In rodents, the infection persists and the

virus is shed throughout the life of the animal. *Mastomys natalensis* was identified in Sierra Leone in 1972 as a rodent reservoir of Lassa virus (4). Disease transmission is primarily through direct or indirect contact with excreta of infected rodents deposited on surfaces such as floors or beds, or in food or water. Infection can also occur by inhalation of tiny droplets (aerosols) of virus - laden rodent excreta. Exposure may also occur during occupational activities such as agricultural works or mining. Person-to-person and laboratory infections occur, especially in the hospital environment, through direct contact with blood (including inoculation with contaminated needles), pharyngeal (throat) secretions or urine of a patient, or by sexual contact. Person to person spread may occur during the acute phase of fever when the virus is present in the throat. Studies have shown that person-to-person spread of virus is common; it contributes less than rodent contact to human infection (5). Infection rates in families are significantly higher in households with rodents that have antibody to Lassa virus (undoubtedly reflecting persistent infection) and where food is stored indiscriminately. Spread of virus from rodents to humans is strongly associated with a large household rodent population as well as practices such as catching, cooking, and eating rodents. Person-to-person transmission in a household is associated with direct contact or care of someone with a febrile illness, as well as sexual contact with a partner during the incubation or convalescent phase of illnesses. This virus may be excreted in the urine of patients for three to nine weeks from the onset of illness. Lassa fever can be transmitted via semen for up to three months. Nosocomial transmission of Lassa fever was well described during the outbreaks that occasioned the discovery of the virus more than three decades ago. Study has suggested that this is not a frequent event, and that basic barrier nursing methods (gloves, gowns, and masks) are highly effective in reducing the risk (1).

Lassa virus transmission is the most consistently endemic of all the arena viruses. More patients are admitted to hospital during the dry season of

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February to May, but cases occur in every month of the year. It is possible that the increased stability to Lassa virus at low relative humidity periods range from 7 to as long as 20 days (6). From 1969, about 12 Lassa fever outbreaks had occurred in Nigeria. These cases were reported from Jos -1969/70, Onitsha 1970, Zonkwe 1974, 1975, 1976 and 1977, Vom- 1975, Aboh-Mbaise and Owerri 1989, Lafiya 1992-1993, Ekpoma 1990 and 1992. Other countries in Africa have reported Lassa outbreaks and these include Central Africa Republic, Liberia and Sierra Leone (Fig. 1).

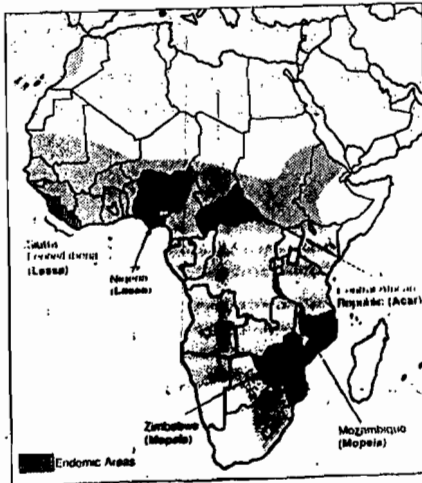


Fig. 1 Geographical locations of Lassa and related viruses from Africa. The stippled area represents the distribution of the single major rodent host (*Mastomys natalensis*) in this continent.

(Fig. 1). Serological evidence of human infection has been found in Democratic Republic of Congo, Guinea, Mali and Senegal. Seroconversion rates ranged from 5 to 20 percent in prospective studies of Lassa fever in susceptible (seronegative) populations of Sierra Leone villages (5, 6). The highest were in crowded, highly mobile populations with lower rates in traditional agricultural villages. These same studies demonstrated disease-to-infection ratios of 10 to 25 percent, and the proportion of febrile illness associated with seroconversion to Lassa virus was 5 to 14 percent. All age group are susceptible to Lassa fever infection as shown by serological surveys as well as studies of hospitalized patients (7). Age and sex specific antibody prevalence shows that the proportion of the population with antibody increases with age and there is no significant difference in antibody prevalence between sexes.

Epidemic investigations of Lassa fever should include assessment of rodent infestation and infection in conjunction with a careful history of human disease. The role of human-to-human transmission is clearly more important and this must be kept in mind when investigating a case or cluster of cases in an endemic area. Investigation in a non-endemic area should center on possible human contacts or recent travel to an endemic Lassa fever area.

The main methods of control are isolation of cases, disinfection, surveillance of contacts and rodent control. In hospital, barrier nursing, strict procedures for handling of both body fluids and excreta should be maintained. Patient relatives should not be allowed to handle secretions, urine or excreta of the patient. Disinfectants such as 0.5% sodium hypochlorite solution, 0.5% phenol with detergent, heating and bleach solution are effective for controlling transmission. Identify all close contact (people living with, caring for, or testing laboratory specimens of patients) within three weeks of onset of illness. Close surveillance of contact should be established by conducting body temperature checks at least two times daily for three weeks after exposure. In case of temperature greater than 38.8°C, hospitalize immediately in isolation facilities. The place of residence of the patient during the three weeks prior to onset should be determined and a search initiated for unreported or undiagnosed cases. Prophylactic oral Ribavirin should be considered in a person who is known to have had a close contact with a confirmed case of Lassa fever during 2 weeks prior to the onset of symptoms, while symptomatic or during the 8 weeks after recovery. Although it is not clear how long this drug need to be given to abort the infection (8, 9). Unintentional ecological manipulation, introduction of crop rotation using soybeans with corn, may be responsible for the reduction of human disease(10).

CLINICAL FEATURES

Most Lassa fever infection probably occurs as a result of viral contact with exposed membranes or skin abrasions. Patients with Lassa fever enter hospital 2 to 4 days after onset of symptoms. At this time viraemia may be absent or present in widely different concentrations. Persistent high viraemia is a significant predictor of outcome of illness. It is not unusual to encounter patients with viraemia on admission to hospital that also have high levels of both IgM of IgG immunofluorescent antibody (IFA). In fact there is no correlation between the viraemia level and that of the IFA for Lassa fever (11).

Neutralizing antibodies to Lassa virus are almost never detectable in the serum of patients at the beginning of convalescence, and in most people they are never detectable. In a minority of patients some low-titer serum neutralizing activity may be observed but only several months after resolution of the disease and clearance of the virus (11).

Lassa fever begins 7 to 8 days after the primary infection with sublet onset of fever, headache, and malaise (7). Fever is sustained with peaks of 39 to 41°C, usually in early morning and early evening. Aching in the large joints and lower back pain develop in more than half of hospitalized patients by the third or fourth day of illness. The physical examination shows these patients to be toxic and anxious. Unless the patient is in shock the skin is usually moist from diaphoresis. There is an elevated

respiratory rate, and the pulse is usually commensurate with elevated body temperature. The systolic blood pressure ranges from > 100 to > 110 with a mean of 103. There is no characteristic skin rash. Petechiae and ecchymosis are not seen, nor is jaundice a feature of Lassa fever. Conjunctivitis occurs in about one-third of patients; conjunctive hemorrhages are occasionally seen and portend a poor prognosis. Seventy percent of patients have pharyngitis with diffusely inflamed and swollen pharynx and tonsils, but few if any petechiae. In over half of the patients the pharyngitis is exudative, with yellow patches, primarily on the tonsils, and rarely with distinct ulcers. The pharyngeal pain associated with Lassa fever is extraordinarily severe, and it is common to see patient expectorate on saliva in a cup because swallowing is so painful. Bleeding occurs in only 15 to 20 percent of all patients. It occurs most often in the gum and nose, but also occurs as gastrointestinal or vaginal bleeding, it is of course associated with severe disease. Oedema of the face and neck are commonly seen also in severe disease, without peripheral oedema – suggesting capillary leakage, rather than cardiac dysfunction and impaired venous return oedema and bleeding may occur together or independently. About 20% of patients have pericardial or pleural rubs, presumably associated with effusions, which though rarely present on admission, develop in early convalescence occasionally in association with congestive cardiac failure.

The ECG may be abnormal, particularly with elevated T-waves and evidence of pericarditis and myocarditis, but there is no correlation between the T-waves abnormalities and the presence of pericardial rub or other evidence of pericarditis. The abdomen is diffusely tender in under half of the patients but there are no localizing signs and bowel signs are usually active. Neurological manifestations may be absent in acute Lassa fever or there may be a range of abnormalities from unilateral to bilateral deafness, with or without tinnitus, to moderate or severe diffuse encephalopathy with or without general seizures. The encephalopathic complications generally carry a poor prognosis, while deafness usually occurs just as recovery is underway. Manifestations during the acute phase range from mild confusion and tremors to grand mal seizures and decerebrate coma. Focal fits are not seen. Cerebrospinal fluid specimens usually show a few lymphocytes but are otherwise normal and virus titers are low. Other than deafness, focal neurological signs rarely occur. Nerve deafness, sometimes permanent occurs in 25 percent of all Lassa fever infections.

The mean white blood cell count on admission is $6 \times 10^9/L$ with early lymphopenia and in a few severe cases late neutropenia (12). A circulating inhibitor of platelet function has been detected in the plasma of severe cases in humans. The haematocrit in Lassa fever patients is often elevated (mean 50.1) due to dehydra-

tion. Proteinuria is common, occurring in two-third of patients. The blood urea nitrogen may be moderately elevated probably due to dehydration. Lassa fever is also a pediatric disease-affecting children of all ages (6). The disease appears to be difficult to diagnose in children because its manifestations are so general. In very young babies, marked oedema may be seen, associated with very severe disease. In older children the disease may manifest as diarrhoea, as pneumonia, or simply as un-explained prolonged fever. The case fatality rate in children is 12 to 14 percent. The clinical course of Lassa fever in children is as diverse as it is in adults, ranging from mild febrile illness to severe fulminating disease. Lassa fever is highly variable disease with a broad range of manifestations and many degrees of severity. This makes it difficult to distinguish clinically, especially in the early stages, from influenza or other upper or lower respiratory viral infections, as well as from other causes of general febrile illness or from febrile gastroenteritis. Typhoid fever is a common misdiagnosis. There are no firm clinical predictors or pathognomonic signs of Lassa fever. Although it is classified as a hemorrhagic fever, it is not frequently a cause of overt bleeding. A case control study of the clinical diagnosis or prognosis of the disease (7). There are several significant complications of Lassa fever, which add to the overall burden of the disease in the poor rural populations of many West Africa countries. One of these is the adverse effect of Lassa fever during pregnancy (13). Limited data suggest that Lassa fever may be a common cause of maternal mortality in many areas of West Africa. Another important complication of Lassa fever is that of acute VIIIth nerve deafness. Nearly 30 percent of patients with Lassa fever infection suffer an acute loss of hearing in one or both ears. Other complications, which appear to occur much less frequently, are uveitis, pericarditis, orchitis, pleural effusion and ascities (7). Renal and hepatic failures are not seen.

The simplest and most common methods of diagnosis are serological tests on paired sera by Immunofluorescent Antibody (IFA) or enzyme-linked immunosorbent assay (ELISA) to detect an increase in antibody titer or an elevated titer (at least 1:32), and presence of specific IgM (11,14). Lassa virus produces sustained viraemia so that virus isolation is studies of South American hemorrhagic fever, particularly infection, show that viraemia is also a consistent feature, although probably not at the same levels as with Lassa fever(1). Thus virus isolations is an alternative diagnostic method in the absence of paired sera. Ideally, a method of rapid diagnosis would help with early identification and isolation of the patients both for therapy and prevention of transmission; however, no such method has yet been developed. The diagnosis of Lassa fever by IFA on fixed tissue using monoclonal antibodies to Lassa virus makes possible postmortem diagnosis in situations where methods of collection and storage of specimens are limited (14). For virus isolation, serum

should be separated from a clotted specimen when possible, although whole blood may be used. Ideally, the specimen should be stored at -60°C but specimens stored at 4°C for several days will still yield the virus. Lassa virus can be cultured from urine, spinal fluid, breast milk pharyngeal secretions and tissues like spleen, liver and lymph node. Specimens should be placed in dry ice or liquid nitrogen as soon as possible; storage at -20°C will maintain virus viability for several days.

CURRENT MANAGEMENT

1. **Drug Treatment:** the only known specific treatment for Lassa fever is Ribavirin. After having made the diagnosis of Lassa fever Intravenous Ribavirin treatment should start as soon as possible.
 - First give a single loading dose of 33mg per kg body weight.
 - Then every six hours give 16mg per kg body weight for four days
 - Then every eight hours give per kg body weight for six days.
 - Total treatment period is ten days.
 - A treatment chart (attached) should be completed for each individual patient clearly laying out correct amount to give for each dose.
 - Once started, a Ribavirin treatment should not be discontinued until the ten-day course is complete.
 - Each ampoule of Ribavirin contains 100mg in 1ml. Ribavirin does not need to be diluted for administration and there are no contraindications to Ribavirin.

- Abnormal bleeding (e.g. gums mouth, nose)
- Red eyes or conjunctivitis
- Spontaneous abortions
- Swollen neck and or face
- Low blood pressure (systolic BP < 100mmHg) or shock.

BOX 1: MAJOR DIAGNOSTIC CRITERIA

Source: FMOH – Abuja.

2. **Supportive Therapy:** Many patients arrive in a moderately dehydrated state with elevated packed-cell volume (PCV), and require fluid replacement. No data are available on specific electrolyte or acid-base imbalances. The major crisis to overcome is the sudden and profound hypotension, which may occur between the fifth and the fourteenth day of illness. For those patients with severe anemia, whole blood or packed cells may be helpful (15). In situation where there is no whole blood, plasma or haemacel can be used. Whenever possible, fluid, electrolyte, and osmotic imbalances should be corrected in anticipation of the development of clinical shock. Other supportive therapies may include:

- Analgesic e.g. Paracetamol for pains
- Quinine injection especially in malaria endemic regions
- Nasogastric-tube feeding when necessary.
- Remember to protect yourself, your staff and the patient's relatives when treating Lassa fever. Simple protective measures such as non-disposable gowns, gloves, and masks as used by hospital personnel are effective in preventing excess risk of Lassa virus infection.
- Strict barrier nursing should be maintained.

- Headache
- Sore throat
- Leucopenia (<400/mm³.)
- Nausea and Vomiting
- Diarrhoea
- Cough
- Pleural effusion or ascities
- Swollen lymph nodes
- Body weakness
- Proteinuria.

BOX 2: MINOR DIAGNOSTIC CRITERIA

Source: FMOH – Abuja

3. **Isolation:** the degree to which patient isolation is accomplished depends on the hospital where the patient is admitted. The patient should be placed in a room with a single entrance, preferably through an adjoining room. The room should contain the materials necessary for patient care and staff protection, including gowns, gloves and masks. The entrance room should also contain hand-washing facilities and decontaminating solutions (antiseptics). Persons entering the patients room should wear gowns, gloves, and masks (non-disposable ones may be decontaminated after use and reused). Feet should be covered, and protective eyewear should be worn by the staff if patient is disoriented and combative or if procedures likely to produce vomiting or bleeding are performed (i.e. nasogastric tube or arterial line). Protective clothing should be put on and removed in the entrance room, and only essential hospital personnel and immediate family members should be allowed in the room. Laboratory tests should be carried out in high containment facilities. If there is no such facility, specimen handling should be kept to a minimum and performed only by experienced technicians using all available precautions, such as gloves and bio-safety cabinets.

- Isolate the patient
- Restrict access to the isolation area
- Only hospital staff and useful family caregivers should have access into the isolation room.
- People with open cuts or wounds should not look after patient with Lassa fever.
- Wear protective clothing e.g. gown, gloves, masks, eyeglasses etc.
- Handle specimens carefully and safely
- Wash hands with antiseptic soap and water after contact with patient or his/her body fluids.
- Sterilize all equipments/instruments used for patient
- Use of invasive procedures should be ver minimal.
- All wastes from patient. should be disposed of carefully
- Strict barrier nursing.

BOX 3: IMPORTANT HINTS FOR SELF PROTECTION WHEN HANDLING LASSA FEVER PATIENT

CONCLUSION

Since there are no firm clinical predictors or pathognomonic signs and symptoms of Lassa fever, it is therefore recommended that a high level of suspicions should be maintained when dealing with a patient with persistent fever and any of the major diagnostic criteria or two minor diagnostic criteria as well as history of contact with Lassa fever case. Good history taking with emphasis on exposure to rodent either at home or during occupational activities may give clue to making a diagnosis.

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