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Recommendations for Initial Management of Suspected or Confirmed Cases of Lassa Fever

U.S. DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE / PUBLIC HEALTH SERVICE

SUPPLEMENT
Recommendations for Initial Management of Suspected or Confirmed Cases of Lassa Fever

INTRODUCTION

Every year there is a risk, albeit small, that Lassa fever and other acute viral hemorrhagic fever agents (Class IV viruses, such as Ebola or Marburg) will be imported into the United States. Laboratory accidents causing exposure to such viruses are also possible. For these reasons, in 1978 the Director of CDC asked a task force* to develop a written plan for action should a suspected or confirmed case of disease caused by one of these viruses occur in the United States. Although Lassa fever is the focus of the report, as it is the most frequently imported disease in the group, the plan could apply, with only minor adjustments, to Ebola, Marburg, and other such viruses. This is a summary of the task force's report.

Lassa fever is spread by direct or indirect contact with infected rodents and by direct person-to-person transmission. People sharing the same household with infected persons and medical workers exposed to patients with the disease are at risk. Accordingly, potential sources of Lassa fever in the United States are (1) imported cases; (2) laboratories conducting research on Lassa virus, or laboratories receiving specimens from patients who have a fever of unknown origin and who were exposed in Africa; and (3) imported, infected rodents. Over the last 2 years, approximately 12 suspected importations of Lassa fever into the United States were identified.† The disease also has probably been imported unknowingly in the past, perhaps even before Lassa fever was recognized as a clinical entity in 1969. During the time this report was being prepared, 2 CDC employees were accidentally exposed to Lassa fever virus in a CDC laboratory; they were subsequently isolated at the facilities of the U.S. Army Medical Research Institute of Infectious Diseases at Ft. Detrick, but they did not become infected. The possibility that Lassa fever may be imported by infected rats is judged highly unlikely since *Rattus rattus,* the main shipborne rat, does not experience chronic infection with Lassa virus. In Africa, the only known natural reservoir for Lassa fever virus exists in the multimammate rat (*Mastomys natalensis*). The natural reservoirs of Marburg and Ebola viruses are still unknown.

When the diagnosis of Lassa fever is considered, further information and advice about the management of the patient, control measures, and the collection and shipment of diagnostic specimens are available on request from the following persons at CDC, Atlanta, Georgia, telephone (404) 329 + extension (#):

1. Chief, Special Pathogens Branch, Virology Division, Bureau of Laboratories: Dr. Karl M. Johnson or his deputy (#3308).
2. Chief, Respiratory and Special Pathogens Branch, Viral Diseases Division, Bureau of Epidemiology: Dr. William G. Winkler (#3727).
3. Director, Viral Diseases Division, Bureau of Epidemiology: Dr. Michael B. Gregg (Acting Director) (#3636).
4. After regular office hours and on weekends the above-mentioned staff members may be contacted by calling the CDC duty officer (#3644).
5. Director, Office of Biosafety: Dr. John Richardson (#3885).

*JA Bryan, MD; JL Conrad, MD; J D'Agnese; RE Dixon, MD; BL Evatt, MD; DR Hopkins, MD, Chairman; KM Johnson, MD; FS Kingma; RA Keenlyside, MBBS; DT Miller, PhD; J Richardson, DVM; RM Zweighaft, MD; all from CDC.

†None of these cases was finally reported as Lassa fever. However, follow-up serologic tests were not performed on all cases.

ISOLATION OF SUSPECTED AND CONFIRMED PATIENTS

Ideally, patients with suspected or confirmed Lassa fever should be immediately placed in a special isolation unit (such as a Vickers Isolator or laminar flow room in which all exhaust air is properly filtered) designed to prevent contamination of the area outside of the patient's immediate environment. However, Lassa fever will probably be suspected or diagnosed most frequently in medical facilities that have no specialized containment rooms or Vickers Isolators immediately available. In this event, strict isolation with barrier nursing is probably satisfactory to care for these patients, at least temporarily* (*1*).

To minimize the risk of transmitting Lassa fever to health personnel caring for the patient, a number of precautions should be instituted:

1. Hospital staff should wear disposable gowns, full-face respirators equipped with high efficiency particulate air (HEPA) filters (or nose and mouth respirators with HEPA filters, plus goggles or face shields), gloves, and head and shoe covers at all times when in contact with the patient.

2. The patient should be placed in a private room which is suitable for respiratory isolation and which should only be centered through an anteroom. The following criteria should be met, if possible:

   —Air from the patient's room should not recirculate to other parts of the hospital.

   —The air pressure in the patient's room should be negative with respect to the outside corridor. (The hospital engineer could confirm this before use.)

3. The anteroom, which should have hand washing facilities, should be allocated for use by persons entering and leaving the patient's room. The anteroom should also be at negative air pressure compared to the outside corridor and any adjoining room other than the patient's. The anteroom should contain supplies for the patient, protective clothing for the medical staff, and facilities for disposal of materials taken from the patient's room. (Such materials should be decontaminated before they are removed from the patient's room; see item #6 below.)

4. Hospital traffic passing the anteroom should be minimized, and the door of the anteroom kept closed. A daily log (including adequate information for contacting persons) should be kept of all persons entering the patient's room.

5. The routine management of the patient should be organized to limit traffic, including that of medical and nursing staff, into and out of the room. Supplies required for routine day-to-day management of the patient should be kept in an adjoining anteroom (see APPENDIX A). Patients who are ambulatory and have few symptoms should be encouraged to take care of themselves as much as possible (for example, noting their routine vital signs and making their beds).

6. The patient should use a chemical toilet, and all bodily secretions and excretions should be treated with Lysol† or 0.5% sodium hypochlorite (10% aqueous solution of household bleach) before being removed from the room. All objects should be double-bagged in sealed plastic bags, which should be sponged with 0.5% sodium hypochlorite before being removed to the anteroom.

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*Since much is still unknown about the transmission of this disease (such as the degree of infectivity and transmissibility by the airborne route), it is recommended that infectious or potentially infectious patients be placed in as strict isolation as possible to minimize any possibility for transmitting the virus.

†Use of trade names is for identification only and does not constitute endorsement by the Public Health Service or the U.S. Department of Health, Education, and Welfare.

If the diagnosis of Lassa fever is confirmed, arrangements can be made for the patient to be transferred to a special isolation facility if the local hospital does not have such an intensive-care unit. CDC should be contacted. (See INTRODUCTION.)

VERIFICATION OF DIAGNOSIS

The clinical syndrome of Lassa fever is often nonspecific and may be difficult to diagnose in the early stages. Thus, a detailed travel history is the most critical element in assessing the possibility of Lassa fever. The disease is known to be endemic only in West Africa. The exclusive reservoir of the virus is the rodent *M. natalensis.* The virus is almost certainly transmitted through infectious urine from rodents. *Mastomys* species are absent or uncommon in large urban centers even in West Africa. Therefore, the important factors are exposure to a rural West African environment in the preceding 3 weeks, or direct contact with ill individuals coming from such areas, as would occur with medical workers stationed in rural hospitals.

Typically, the illness presents with fever and pharyngitis, but myalgia, headache, abdominal pain, nausea, vomiting, and diarrhea are common. The differential diagnosis includes any of the following febrile illnesses: malaria, typhoid fever, yellow fever, streptococcal tonsillitis, infectious mononucleosis, influenza, arboviral and adenovirus infections, meningococcemia, relapsing fever, typhus fever, and leptospirosis (*2-5*).

The laboratory diagnosis of Lassa fever is confirmed by: 1) isolating the virus from the patient's blood, throat, or urine; or 2) demonstrating a serologic response to Lassa fever in serum. Four days are required for virus isolation. Antibodies develop in most, but not all, patients during the second week of illness.

HANDLING AND TRANSPORT OF LABORATORY SPECIMENS

Collection of Specimens

The following initial specimens should be taken to confirm a diagnosis of Lassa fever and to rule out other possible diagnoses:

1. A throat swab rinsed in 1 ml of sterile, phosphate-buffered neutral saline, containing 1% human serum albumin or 25% rabbit serum, collected in a plastic, screw-cap container.
2. A clean-catch, midstream urine specimen obtained in a sterile container. Five ml of urine should be stabilized by the addition of human serum albumin or rabbit serum to a final concentration of 1% or 25%, respectively, and placed in a plastic, screw-cap container.
3. Venous blood for antibody studies, blood chemistries, and hematological tests.
   - 5 ml in a sealed, plastic tube with ethylenediaminetetraacetate (EDTA) for use in determining hemoglobin levels and white blood cell counts.
   - 10 ml of clotted blood in a sealed, plain plastic tube for blood chemistry and serology. To avoid unnecessary exposure of laboratory personnel, these blood specimens should not be centrifuged or separated.
   - 10 ml, in a tube with citrate, for coagulation studies. (The ratio of blood to citrate should be 9:1, and the concentration of sodium citrate used should be from 3.2% to 3.8%.) Samples for coagulation studies should be kept on ice if tests are done within 4 hours after the blood is drawn. Otherwise the plasma should be separated from the cells, quick frozen in alcohol and dry ice, and transported or held on dry ice. (See Packaging and Transport of Specimens.)

4. Venous blood (10 ml) for aerobic and anaerobic blood cultures.

5. A thick blood smear and a thin smear. Fix the thick smear on air-dried slides directly in 10% buffered formalin for 10 minutes; wash 3 times in buffered water (ph7); then stain with Giemsa. The slide containing the thin smear should be fixed initially in methanol for 5 minutes; then the procedure used for the thick smear should be followed. Slides prepared in this manner can be safely examined for malaria parasites.

Procedures for Venipuncture

All equipment for venipuncture should be available in an anteroom adjoining the patient's room (APPENDIX A).

Enough blood should be taken during a single venipuncture for serology, hematology, blood chemistry, and blood-culture examination (40-50 ml). Personnel should be acutely aware of the danger of accidental self-inoculation and of sprays, spills, or aerosols when collecting and dispensing blood from a patient with confirmed or suspected Lassa fever. Where available, plastic tubes should be used to minimize the chance of breakage. Using vacutainers simplifies collection of multiple samples but may require using glass collection tubes. Personnel should not attempt to replace the plastic needle guard on a used needle, but should discard the needle and vacutainer sleeve, or needle and syringe, into a covered pan containing 0.5% sodium hypochlorite (10% aqueous solution of household bleach). The container should then be autoclaved.

The outside of each specimen container should be swabbed with 0.5% sodium hypochlorite, and a label should be affixed with the patient's name, the date of the specimen, and the nature of the suspected infection. Specimens should then be double bagged in airtight bags and similarly labeled with the special handling requirements and the destination. Bags containing specimens should be immersed in a solution of 0.5% sodium hypochlorite before being taken from the room.

Packaging and Transport of Specimens

CDC (Office of Biosafety or contacts listed in the Introduction) or the state health department should be contacted for instructions on the collection, packaging, labeling, and shipment of specimens for laboratory examination, according to the Interstate Quarantine Regulations (*6*). (See APPENDIX B.)

Exposure of Laboratory Personnel to Specimens

A person testing laboratory specimens from patients suspected of having Lassa fever should wear surgical gloves and a full-face respirator with an HEPA filter. Care should be taken to minimize potentially hazardous procedures, such as ones that produce aerosols, and use of potentially hazardous equipment, such as glass microhematocrit tubes.

Laboratory personnel may have been exposed to specimens from the patient during tests carried out early in the illness, before the diagnosis of Lassa fever was considered. All laboratory personnel who were exposed, when not adequately protected, to these specimens should be placed under surveillance. (See IDENTIFICATION, SURVEILLANCE, AND MANAGEMENT OF CONTACTS OF LASSA FEVER SUSPECTS/CASES.) The equipment used to carry out these tests should be decontaminated before being returned to routine use. (See DECONTAMINATION PROCEDURES.) If the diagnosis of Lassa fever seems likely, subsequent specimens should be transported to CDC for testing in its maximum-containment facilities.

CDC is prepared to perform certain routine, clinical diagnostic tests in its maximum containment facility during the period between initial suspicion and final diagnostic confirmation of a suspected case. It is recognized that there may be reluctance on the part of hospital laboratories to expose personnel or equipment to possible contamination with Lassa virus. On the other hand, handling all clinical specimens at CDC is not practical for good patient management because of the large time delays. CDC is currently developing a plan to assist local laboratories with this problem. In the interim, close consultation with the Center will be necessary to solve problems in the handling of clinical diagnostic specimens.

CLINICAL MANAGEMENT OF PATIENTS WITH CONFIRMED LASSA FEVER

The management of patients severely ill with Lassa fever represents a major challenge to the practitioner of intensive medical care and cannot be covered in this report, except for a few general observations. Further details may be obtained from the references.

The pathogenesis of this disease is not clearly understood. Multiple organ systems may be compromised by a viral infection which, although not highly inflammatory, is widely disseminated. A hallmark of the disease is high viremia, persisting for 2 weeks or longer. Studies in progress in West Africa show that approximately 1 in 5 Lassa fever patients admitted to a hospital dies. Many of these deaths occur among patients who are admitted during the second week of illness and may be dehydrated and have low blood pressure. Thus, careful management of fluid and electrolyte balance from the onset of disease is perhaps the most important aid to recovery. Enzyme studies reveal that the liver and pancreas are regularly affected, although it is doubtful that either is very often sufficiently compromised to cause death. Half of the West African patients who experience overt bleeding die. Disseminated intravascular coagulation has not been documented in these patients, but its presence may help explain the clinical illness. Detection and treatment of bleeding should be given high priority. Other acute problems which may occur include myocarditis and pericarditis, pleural effusion, intrauterine death, and spontaneous abortion.

Therapy is mainly supportive. It has been proposed that passively administered Lassa virus antibodies may suppress viremia and favorably alter the clinical outcome, but this hypothesis has not been proven. Indeed, the simultaneous presence of the virus and its naturally induced antibodies in patient's blood during the second week of illness suggests that some of the pathology may be due to deposition of antigen-antibody complexes. Administration of Lassa virus antibodies under such circumstances may only aggravate the patient's condition.

Lassa fever patients arriving unexpectedly in the United States will rarely be desperately ill, and some patients may have onset of disease only after arrival in this country. The physician typically would see such patients either in the early stages of the disease, when they have a nonspecific febrile illness, or in convalescence, when they are able to travel. For patients with nonspecific febrile illness, prompt diagnosis and use of Lassa immune plasma before antibodies develop may be useful, whereas in the case of convalescent patients, isolation of the patient until urinary excretion of the virus ceases is probably the most important medical action to take.

Clinical studies to be conducted in West Africa hopefully will clarify the utility of Lassa immune plasma and of certain antiviral drugs in the treatment of patients with

Lassa fever. Limited supplies of Lassa immune plasma may be available for treating confirmed cases of Lassa fever. Contact CDC.

Autopsy and Handling of Corpse

Careful consideration should be given to the potential risks and benefits of autopsy in any patient suspected to have had Lassa fever. If an autopsy is performed, extreme precautions must be taken to prevent dissemination of the virus. Precautions similar to those suggested for handling the corpse of a smallpox victim (*1*) are appropriate.

DECONTAMINATION PROCEDURES

Decontamination of transport and bed isolation units, hospital rooms, and conveyances other than aircraft (ambulances, for example) requires a combination of liquid chemical disinfectants and gaseous fumigants.

Surfaces

Known or potentially contaminated surfaces of transport and isolation equipment, hospital rooms, and conveyances can be decontaminated by applying phenolic detergent disinfectants (such as Osyl and Amphyl*) or hypochlorite solutions (1:10 aqueous solution of laundry bleach) known to be virucidal.

Spaces

Interior spaces of isolation equipment, rooms, and conveyances that are known or suspected to be contaminated can be decontaminated by fumigation with formaldehyde gas, which may be generated by heating formalin (0.5 ml/ft^3 of space) or paraformaldehyde powder (0.3 gm/ft^3 of space). Openings in rooms, isolation equipment, and conveyances (such as doors and windows) should be sealed with masking or duct tape before formaldehyde gas is generated. Ideally, formaldehyde fumigation should be conducted at an ambiant temperature of at least 70 F (21 C) and a relative humidity of 60%. The gas should remain in contact with the contaminated area for 4 hours. After fumigation, the area should be thoroughly ventilated before personnel are allowed to enter. Appropriate respiratory protection is essential if personnel need to enter the fumigated area for any purpose before the formaldehyde gas is exhausted and the area ventilated.

Laboratory Equipment

Laboratory equipment used to process specimens from patients with suspected Lassa fever should be thoroughly decontaminated before being returned to routine use. Surfaces in contact with potentially contaminated liquids, such as flow-through optical and sampling systems, may be effectively decontaminated by flushing with 0.5% sodium hypochlorite. Sufficient solution should be used for the fluid to enter instrument waste-disposal reservoirs. Items, such as complex instruments, that may have been contaminated with aerosols and cannot be effectively treated with hypochlorite can be decontaminated with ethylene oxide. Disposable components, such as pipet tips, plastic cuvettes, and excess specimens should be placed in a 0.5% hypochlorite solution and autoclaved.

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IDENTIFICATION, SURVEILLANCE, AND MANAGEMENT OF CONTACTS OF LASSA FEVER SUSPECTS/CASES

A contact is defined as a person who has been exposed to an infected person or a contaminated environment so as to have had opportunity to acquire the infection. For Lassa fever, this includes anyone who has associated with an infected person—at any time from onset of fever to 3 weeks later—in any of the following ways:

1. Had face-to-face contact.
2. Shared the same residence.
3. Traveled on the same conveyance. (In 2 known instances, infectious patients with Lassa fever were transported on commercial aircraft, and no secondary transmission was confirmed, despite extensive surveillance.)
4. Worked in a hotel, restaurant, or other business establishment visited by a patient. (Unless they had face-to-face contact, guests in a hotel or persons who were in the same airport with a person with a confirmed or suspected case should not be considered contacts.)
5. Was exposed to specimens (for example, blood, urine, sputum) of a patient.

CDC will work with state and local health authorities, as appropriate, to implement surveillance and management of contacts of patients with Lassa fever. The details of such activities (*7*) are not included here. Initially, however, clinicians and hospital authorities should take 2 steps:

1. Report immediately to CDC, through the state health department, the identity and address of any patient with suspected or confirmed Lassa fever.
2. Interview the patient and arrange for collection of specimens. This will be initiated by local and state health personnel in consultation with CDC. A summary—including clinical history, physical examination, laboratory findings, travel history, potential sources of Lassa fever, and a list of known contacts (names, addresses, telephone numbers)—should be prepared. (See VERIFICATION OF DIAGNOSIS.)

APPENDIX A

SUGGESTED LIST OF ESSENTIAL SUPPLIES AND EQUIPMENT TO BE KEPT IN ANTEROOM ADJOINING PATIENT'S ROOM*

Equipment for full physical examination

Emergency equipment

Portable X-ray machine

EKG machine

IV equipment and supplies

Tourniquets

Dry gauze

Alcohol swabs

Needles and adapters

Syringes

Blood tubes for CBC, blood chemistry, and coagulation studies

Containers with Hanks' solution for throat washing and urine specimens

Printed specimen labels with patient's name

Marker pens

Plastic airtight bags, large and small

Large, plastic trash bags

0.5% sodium hypochlorite (10% aqueous solution of household bleach), Lysol† solution

Autoclave bags

Chemical toilet

Urinals

Bed linen (disposable)

Pajamas (disposable)

Thermometers (disposable)

Toiletries, etc. (disposable)

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*This list does not include medications.

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APPENDIX B

INSTRUCTIONS FOR PACKAGING, LABELING, AND SHIPPING OF LASSA FEVER SPECIMENS

Specimens should be packaged, labeled, and shipped according to the Interstate Quarantine Regulations governing etiological agents (*6*).

Specimens should be packaged as described below:

1. Place the specimen in a securely closed, watertight, primary container (screwcap test tube or vial) and seal the cap with tape. Heat-sealed plastic vials are also ideal primary containers for etiologic agents, provided they are formulated from a plastic that is not prone to shatter at temperatures ≤-20 C.
2. Wrap the primary container with sufficient absorbent material (for example, paper towels or tissue) to absorb the entire contents, should breakage or leakage occur.
3. Place the wrapped, sealed primary container in a durable, watertight secondary container (screwcap metal mailing tube or sealed metal can). Screwcap metal mailing tubes should be sealed with tape. Several primary containers of specimens, each individually wrapped in absorbent material, may be placed in the secondary container, provided that the secondary container does not contain more than 50 ml of specimen material.
4. Place on the outside of the secondary container the specimen data forms, letters, and other information identifying or describing the specimen.
5. Place the secondary container and specimen information form in an outer mailing tube or box.
6. Place an address label and etiologic agent/biomedical material label on the outer mailing tube or box.
7. Keep the specimens for virus isolation frozen, preferably by placing dry ice around the secondary container in the mailing tube or box.
8. Contact Dr. John H. Richardson (404-329-3885), CDC's Office of Biosafety Director, if instructions are needed on packaging or advice on whether wet or dry ice refrigeration is required.
9. Complete and affix to the outer shipping container a notice to the carrier.
10. Contact the Office of Biosafety at CDC for assistance in determining shipping, labeling, and document requirements for various classes and volumes of biomedical materials.

Present airline operational procedures and Department of Transportation (DOT) regulations preclude the shipment of etiologic agents, materials refrigerated with dry ice, and other restricted articles by expedited, air-parcel-delivery services, such as DASH and SPRINT, or by transport as checked baggage. All airline personnel who receive and handle restricted articles must receive appropriate training, as specified by DOT. At the present time, specimens can be most expeditiously transported by air-express services offered by the various airline carriers or by air parcel carriers, such as Federal Air Express. Irrespective of the mode of transport, the recipient must acknowledge receipt of such specimens in writing to the shipper.

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The editor welcomes accounts of interesting cases, outbreaks, environmental hazards, or other public health problems of current interest to health officials. Send reports to: Center for Disease Control, Attn: Editor, Morbidity and Mortality Weekly Report, Atlanta, Georgia 30333.

Send mailing list additions, deletions, and address changes to: Center for Disease Control, Attn: Distribution Services, GSO, 1-SB-36, Atlanta, Georgia 30333. When requesting changes be sure to give your former address, including zip code and mailing list code number, or send an old address label.

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