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Management of Patients With Suspected Viral Hemorrhagic Fever

INTRODUCTION

The term viral hemorrhagic fever (VHF) refers to the illness associated with a number of geographically restricted viruses. This illness is characterized by fever and, in the most severe cases, shock and hemorrhage (1). Although a number of other febrile viral infections may produce hemorrhage, only the agents of Lassa, Marburg, Ebola, and Crimean-Congo hemorrhagic fevers are known to have caused significant outbreaks of disease with person-to-person transmission. Therefore, the following recommendations specifically address these four agents.

The increasing volume of international travel, including visits to rural areas of the tropical world, provides opportunity for the importation of these infections into countries with no endemic VHF, such As the United States. Since most physicians have little or no experience with these viruses, uncertainty often arises when VHF is a diagnostic possibility. Lassa, Marburg, and Ebola viruses are restricted to sub-Saharan Africa, and the differential diagnosis of VHF will most often be made for illness in travelers to this region. Since 1976, no imported cases of VHF have been confirmed in the United States, but every year there are approximately five to 10 suspected cases.

These guidelines review the clinical and epidemiologic features of these diseases; provide recommendations on diagnosis, investigation, and care of patients; and suggest measures to prevent secondary transmission. This document updates earlier recommendations, issued in 1983 (2), for the management of suspected and confirmed cases of VHF. Accumulated evidence shows that transmission of these viruses does not occur through casual contact; thus, some earlier recommendations for preventing secondary transmission have been relaxed. Similarly, therapy recommendations have taken into account recent knowledge of the effects of antiviral drugs.

Further information on investigating and managing patients with suspected VHF, collecting and shipping diagnostic specimens, and instituting control measures is available on request from the following persons at CDC in Atlanta, Georgia. For all telephone numbers, dial 404-639 + extension:

1. Epidemic Intelligence Service (EIS) Officer, Special Pathogens Branch, Division of Viral Diseases, Center for Infectious Diseases (ext. 1344).

2. Chief, Special Pathogens Branch, Division of Viral Diseases, Center for Infectious Diseases: Joseph B. McCormick, M.D. (ext. 3308).

3. Senior Medical Officer, Special Pathogens Branch, Division of Viral Diseases, Center for Infectious Diseases: Susan P. Fisher-Hoch, M.D. (ext. 3308).

4. Director, Division of Viral Diseases, Center for Infectious Diseases (ext. 3574).

5. After regular office hours and on weekends, the persons named above may be contacted through the CDC duty officer (ext. 2888).

LASSA FEVER

Lassa virus, named after a small town in northeastern Nigeria, is an enveloped, single-stranded, bisegmented ribonucleic acid (RNA) virus classified in the family Arenaviridae. Its natural host is the multimammate rat Mastomys natalensis. This ubiquitous African rodent lives in close association with humans and is commonly found in and around houses in rural areas. The rats are infected throughout life and shed high levels of virus in their urine. Although the rodent reservoir exists across wide areas of Africa, Lassa virus appears to be restricted to the continent's western part. Closely related viruses are found in other areas, but their potential for causing human disease is poorly understood.

Lassa fever was first recognized in 1969 in northern Nigeria (3) when two of three nurses infected in a rural hospital died. Two persons working in a U.S. laboratory with material from the original outbreak subsequently became infected, one fatally. One person had worked with animals infected with live virus, but it is uncertain how the other person acquired the infection (4,5). Naturally occurring infections, often associated with subsequent nosocomial outbreaks, have been recognized in Nigeria, Sierra Leone, and Liberia (6). On the basis of historical information, as well as serologic testing, sporadic Lassa infection may have occurred also in Guinea, Senegal, Mali, and the Central African Republic (6,7). In at least 10 instances, Lassa fever has been imported into countries outside of Africa (3,8-15). In the United States, the last imported case occurred in 1976 (15). No secondary transmission from these imported infections has been documented, despite intensive surveillance of many potentially exposed people (16).

Under natural circumstances, infection with Lassa virus occurs through contact with M. natalensis or its excreta, probably within the household. Subsequent person-to-person transmission occurs, although it is difficult to distinguish epidemiologically between these two modes of infection (17,18). Person-to-person spread requires close personal contact or contact with blood or excreta. Careful follow-up of household and other close contacts of cases imported into western Europe and North America has not shown any evidence of secondary transmission from casual contact. Early reports of Lassa fever stressed the high infectivity of the condition and the risks of nosocomial transmission. Recent evidence shows that avoiding direct contact with infected tissue, blood, secretions, and excretions, even in poorly equipped rural African hospitals, virtually eliminates the risk of infection (19,20).

In areas where it is endemic, Lassa fever occurs more frequently in the dry than in the rainy season. The clinical spectrum of disease is wide, and the ratio of illness to infection is 9%-26% (18). After an incubation period of 1-3 weeks, illness begins insidiously, with early symptoms of fever, sore throat, weakness, and malaise (21). Pains in the joints and lower back, headache, and nonproductive cough commonly follow. Retrosternal or epigastric pain, vomiting, diarrhea, and abdominal discomfort are also common. Frequent physical signs include fever, exudative pharyngitis, and conjunctival injection. Jaundice and skin rash are rare. Diffuse rales may be heard by auscultating the chest, and pleural and pericardial friction rubs may sometimes be detected. Edema of the face and neck, conjunctival hemorrhages, mucosal bleeding, central cyanosis, encephalopathy, and shock characterize the most severe cases. Some patients experience adult respiratory distress syndrome.

After the first week of illness, the patient begins to recover in milder cases, but starts to deteriorate clinically in more serious ones. The mortality rate for patients hospitalized with Lassa fever is 15%-20% (21), despite higher earlier estimates. The prognosis is particularly poor for women in the third trimester of pregnancy, and a high rate of fetal wastage occurs. Overall, the case-fatality rate is about 1%-2% (18). Various degrees of permanent, sensorineural deafness result in nearly one-fourth

Specific diagnosis of Lassa fever can be made in three ways: by isolating the virus from blood, urine, or throat washings; by demonstrating the presence of immunoglobulin M (IgM) antibody to Lassa virus; or by showing a fourfold rise in titer of IgG antibody between acute- and convalescent-phase serum specimens. Antibodies are measured with the indirect fluorescent antibody technique (IFA), which remains the diagnostic method of choice. Nonspecific laboratory abnormalities include protein- uria and elevated liver, enzymes, with aspartate aminotransferase (AST) levels exceeding those of alanine aminotransferase (ALT).

Adverse prognostic factors are AST elevation above 150 international units/liter, and high levels of viremia during hospitalization (22,23). Treatment is supportive and may require all the modern intensive-care facilities, including renal dialysis and mechanical ventilation. It is essential to pay attention to fluid and electrolyte balance, maintenance of blood pressure and circulatory volume, and control of seizures.

A controlled clinical trial has shown an increased survival rate for Lassa fever patients treated with ribavirin (22). All patients with the disease should now receive this drug. Side effects are largely restricted to reversible hemolysis. Severely ill patients should receive ribavirin parenterally. Lassa fever convalescent plasma has not been shown to be beneficial (22) and currently cannot be recommended, particularly when the potential for transmitting other viruses such as human immunodeficiency virus, hepatitis B virus, and the agent(s) of non-A, non-B hepatitis is considered.

Prevention of Lassa virus infection requires an understanding of the disease and its modes of transmission. Persons who intend to work in areas with endemic disease should be briefed about Lassa fever (20). Currently, no vaccine is available for use in humans.

EBOLA HEMORRHAGIC FEVER

Ebola virus is a single-stranded, unsegmented, enveloped RNA virus with a characteristic filamentous structure. Classification of the virus in the new family Filoviridae has been accepted. The virus is named after a small river in northwest Zaire. It is morphologically similar to, but antigen- ically distinct from Marburg virus. The reservoir of the virus in nature remains unknown.

Ebola hemorrhagic fever was first recognized in 1976. Two epidemics occurred within a short time of each other, the first in southern Sudan (24) and the second in northwest Zaire (25). The index case in the Sudan epidemic occurred in a worker in a cotton factory, who subsequently was the source of hospital transmission. The mortality rate among the 284 recognized cases was 53%. In the Zaire outbreak, which from the beginning centered around a hospital, 88% of the 318 affected persons died. Having close contact with a case and receiving injections at the hospital were strong risk factors for acquiring infection.

Two cases were identified elsewhere in northwest Zaire in 1977 and 1978. Retrospectively, another case was diagnosed in a physician in the same area, who cut himself while performing an autopsy in 1972 and contracted an Ebola-like illness 12 days later (26).

In 1979 another small outbreak occurred in the same area as the 1976 outbreak in Sudan. The index case involved a worker in the same cotton factory (27). The case-fatality rate was 65%. Evidence from serologic studies suggested that Ebola virus may be endemic in certain areas of Sudan and Zaire, as well as in other parts of East and Central Africa (28).

The mode of acquiring natural infection with Ebola virus is unknown. Secondary person-to-person transmission results from close personal contact, which, in the epidemics described above, frequently included the nursing of sick patients. Nosocomial transmission depends on contact with blood, secretions, and excretions. Transmission of infection has been documented in the case of a laboratory worker who experienced a needle-stick inj not suggest that spread occurred through casual contact or by aerosol transmission.

The incubation period ranges from 2 to 21 days; the average is approximately 1 week. In the cases resulting from a needle stick (25,29), the incubation period was 6 days; however, this may not characterize the natural illness.

The illness-to-infection ratio for Ebola virus is unknown, but seroepidemiologic investigations suggest that mild or asymptomatic infections can occur.

The onset of illness is abrupt, and initial symptoms resemble those of an influenza-like syndrome. Fever, headache, general malaise, myalgia, joint pain, and sore throat are commonly followed by diarrhea and abdominal pain. A transient morbilliform skin rash, which subsequently desquamates, often appears at the end of the first week of illness. Other physical findings include pharyngitis, which is frequently exudative, and occasionally conjunctivitis, jaundice, and edema. After the third day of illness, hemorrhagic manifestations are common and include petechiae as well as frank bleeding, which can arise from any part of the gastrointestinal tract and from multiple other sites.

Specific diagnosis requires isolating the virus from blood or demonstrating IgM or rising IgG antibodies by IFA. Proteinuria occurs early, and elevation of liver enzymes, AST more than ALT, is typical. Experimental infections in primates have shown that neutrophilia, lym- phopenia, and thrombocytopenia occur early in the illness (30).

Treatment is supportive and may require intensive care. Limited information exists on the efficacy of antiviral drugs or immune plasma to prevent or ameliorate Ebola hemorrhagic fever. Ribavirin shows no in vitro activity. Since the Zaire and the Sudan strains of the virus are distinct (31), if immune plasma is considered for therapeutic use, it must be strain specific. The dangers of transmitting other viral infections through plasma should be remembered. No vaccine exists against Ebola virus.

MARBURG HEMORRHAGIC FEVER

Marburg virus is a single-stranded, unsegmented, enveloped RNA virus that is morphologically identical to, but antigenically distinct from Ebola virus. Classification of the virus in the new family Filoviridae has been accepted. Marburg virus is named after the town in Germany where some of the first cases were described (32). Its reservoir in nature remains unknown.

In 1967, 25 people in Europe became ill after handling material from infected African green monkeys, Cercopithecus aethiops, imported from Uganda (32). The case-fatality rate was 23% for the primary cases, but no deaths were reported for the six secondary cases.

An Australian traveler died of Marburg virus disease in South Africa in 1975, after apparently acquiring his infection in Zimbabwe (33). Two persons with secondary cases -- a female companion and a nurse of the index patient -- survived. The third recognized outbreak of Marburg virus disease occurred in Kenya in 1980 (34). A French engineer contracted the infection in western Kenya, and a physician in a Nairobi hospital became infected while trying to resuscitate the engineer from a terminal bout of hema- temesis. The physician survived. Despite extensive contact with other staff before his illness was diagnosed, the infected physician did not spread the disease further. Another case of Marburg virus disease occurred in South Africa in 1982, with no secondary cases identified (35). The most recent case of Marburg virus disease occurred in Kenya in 1987; it involved a boy visiting a park in the western part of the country near where the engineer had acquired the infection in 1980. The boy died, but no secondary cases occurred.

The mode of acquiring natural infection with Marburg virus is unknown. Secondary spread results from close contact with infected persons or contact with blood or body secretions or excretions. In the original epidemic (32), the only persons primarily infected had direct contact with animal blood or tissues, without taking precautions to prevent infection. Sexual transmission apparently occurred in one instance in Germany (32), and virus has been isolated from seminal fluid up to 2 months after illness (34). Marburg virus was also isolated from the anterior chamber of the eye in a patient who developed uveitis 2 months after the acute illness (33). Although the geographic distribution of Marburg virus is ill-defined, Central and East Africa should be considered endemic areas.

The illness-to-infection ratio is unknown but seems high for primary infections, judging from experience with the original 1967 epidemic. The incubation period ranges from 3 to 10 days, but was typically 5-7 days in the original outbreak (32). The physician infected in the Nairobi hospital had a 9-day incubation period.

Clinical and laboratory features of Marburg virus disease are essentially similar to those described for Ebola virus disease. Diagnosis is confirmed by isolating the virus or demonstrating IgM or rising IgG antibodies by IFA. The treatment is the same as for Ebola virus disease, and the same comments about antiviral drugs and the use of immune plasma apply.

CRIMEAN-CONGO HEMORRHAGIC FEVER

Crimean-Congo hemorrhagic fever (CCHF) virus is an enveloped, single-strande Bunyaviridae. A hemorrhagic fever that had long been recognized in Asia came to international attention after a disease outbreak in the Crimean peninsula in 1944 and 1945 (36). The causative agent was later recognized to be identical to the Congo virus (37,38), isolated in Zaire, hence the name CCHF. Many wild and domestic animals act as reservoirs for the virus, including cattle, sheep, goats, and hares. Ixodid (hard) ticks, particularly those of the genus Hyalomma, act both as a reservoir and vector for CCHF virus. Ground-feeding birds may disseminate infected vectors. Twenty-seven species of ticks are known to harbor the CCHF virus (36).

CCHF is endemic in eastern Europe, particularly in the Soviet Union. However, it may occur in other parts of Europe, especially around the Mediterranean. CCHF has been recognized in northwest China (39), Central Asia, and the Indian subcontinent and may occur in the Middle East and throughout much of Africa. Humans become infected by being bitten by ticks or by crushing ticks, often while working with domestic animals or livestock. Contact with blood, secretions, or excretions of infected animals or humans may also transmit infection. In areas with endemic CCHF, the disease may occur most often in the spring or summer.

Nosocomial transmission is well described in recent reports from Pakistan (40), Iraq (41), Dubai (42), and South Africa (43-48). Available evidence, including recently unpublished experiences, suggests that blood and other body fluids are highly infectious, but simple precautions, such as barrier nursing, effectively prevent secondary transmission (41). Concern has been raised about two nosocomial cases in South Africa that occurred without documented evidence of direct exposure to infectious material (43-47). However, all other evidence rules out airborne trans- mission.

The incubation period for CCHF is about 2-9 days. Initial symptoms are nonspecific and sometimes occur suddenly. They include fever, headache, myalgia, arthralgia, abdominal pain, and vomiting. Sore throat, conjunctivitis, jaundice, photophobia, and various sensory and mood alterations may develop. A petechial rash is common and may precede a gross and obvious hemorrhagic diathesis, manifested by large ecchymoses, bleeding from needle-puncture sites, and hemorrhage from multiple other sources. The case-fatality rate has been estimated to range from 15% to 70% (2), but mild or inapparent infections occur. One study suggested an illness-to-infection

Diagnosis requires isolating the virus from blood during the first week of illness or detecting rising antibody titer by IFA, complement fixation, or one of several other methods. No data are available on the evaluation of IgM antibody response. Nonspecific laboratory abnormalities include progressive neutropenia, lymphopenia, thrombocytopenia, and anemia. Hyperbilirubinemia and elevated liver enzymes are common.

Treatment is supportive and may require intensive care. Ribavirin inhibits CCHF virus in vitro, but its efficacy in clinical practice remains unconfirmed. Although immune plasma has been used its effectiveness has not been evaluated.

APPROACH TO A SUSPECTED CASE OF VHF

General Principles

The patient's travel history, symptoms, and physical signs provide the most important clues to the potential diagnosis of VHF. Under natural circumstances, infection is most often acquired in rural areas, and for most visitors and tourists to areas with endemic VHF, exposure to the causative agents is extremely unlikely. If the patient has visited exclusively urban zones, a diagnosis of VHF is improbable. The diagnosis is realistically

excluded if the interval between the onset of symptoms and the last possible exposure exceeds 3 weeks. A careful history must be taken about the patient's possible exposure to ill persons or traveling companions in an area with endemic VHF.

Initial symptoms may include fever, headache, sore throat, myalgia, abdominal pain, and diarrhea. Diagnosis at this stage is difficult, since these symptoms are nonspecific. The differential diagnosis is wide and includes other viral infections -- particularly arbovirus infections -- bacterial infections such as typhoid fever, rickettsial diseases, and parasitic infections such as malaria. Symptoms and signs supporting the diagnosis of VHF are pharyngitis and conjunctivitis, a skin rash (particularly for Marburg and Ebola virus diseases), and later, hemorrhage and shock.

Two critical studies should be done for any patient who has recently returned from the tropics and has fever; these are a blood-film examination for malaria and blood cultures. An experienced technician may need to examine several blood smears to identify malarial parasites, particularly for patients who have taken prophylactic antimalarial chemotherapy. When VHF is a diagnostic possibility, blood cultures must be done in a closed system. These initial specimens should be handled with the same precautions used for samples infected with hepatitis B virus or human immunodeficiency virus. An experienced technician should be briefed about the safe handling of such material. All of the patient's body fluids, secretions, and excre-tions

If clinicians feel that VHF is a likely diagnosis, they should take two immediate steps: 1) isolate the patient, and 2) notify local and state health departments and CDC.

The aim of management is to provide optimal care to the patient with the least hazard to staff. A mobile laboratory capable of performing routine laboratory tests is available on request from CDC (see below). Laboratory tests essential for the patient's immediate care must be done by trained staff using the precautions outlined in this document. Meticulous adherence to barrier-nursing procedures and precautions to prevent contact with blood or other body fluids are fundamental to the effective management of patients with possible VHF and to the protection of the staff.

ISOLATION OF PATIENTS WITH SUSPECTED AND CONFIRMED VHF

General Principles

Extensive experience in West Africa has shown that the ordinary pre-cautions patients infected with hepatitis B virus or human immunodeficiency virus, combined with barrier nursing, effectively prevent Lassa virus transmission in hospitals (19). Ideally, patients should be cared for at the hospital where they are first seen, since patients ill with VHF tolerate the stress of transfer poorly, and a move only increases the potential for secondary transmission. If care at the hospital where the patient presented is not possible, transfer to another local facility is preferable to travel to a more distant center. Personnel involved in the transfer of patients with suspected VHF must follow the same precautions recommended for medical and nursing staff.

The patient should be isolated in a single room with an adjoining anteroom serving as its only entrance. The anteroom should contain supplies for routine patient care, as well as gloves, gowns, and masks for the staff. The Appendix lists suggested supplies for the anteroom. Hand-washing facilities should be available in the anteroom, as well as containers of decontaminating solutions. If possible, the patient's room should be at negative air pressure compared with the anteroom and the outside hall, and the air should not be recirculated. However, this is not absolutely required, and does not constitute a reason to transfer the patient. If a room such as described is not available, use adjacent rooms to provide safe and adequate space.

Strict barrier-nursing techniques should be enforced: all persons entering the patient's room should wear disposable gloves, gowns, masks, and shoe covers. Protective eye wear should be worn by persons dealing with disoriented or uncooperative patients or performing procedures that might involve the patient's vomiting or bleeding (for example, inserting a nasogastric tube or an intravenous or arterial line). Protective clothing should be donned and removed in the anteroom. Only essential medical and nursing personnel should enter the patient's room and anteroom. Isolation signs listing necessary precautions should be posted outside the anteroom.

The patient should use a chemical toilet. All secretions, excretions, and other body fluids (other than laboratory specimens) should be treated with disinfectant solution. All material used for patients, such as disposable linen and pajamas, should be double-bagged in airtight bags. The outside bags should be sponged with disinfectant solution and later incinerated or autoclaved. Disposable items worn by staff, such as gowns, gloves, etc., should be similarly treated. Disposable items used in patient care (suction catheters, dressings, etc.) should be placed in a rigid plastic container of disinfectant solution. The outside of the container should be sponged with disinfectant, and the container should be auto- claved, incinerated, or otherwise safely discarded.

If surgery is required, surgical staff should wear protective eye wear and double gloves. Advice should be sought from CDC.

Disinfectant Solutions

Lipid-containing viruses, including the enveloped viruses, are among the most readily inactivated of all viral agents (50). Suitable disinfectant solutions include 0.5% sodium hypochlorite (10% aqueous solution of household bleach), as well as fresh, correctly prepared solutions of glutaraldehyde (2% or as recommended by the manufacturer) and phenolic disinfectants (0.5%-3%) (50,51). Soaps and detergents can also inactivate these viruses and should be used liberally.

CONFIRMATION OF THE DIAGNOSIS

General Principles

The diagnosis of VHF is confirmed by isolating the virus or by demonstrating IgM antibody or a fourfold rise in IgG antibody in serum, as described earlier. Antibody may not appear in blood until the second week of illness. Virus is usually recovered from blood, although Lassa virus may also be isolated from the throat or urine. Liver tissue collected after death may also be a rich source of virus.

Virus isolation must only be attempted in Biosafety Level 4 facilities (52), such as are available at CDC. Serologic tests can be performed either at CDC or in the mobile laboratory (see below). Serologic tests for antibodies are done with gamma-irradiated antigens and serum samples that have been inactivated with heat or gamma irradiation.

Handling Laboratory Specimens

Collecting Specimens

Recommendations for safely collecting and transporting specimens remain unchanged. The essential specimens to be submitted for virus isolation are a sample of venous blood, a midstream ("clean catch") specimen of urine, and a throat swab. If postmortem specimens are available, serum, liver, spleen, and kidney tissue are desirable. The following procedures should be followed:

1. Glass containers should not be used. Disposable sharp objects, such

as scalpel blades, also should not be handled unnecessarily after use and should be autoclaved or incinerated.

2. Venous blood samples must be collected with extreme care to avoid self-inoculation. Ten milliliters of clotted blood should be placed in a sealed plastic container. Needles should not be recapped, bent, broken, removed from disposable syringes, or otherwise handled. Blood-taking equipment should be put in a rigid plastic container filled with disinfectant solution and autoclaved or incinerated.

3. Midstream urine specimens should be collected by clean catch. Five milliliters of urine should be put in a plastic screw-cap container with one of the following: rabbit serum albumin diluted to a final concentration of 25%, human serum albumin diluted to a 1% concentration, or bovine serum albumin at a final concentration of

10%.

4. Throat swabs should be placed in plastic screw-cap containers in 1 ml of sterile, phosphate-buffered neutral saline containing 25% rabbit serum, 1% human serum albumin, or 10% bovine serum albumin.

The outside of each specimen container should be swabbed with disinfectant, and a label should be attached bearing the patient's name, hospital identification, the date of collection, and the nature of the suspected infection. Then, the specimens should be double-bagged in secure, airtight and watertight bags, which have been similarly labeled. Bags containing specimens should be sponged with disinfectant before they are removed from the patient's room.

Packaging and Transporting Specimens

The Office of Biosafety at CDC (ext. 3883), the persons listed in the Introduction, or the state health department should be contacted for instructions on packaging, labeling, and shipping diagnostic laboratory specimens since shipment of specimens is subject to the applicable provisions of the Federal interstate quarantine regulations (53). In general, the specimens should be packaged as follows:

1. Place the specimens for transport in a tightly sealed, watertight

container, such as a screw-cap plastic tube or vial, and seal the cap with tape. Make sure plastic containers are resistant to temperatures as low as -80 degrees C. If the specimen is in a glass or other unsuitable container, it should be carefully transferred using the laboratory precautions listed below.

2. Wrap the primary container in sufficient absorbent material (for example, tissue) to absorb the entire contents in case the container leaks or breaks.

3. Place the wrapped, sealed primary container in a durable, watertight screw-cap mailing tube or metal can. This secondary container should be sealed with tape. Several primary containers of specimens, each individually wrapped in absorbent material, may be placed in one secondary container, to a maximum of 50 ml of specimen material.

4. On the outside of the secondary container, attach the specimen labels and other relevant information.

5. Place the secondary container in a secure box or mailing tube addressed to one of the individuals listed in the Introduction.

6. Transport the specimen for virus isolation on dry ice. 7. Since individual commercial and noncommercial carriers or shipping services may apply different regulations for transporting biologic specimens, contact a representative of the chosen carrier beforehand to ensure that all necessary formalities are fulfilled. One person listed in the Introduction must be contacted by telephone about the specimen's nature, the method of shipment, and the expected date and time of arrival at CDC.

Exposure of Laboratory Personnel to Specimens

Laboratory tests should be kept to the minimum required for the immediate care of the patient until the mobile laboratory arrives. Critical investigations, such as examination of a blood smear for malaria and the inoculation of blood cultures, must not, however, be postponed. Laboratory staff dealing with specimens from patients who might have a VHF must take the same personal precautions as patient-care staff. Surgical gloves, gowns, shoe covers, and masks should be worn. When possible, laboratory tests should be performed in biological safety cabinets. Blood cultures should be prepared in a closed system. Every effort should be made to avoid creating an aerosol or splashing, and protective eye wear should be worn if possible. A full-face respirator with an HEPA (high efficiency particulate air) filter is an acceptable, but cumbersome alternative to masks and protective eye wear. Nonessential tests should not be performed, nor should routine automated equipment be used unless the specimen has been inact- ivated. Abundant supplies of disinfectant solutions should be readily available. Safe

laboratory work has been done with use of these precautions for many years in VHF-endemic areas with poorly equipped hospitals.

Laboratory personnel accidentally exposed to potentially-infected material (for example, through injections or cuts or abrasions on the hands) should immediately wash the infected part, apply a disinfectant solution such as hypochlorite solution, and notify the patient's physician. The person should then be considered as a high-risk contact and placed under surveillance (see below).

Accidental spills of potentially contaminated material should be liberally covered with disinfectant solution, left to soak for 30 minutes, and wiped up with absorbent material soaked in disinfectant.

CLINICAL CARE OF PATIENTS WITH SUSPECTED VHF

General Principles

The challenge of managing patients with VHF is to provide the highest quality of care with the least risk of transmitting infection. Detailed discussion about therapy is beyond the scope of this document. Patients require close supervision, and some will need modern intensive-care facilities. Since pathogenesis is not entirely understood and antiviral therapy is limited, treatment is largely supportive. It is essential to give careful attention to fluid and electrolyte balance. In severe cases, therapy will be required for shock and blood loss. The supportive care of patients critically ill with VHF is the same as the conventional care provided to patients with other causes of multisystem failure. Adult respiratory distress syndrome, renal failure, seizures, and coma may require specific interventions, such as mechanical ventilation, dialysis, and neurologic intensive care. If surgery is required (for example, obstetric intervention), it should be done.

The prognosis for patients with Lassa fever has been shown to correlate with levels of viremia, but not with the development of IgM or IgG anti-bodies (virus. Experimental infections with Lassa and Ebola viruses in rhesus monkeys suggest that shock results from platelet and endothelial dysfunction, with subsequent leakage of fluid from the intravascular system and hemorrhage. To date, therapeutic use of heparin or corticosteroids has not proven effective and is probably contraindicated.

Patients with Lassa fever should receive ribavirin (see box). For severely ill persons, treatment may begin while confirmation of the diagnosis is pending. Ribavirin is recommended both therapeutically for patients with Lassa fever and prophylactically for high-risk contacts of such patients. Its use for patients with CCHF and their high-risk contacts may be justified but is unstudied.

Treatment Regimen

Ribavirin 30 mg/kg intravenously (IV) loading dose, then 16 mg/kg IV every 6 hours for 4 days, and then 8 mg/kg IV every 8 hours for 6 days (total treatment time 10 days).

Prophylactic Regimen

Ribavirin 500 mg by mouth every 6 hours for 7 days.

Use of convalescent plasma for Lassa fever Is not currently recommended. Analogues of prostacyclin are being evaluated as to their efficacy in restoring the endothelial cell defect (20). Therapy can be discussed with persons listed in the Introduction.

Clinical experience with Ebola and Marburg virus diseases is limited, and individual judgment must determine whether convalescent plasma or antiviral drugs should be used. Interferon and ribavirin show no in vitro effect against these agents.

Ribavirin has been shown effective against some of the Bunyaviridae in vitro, and its use in patients with CCHF seems reasonable, although no clinical experience is available.

MOBILE LABORATORY

CDC has adapted a mobile isolator that can be used as a portable laboratory to investigate cases of suspected or confirmed VHF safely (54). This facility can be transported immediately to any part of the United States, with an accompanying technician and physician experienced in dealing with hemorrhagic fevers. The mobile laboratory has facilities for routine hematologic and biochemical studies, as well as for basic bacter- iologic and coagulation investigations. Serodiagnostic tests for VHF can be performed in this facility, but cultures for virus isolation cannot. Electrolyte measurements on inactivated serum specimens are also possible, but blood gas analysis is not. Early use of this facility is preferable to delays in investigating the suspected case because of concern about the hazards of handling specimens. Further information about the mobile laboratory and its use can be obtained from the persons listed in the Introduction.

AUTOPSY AND HANDLING OF A CORPSE

Before an autopsy is done on a patient suspected to have died from VHF, the possible risks and benefits must be carefully considered. Autopsies have been conducted safely on these patients, sometimes without prior knowledge of the diagnosis (34), but under some circumstances it may be wiser to forego this procedure. Limited autopsy or postmortem collection of blood and percutaneous liver biopsy material may be appropriate.

The same precautions recommended for clinicians and laboratory staff working with infected patients and specimens must be followed. Double gloves, caps and gowns, waterproof aprons, shoe covers, and protective eye wear are required. Aerosol formation must be avoided (for example, electrical cutting instruments must not be used). All solid and liquid waste should be decontaminated with disinfectant solution or by heating for 1 hour at 60 degrees C. Liquid waste can then be washed down the drain; solid waste should be incinerated.

All unnecessary handling of the body, including embalming, should be avoided. Persons who dispose of the corpse must take the same precautions outlined for medical and laboratory staff. The corpse should be placed in an airtight bag and cremated or buried immediately.

DECONTAMINATION PROCEDURES

Disposable items, such as pipette tips, specimen containers, swabs, etc., should be placed in a container filled with disinfectant solution and incinerated. Clothes and blankets that were used by the patient should be washed in a disinfectant, such as hypochlorite solution.

Nondisposable items such as endoscopes used in patient care must be cleaned with decontaminating fluids (for example, gluteraldehyde or hypochlorite). Laboratory equipment must be treated similarly. All non- disposable materials that withstand autoclaving should be autoclaved, after they have been soaked in disinfectant solution. The patient's bed and other exposed surfaces in the hospital room, or in vehicles used to transport the patient, should be decontaminated with disinfectant solution.

IDENTIFICATION, SURVEILLANCE, AND MANAGEMENT OF PATIENT CONTACTS

A contact is defined as a person who has been exposed to an infected person or to an infected person's secretions, excretions, or tissues within 3 weeks of the patient's onset of illness. Contacts may be subdivided into three levels of risk.

1. Casual contacts are persons who had remote contact with the ill

patient. These include persons on the same airplane, in the same hotel, etc. Since the agents of VHF are not spread by such contact, no special surveillance is indicated.

2. Close contacts are persons who had more than casual contact with the patient. They include persons living with the patient, nursing or serving the patient when he or she was ill, shaking hands with or hugging the patient, handling the patient's laboratory specimens, etc. These contact persons should be identified by state and local

health departments, in collaboration with CDC, as soon as VHF is considered a likely diagnosis for the index case. Once the diagnosis is confirmed, close contacts should be placed under surveillance. This requires these individuals to record their temperatures twice daily and report any temperature of 101 degrees F (38.3 degrees C) or above or any symptom of illness to the public health officer responsible for surveillance. Surveillance should be continued for 3 weeks after the person's last contact with the index patient.

3. High-risk contacts are persons who have had mucous membrane contact with the patient, such as kissing or sexual intercourse, or have had a needle stick or other penetrating injury involving contact with the patient's secretions, excretions, blood, tissues, or other body fluids. These individuals should be placed under surveillance as soon as VHF is considered a likely diagnosis in the index case.

Any contact who develops a temperature of 101 degrees F (38.3 degrees C) or higher or any other symptoms of illness should be immediately isolated and treated as a VHF patient. Ribavirin should be prescribed as postexposure prophylaxis for high-risk contacts of patients with Lassa fever. Dosage schedules are given in the box on page 11. Although experience is more limited, postexposure prophylaxis with ribavirin is also recommended for high-risk contacts of patients with CCHF.

Convalescent patients and their contacts should be warned that some of the causative agents of VHF may continue to be excreted for many weeks in semen, as demonstrated with Marburg (32,34) and Ebola (29) viruses, and in urine, as occurs sometimes with Lassa virus (13). It is recommended that the persons listed in the Introduction be contacted about arranging shipment to CDC of seminal fluid and urine specimens from patients in the convalescent period for virus isolation. Convalescent patients must be meticulous about personal hygiene. While data are limited concerning infectivity in the convalescent period, abstinence from sexual intercourse is advised until genital fluids have been shown to be free of the virus. If the patient does engage in sexual intercourse before tests are done, the use of condoms is advised.

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Appendix: Suggested Equipment and Supplies for Anteroom Adjoining Patient's Room

Prescribed medications (analgesics, Containers with solution for throat

antipyretics, antibiotics, etc.) swabs and urine specimens (see Resuscitation equipment text) Material for physical examination Labels Portable X-ray machine Marker pens Electrocardiogram machine Plastic airtight bags (various Intravenous equipment and supplies sizes) Tourniquets Plastic trash bags Dry gauze Disinfectant solutions (see text) Alcohol swabs Chemical toilet Needles (various sizes) Urinals Syringes (various sizes) Nursing supplies Plastic container for disposal of Disposable linen, towels, pajamas,

needles and other sharp equipment etc. Tubes for hematologic and Toilet articles

biochemical investigations Gowns, masks, surgical gloves, shoe Blood-culture bottles covers, and protective eye wear

for staff Housekeeping materials

(absorbent towels for spills, etc.)

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