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LASSA FEVER OR LASSA HEMORRHAGIC FEVER RISK TO HUMANS FROM RODENT-BORNE ZOONOSES

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Abstract

Viral hemorrhagic fevers (VHFs) typically manifest as rapidly progressing acute febrile syndromes with profound hemorrhagic manifestations and very high fatality rates. Lassa fever, an acute hemorrhagic fever characterized by fever, muscle aches, sore throat, nausea, vomiting, diarrhea and chest and abdominal pain. Rodents are important reservoirs of rodent-borne zoonosis worldwide. Transmission rodents to humans occur by aerosol spread, either from the genus *Mastomys* rodents' excreta (multimammate rat) or through the close contact with infected patients (nosocomial infection). Other rodents of the genera *Rattus, Mus, Lemniscomys,* and *Praomys* are incriminated rodents hosts. Now one may ask do the rodents' ectoparasites play a role in Lassa virus zoonotic transmission.

This paper summarized the update knowledge on LHV; hopping it might be useful to the clinicians, nursing staff, laboratories' personals as well as those concerned zoonoses from rodents and rodent control.

Key words: Lassa fever, West Africa, Human infection, clinical picture & fatality, Rodents.

Introduction

The Lassa fever or Lassa hemorrhagic fever (LHF) is an acute viral hemorrhagic fever caused by the Lassa-virus and first described in 1969 when two missionary nurses died in the town of Lassa, in Bornu State Nigeria and named after the town (Frame *et al*, 1970). Lassa fever is a member of the family Arenaviridae virus, similar to Ebola, and occurs in West Africa. The virus, a member of the virus family *Arenaviridae*, is a single-stranded RNA virus and is zoonotic, or animal-borne (Ogbu *et al*, 2007). Lassa virus is endemic in Sierra Leone, Guinea and Liberia (known as the Mano River region) and Nigeria and Lassa fever cases from these countries are being reported annually. Recent investigations have found evidence for an expanded the endemic zone between the two known Lassa endemic regions indicating that LASV is more widely distributed throughout the Tropical Wooded Savanna Eco-zone in West Africa (Sogoba *et al*, 2012).

Lassa fever was restricted to West Africa and transmission to humans occurs through aerosol spread, either from the rodents or through close contact with infected patients. The incubation period is about ten days (range 6 to 21 days). A CDC Health Advisory described a 38 year-old man who had been in Liberia for five months and who died in a New Jersey hospital from probable Lassa fever in August 2004; this was the first reported case in the United States since 1989 (CDC, 2004). Person-to-person transmission can occur via exposure via percutaneous injury to body fluids that are infectious (e.g., blood, urine, vomitus), unprotected contact with potentially infectious material (e.g., touching vomitus), and mucosal exposure from splashes of body fluids

Review and Discussion

Abroad, many scientists were interested in Lassa hemorrhagic fever and published much valuable work the following were selected ones of great concern.

Lassa fever is restricted to West Africa, however importation of Lassa fever into Germany (Haas *et al*, 2003), the Netherlands

(Veldkamp and Schippers, 2002), the United Kingdom (CDC, 2000), Europe (Schmitz *et al*, 2002), and the United States (CDC, 2004) by travelers on commercial airlines illustrated the potential for the spread of this highly dangerous and contagious pathogen. In addition, Lassa virus has gained notoriety because it is classified as a Category A bioweapon agent (Borio *et al*, 2002)

Armignacco *et al*. (2001) stated that only the LHV, CCHV, Ebola and Marburg viruses are capable of person-to-person spread, and added that these four diseases are endemic only in few areas in the world; most notably Africa and some rural parts of the Middle East and the Eastern Europe, but the increasing in international travel gave a greater chance for the introduction of these infections and/or suspected cases into other countries. These might: 1) patients arriving as a result of a planned medical evacuation; 2) persons who became sick on route to their destination; 3) persons discovered ill when entering a country, by routine clinical examination at the airport; 4) persons becoming sick after their arrival. Günther *et al*. (2001) reported that there was a range of laboratory investigations that are performed to diagnose the disease and assess its course and complications. ELISA test for the antigen and IgM antibodies gave 88% sensitivity and 90% specificity for the presence of the infection. Other laboratory included the lymphopenia (low white blood cell count), thrombocytopenia (low platelets), proteinuria & elevated aspartate aminotransferase (AST) levels in the blood. Normal cerebrospinal fluid, but may contain a few leukocytes. The pleural effusions and interstitial infiltrates could be noted on chest X-ray..

Dietrich (2004) reported that the primary animal host is the natal multimammate mouse (*Mastomys natalensis*), an animal indigenous mostly to the Sub-Saharan Africa, and transmission by the contact with the feces or urine of animals accessing grain stores in the residences. Other rodent hosts, as *M. erythroleucus*, and the *Rattus* and *Mus* genera, have been incriminated (Bonner *et al*, 2007).

Idemyor (2010) reported that Lassa fever is a severe, often fatal, hemorrhagic fever caused by Lassa virus, an Arenavirus that can be transmitted to humans from asymptomatically infected multimammate rats. The speculation is that Lassa viral infection might affect between 2 to 3 million people each year in certain portions of the West African region, causing a mortality of about 10000 during the same period. Lassa fever is one of the endemic zoonosis in Nigeria with a high probability for nosocomial transmission due to several health care sector challenges. Although treatment is available for Lassa fever, early diagnosis is still difficult in almost all Nigerian health care institutions. The intention of this clinical overview is to: (1) summarize the pertinent literature for clinicians in primary, secondary, and tertiary health care centers; and (2) suggest a need to use the information from basic research and laboratory diagnosis to incorporate international best practices into public health and clinical practice guidelines.

Hastie *et al*. (2011) stated that Arenaviruses cause disease in industrialized and developing nations alike. Among them, the hemorrhagic fever virus Lassa is responsible for ~300,000-500,000 infections per year in the Western Africa. The arenavirus nucleoprotein (NP) forms the protein scaffold of the genomic ribonucleoprotein complexes and is critical for transcription and replication of the viral genome. Here, we present crystal structures of the RNA-binding domain of Lassa virus NP in complex with ssRNA. This structure showed, in contrast to the predicted model, that RNA binds in a deep, basic crevice located entirely within the N-terminal domain. Moreover, the NP-ssRNA structures presented here, combined with hydrogen-deuterium exchange/MS and functional studies, suggest a gating mechanism by which NP opens to accept RNA. Directed mutagenesis and functional studies provide a unique look into how the arenavirus NPs

bind to and protect the viral genome and also suggest the likely assembly by which viral ribonucleoprotein complexes are organized.

Branco *et al.* (2011a) reported that Lassa fever (LF) is a devastating hemorrhagic viral disease that is endemic to West Africa and responsible for thousands of human deaths each year. Analysis of humoral immune responses (IgM and IgG) by antibody-capture ELISA (Ab-capture ELISA) and Lassa virus (LASV) viremia by antigen-capture ELISA (Ag-capture ELISA) in suspected patients admitted to the Kenema Government Hospital (KGH) Lassa Fever Ward (LFW) in Sierra Leone over the past five years is reshaping our understanding of acute LF. They added that LF patients who were Ag positive were more likely to die than suspected cases who were only IgM positive. Analysis of metabolic and immunological parameters in Ag positive LF patients revealed a strong correlation between survival and low levels of IL-6, -8, -10, CD40L, BUN, ALP, ALT, and AST. Despite presenting to the hospital with fever and in some instances other symptoms consistent with LF, the profiles of Ag negative IgM positive individuals were similar to those of normal donors and nonfatal (NF) LF cases, suggesting that IgM status cannot necessarily be considered a diagnostic marker of acute LF in suspected cases living in endemic areas of West Africa.

Branco *et al.* (2011b) mentioned that recent capacity building at the Kenema Government Hospital Lassa Fever Ward (KGH LFW) in Sierra Leone has lead to a major turning point in the diagnosis, treatment and study of LF. They present the first comprehensive rapid diagnosis and real time characterization of an acute hemorrhagic LF case at KGH LFW. The case report focused on a third trimester pregnant in a Sierra Leonean woman from the historically non-endemic Northern district of Tonkolili who survived the illness despite fetal demise. Employed in this study were newly developed recombinant LASV Antigen Rapid Test cassettes and the dipstick lateral flow immunoassays (LFI) that enabled the diagnosis of LF within twenty minutes of sample collection. Deregulation of overall homeostasis, significant hepatic and renal system involvement, and the immunity profiles were extensively characterized during the course of hospitalization. Rapid diagnosis, prompt treatment with a full course of intravenous (IV) ribavirin, IV fluids management, and the real time monitoring of clinical parameters resulted in a positive maternal outcome despite admission to the LFW seven days post onset of symptoms, fetal demise, and a natural still birth delivery. These studies solidified the growing rapid diagnostic, treatment, and surveillance capabilities at the KGH LF Laboratory, and the potential to significantly improve the current high mortality rate caused by LF. As a result of the growing capacity, the authors were able to isolate Lassa virus (LASV) RNA from the patient and perform Sanger sequencing and they found significant genetic divergence from the commonly circulating LV Sierra Leonean strains, showing potential for the discovery of a newly emerged LASV strain with expanded geographic distribution. Besides, the emergence of LF cases in Northern Sierra Leone highlights the need for the superior diagnostics to aid in monitoring of the LASV strain divergence with the potentially increased geographic expansion.

Hensley *et al*. (2011) performed a pilot study to begin to understand the progression of LASV infection in nonhuman primates. The dendritic cells were identified as a prominent target of LASV infection in a variety of tissues in all animals at day 7 while Kupffer cells, hepatocytes, adrenal cortical cells, and endothelial cells were more frequently infected with LASV in tissues of terminal animals (days 13.5-17). Meningoencephalitis and neuronal necrosis were noteworthy findings in terminal animals. Evidence of coagulopathy was noted; however, the degree of fibrin deposition in tissues was less prominent than has been reported in other

viral hemorrhagic fevers. They concluded that the sequence of pathogenic events identified in this study begins to shed light on the development of disease processes during Lassa fever and also may provide new targets for rational prophylactic and chemotherapeutic interventions.

Grove *et al*. (2011**)** stated that Lassa fever is a neglected tropical disease with a significant impact on the health care system of endemic West African nations. To date, case reports of Lassa fever have focused on laboratory characterization of serological, biochemical and molecular aspects of the disease imported by infected individuals from Western Africa to the United States, Canada, Europe, Japan and Israel. Our report presents the first comprehensive real time diagnosis and characterization of a severe, hemorrhagic Lassa fever case in a Sierra Leonean individual admitted to the Kenema Government Hospital Lassa Fever Ward. Fever, malaise, unresponsiveness to anti-malarial and antibiotic drugs, followed by worsening symptoms and onset of the hemorrhaging prompted medical officials to suspect Lassa fever. A recombinant Lassa virus protein based diagnostic was employed in diagnosing Lassa fever upon admission. This patient experienced a severe case of Lassa hemorrhagic fever with dysregulation of overall homeostasis, significant liver and renal system involvement, the interplay of pro- and anti-inflammatory cytokines during the hospitalization course and an eventual successful outcome. These studies provided new insights into the pathophysiology and management of this Lassa viral illness and outline the improved infrastructure, the research and real-time diagnostic capabilities within LASV endemic areas.

Pannetier *et al*, (2011) compared the Lassa virus with its genetically close but nonpathogenic homolog Mopeia virus (MV), which was used to model nonfatal LF. They added that strong and early activation of antigen-presenting cells (APC) may play a crucial role in controlling infection. They developed an *in-vitro* model of the dendritic-cell (DC)-T-cell co-culture in order to characterize the human T-cell responses induced by MV- or LV-infected DCs. Our results show very different responses to infection with LV and MV. MV strongly and durably stimulated CD8 (+) and CD4(+) T cells, showing early and high activation, a strong proliferative response, and acquisition of effector and memory phenotypes.

Furthermore, robust and functional CD4 (+) and CD8 (+) cytotoxic T lymphocytes (CTL) were generated. LV, however, induced only weak memory responses. Thus, this study allows an improved understanding of the pathogenesis and immune mechanisms involved in the control of human LV.

Ölschläger *et al.* (2011) compared the anti-arenaviral effect of ribavirin with that of two other IMPDH inhibitors, mycophenolic acid (MPA) and 5-ethynyl-1-β-d-ribofuranosylimidazole-4-carboxamide (EICAR). All three compounds were able to inhibit LHV replication by ≥2 log units in cell culture. Restoring the intracellular GTP pool by exogenous addition of guanosine reversed the inhibitory effects of the MPA and EICAR, while ribavirin remained fully active. Analogous experiments performed with Zaire Ebola virus showed that IMPDH inhibitors were also active against this virus, although to a lesser extent than against Lassa virus. They concluded that the experiments with MPA and EICAR indicated that replication of Lassa and Ebola virus is sensitive to depletion of the GTP pool mediated via inhibition of IMPDH and added that this was not the predominant mechanism by which ribavirin exerts its *in-vitro* antiviral effect on Lassa virus.

Zapata *et al*. (2011) found that the Arenaviruses such as Lassa fever virus (LASV) and lymphocytic choriomeningitis virus (LCMV) were benign in their natural reservoir hosts, and could occasionally cause severe viral hemorrhagic fever (VHF) in the non-human primates and in human beings. LCMV is considerably more benign for hu-

man beings than Lassa virus, however certain strains, like the LCMV-WE strain, can cause severe disease when the virus is delivered as a high-dose inoculum. Here we describe a rhesus macaque model for Lassa fever that employs a virulent strain of the LCMV. Since LASV must be studied within Biosafety Level-4 (BSL-4) facilities, the LCMV-infected macaque model has the advantage that it can be used at BSL-3. LCMV-induced disease is rarely as severe as other VHF, but it is similar in cases where vascular leakage leads to lethal systemic failure. The LCMV-infected macaque has been valuable for describing the course of disease with differing viral strains, doses and routes of infection. By monitoring system-wide changes in physiology and gene expression in a controlled experimental setting, it was possible to identify events that were pathognomonic for developing VHF and potential treatment targets

Weidmann *et al*. (2011) mentioned that information on the replication of viral hemorrhagic fever viruses was not readily available and had never been analyzed in a comparative approach. When compared the cell culture growth characteristics of hemorrhagic fever viruses (HFV), of Arenaviridae, Filoviridae, Bunyaviridae, and Flavivridae virus families by the performing quantitative analysis of cell culture supernatants by (i) EM for the quantification of virus particles, (ii) quantitative real time PCR for the quantification of genomes, and (iii) determination of focus forming units by coating fluorescent antibodies to infected cell monolayers for the quantification of virus infectivity. The comparative analysis revealed that filovirus and RVFV replication results in a surplus of genomes but varying degrees of the packaging efficiency and infectious particles. More efficient replication and packaging was observed for Lassa virus, and Dengue virus resulting in a better yield of infectious particles while, YFV turned out to be most efficient with only 4 particles inducing one FFU. For Crimean-Congo hemorrhagic fever virus (CCHFV) a surplus of empty shells was observed with only one in 24 particles equipped with a genome. The complete particles turned out to be the extraordinarily infectious.

Asogun *et al*. (2012) stated that in West Africa, where Lassa is most prevalent, it was difficult for doctors to diagnose the infection due to the absence of both facility and proper equipment to perform tests.

Kolokoltsov *et al*. (2012) mentioned that Arenaviruses and filoviruses are capable of causing hemorrhagic fever syndrome in humans. Limited therapeutic and/or prophylactic options are available for humans suffering from viral hemorrhagic fever. In this report, we demonstrate that pre-treatment of host cells with the kinase inhibitors genistein and tyrphostin AG1478 leads to inhibition of infection or transduction in cells infected with Ebola virus, Marburg virus, and Lassa virus. The results demonstrated that a kinase inhibitor cocktail consisting of genistein and tyrphostin AG1478 is a broad-spectrum antiviral that may be used as a therapeutic or prophylactic against arenavirus and filovirus hemorrhagic fever.

Animals: The reservoir, or host, of LHV is a rodent known as the "multimammate rat" (*Mastomys natalensis*). Once infected, this rodent is able to excrete virus in urine for an extended time period, maybe for the rest of its life. *Mastomys* rodents breed frequently, produce large numbers of offspring, and are numerous in the savannas and forests of west, central, and east Africa (Tayeh *et al*, 2010). In addition, *Mastomys* readily colonize human homes and areas where food is stored. All of these factors contribute to the relatively efficient spread of Lassa virus from infected rodents to humans. *Mastomys* rodents shed the virus in urine and droppings and direct contact with these materials, through touching soiled objects, eating contaminated food, or exposure to open cuts or sores, can lead to infection. Moreover, Gryseels *et al.* (2015) reported that despite its near pan-African range, M. nata-

lensis carried distantly related viruses even in the same geographical area is a potent reservoir host for a variety of arenaviruses.

Apart from rodents of the genus *Mastomys* the main reservoir of LHV, other rodent species have been involved as well; Wulff *et al*. (1975) reported that a total of eight Lassa virus strains were isolated from the tissues and blood of rodents identified in the field as they were of three different species: *M. natalensis*, *Rattus rattus,* and *Mus minutoides*. Garba *et al.* (2014) in Niger stated that the invasive rodents have been responsible for the diffusion worldwide of many zoonotic agents, thus representing major threats for public health. Cities are important hubs for people and goods exchange and are thus expected to play a pivotal role in invasive commensal rodent dissemination. They added that (i) two species (rural-like vs. truly commensal) assemblages can be identified, and that (ii) within commensal rodents, invasive (*Rattus rattus* and *Mus musculus*) and native (*M. natalensis*) species are spatially segregated. Fichet-Calvet *et al*. (2014) experimentally found that *M. natalensis* rodents become horizontally infected, clearing the virus within a period significantly shorter than their life span, and develop antibodies. In addition, the detection of antibodies in other species (*Lemniscomys striatus, Praomys daltoni, Mus minutoides*, and *Praomys rostratus*) trapped in the habitats of *M. natalensis* suggested spillover infections.

Transmission: As zoonosis, Lassa fever could be transmitted directly from rodent-to-rodent, rodent-to-human, and human-to-human (Colebunders *et al*, 2002), and even human-to-rodent transmission patterns were possible (Lo Iacono *et al,* 2015). LHV can be contracted by an air-borne route or with direct contact with infected human blood (Frame *et al*, 1979), LHV could be isolated in the blood, feces, urine, throat swab, vomit, semen and saliva of infected persons or even mucosal exposure from splashes of body fluids and the secretion of the virus from infected individuals can continue for 30 days or more (WHO, 2005). Besides, transmission across placenta and via breast milk could also occur as well as laboratory-acquired infection was documented (CDC, 1988). In a Nigerian Teaching Hospital, three doctors and four nurses were among 108 patients' fatalities (WHO, 2012). Ftika and Maltezou (2013) stated that the potentiality of human-to-human transmission in VHFs led to the onset of large nosocomial outbreaks include Crimean-Congo hemorrhagic fever, Ebola hemorrhagic fever, Marburg hemorrhagic fever and Lassa fever that nosocomial outbreaks were increasingly reported nowadays and likely reflects the dynamics of VHFs emergency.

Signs and Symptoms: Signs and symptoms of Lassa fever typically occur 1-3 weeks after the patient comes into contact with the virus. For the majority of Lassa fever virus infections (approximately 80%), symptoms are mild and are undiagnosed. Mild symptoms include slight fever, general malaise, weakness, headache dizziness, retrosternal pain and sore throat as well as gastro-intestinal symptoms as nausea, vomiting and diarrhea (McComick *et al*, 1987). In the 20% of infected individuals, however, disease may progress to more serious symptoms including the hemorrhaging (in gums, eyes, or nose, as examples), respiratory distress, repeated vomiting, and facial swelling, pain in the chest, back, and abdomen, and shock. The neurological problems have also been des-cribed, including the hearing loss, tremors, and encephalitis. Death might occur within two weeks after symptom onset due to multi-organ failure (CDC, 200). The LHF commonest complication is deafness. Various degrees of deafness occur in about one-third of infections, and in many cases hearing loss is permanent. As far as is known, severity of the disease does not affect this complication: deafness may develop in mild as well as in severe cases (Ajayi *et al*, 2013).

Differential diagnosis: As the Lassa fever symptoms are so varied and nonspecific, clinical diagnosis is often difficult especially

early in the course of infection. The signs and symptoms of Lassa fever may be difficult to distinguish from diseases that are common in the tropics such as severe Malaria, Typhoid fever, Streptococcal pharyngitis, Diphtheria, Infectious mononucleosis, Leptospirosis, Rickettsia infections, Meningococcemia as well as Dengue fever, Yellow fever and other viral hemorrhagic fevers as Ebola and Marburg (Wilson, 1991).

Laboratory diagnosis: Isolation of the Lassa virus from blood, throat washings, urine, other tissue of body fluids; demonstration of Lassa-IgM antibody in about 2/3 of the patients on day of hospital administration; and demonstration of fourfold change of the IgG (Wilson, 1991). In Lassa virus-specific RT-PCR was recommended (Vieth *et al*, 2007).

Vaccination: The development of effective vaccines against emerging infectious diseases (EID) can take as much or more than a decade to progress from pathogen isolation/identification to clinical approval. As a result, conventional approaches fail to produce field-ready vaccines before the EID has spread extensively. Falzarano and Feldmann (2013) stated that with a few exceptions, vaccines for viruses that cause hemorrhagic fever remain the unavailable or lack of well-documented efficacy. The two exceptions to this are vaccines against Dengue virus and Rift Valley fever virus, which have proved significant progress in putting forward new and improved vaccines, respectively. Olschläger and Flatz (2013) stated that several promising studies toward the development of a Lassa fever vaccine were published, but no vaccine candidate has been tested in human volunteers or patients. Leblanc *et al*. (2014) used a distributed R&D model involving experts in the fields of protein engineering and production, bioinformatics, peptide synthesis/design and GMP/GLP manufacturing and testing standards. The self-assembled vaccine (SAV immunogenicity was first tested by using the H1N1 influenza specific peptides and the entire VaxCelerate process was tested in a mock live-fire exercise targeting Lassa fever virus. They demonstrated that the Lassa fever vaccine induced significantly increased class II peptide specific interferon-γ CD4(+) T cell responses in HLA-DR3 transgenic mice compared to peptide or MAV alone controls.

Treatment: Ribavirin, an antiviral drug, was successfully used with the Lassa fever patients, in early in the course of illness (Mc-Cormick *et al*, 1986) and post-exposure prophylaxis (Hadi *et al*, 2010). Supportive treatment was often necessary and included fluid replacement, blood transfusion, oxygenation and administration of paracetamol, phylometadione, ringer lactate, haemocoel quinine, broad spectrum antibiotics as well as any other complicated infections (Holmes *et al*, 1990). Debing *et al*. (2013) reported that small molecule antiviral drugs were available for the treatment of infections with herpes-viruses, HIV, HBV and HCV as well as with influenza viruses. Ribavirin, a broad-spectrum (but a specific) antiviral, has been approved for the treatment of infections with respiratory syncytial virus, HCV and Lassa virus. For treatment: Ribavirin 30mg/kg intravenously (IV) loading dose, then 16mg/kg IV every 6 hours for 4 days, and then 8 mg/kg IV every 8 hours for another 6 days (total treatment time 10 days). For prophylactic regimen: Ribavirin 500mg by mouth every 6 hours for 7 days but the use of convalescent plasma for Lassa fever was not currently recommended (CDC, 1988).

Prevention: Primary transmission of the Lassa virus from its host to humans could be prevented by avoiding contact with the *Mastomys* rodents, especially in the geographic regions where outbreaks occurred. Putting food away in rodent-proof containers and keeping the home clean help to discourage rodents from entering indoors. Using these rodents in some areas as a food source was not recommended at all. Trapping in and around homes can help reduce rodent populations; however, the wide distribution of the *Mastomys* in Africa made the complete control of this rodent reservoir impractical. The

Office of Biosafety at CDC (ext. 3883), the persons listed in the introduction, or the state health department should be contacted for the instructions on packaging, labeling, and shipping diagnostic laboratory specimens as the shipment of specimens were subjected to the applicable provisions of the Federal Interstate Quarantine Regulations (CDC, 1980).

In Egypt, at least six families of order Rodentia as well as orders of wild and domestic carnivores were recorded (Osborn and Helmy (1980) most of them were reported in Sinai Peninsula (Morsy *et al*, 1988). On the other hand, Shlaeffer *et al*. (1988) only mentioned that "Lassa fever-first case diagnosed in Israel" without any details.

Conclusion and Recommendations

The Lassa fever is highly contagious and commonly results in death. It is therefore necessary to diagnose and report any suspected case to facilitate the preventive strategies.

Generally, patient's travel history, symptoms, and physical signs provide the most important clues to the potential diagnosis of VHFs. Other challenges include developing more rapid and dependable diagnostic tests and increasing the availability of the only known drug treatment, ribavirin. Research is presently under way to develop a vaccine for Lassa fever.

Undoubtedly, the management and treatment of patients with highly contagious, life threatening diseases such as VHFs are complex and wide-ranging tasks. The strict barrier-nursing techniques should be enforced as wear disposable gloves, gowns; masks, protective eye wear and shoe covers. The availability of appropriate protective equipment and education of health-care workers about the safe clinical practices and infection control is the mainstay for the prevention of the nosocomial spread of not only the VHFs but also the arthropod-borne infectious diseases as pneumonic plague.

No doubt, the controlling of rodents and the protection of food materials from them is a must as transmission of Lassa virus to humans occurs most commonly by the ingestion or inhalation. Nevertheless, one must take into consideration that the rat poisons are controversial, due to the secondary poisoning and risks to children, pets and wildlife. Rodents are difficult to kill with poisons as their feeding habits reflect their place as scavengers. They would eat a small bit of something and wait, and if they don't get sick, they continue. Two generations of poisons were given to rats. The 1st included the Warfarin and Coumatetralyl and the 2nd included Difenacoum, Brodifacoum, Flocoumafen and Bromadiolone. Unfortunately, the rats have developed increasingly resistant to these rodenticides. More researches is also needed to characterize risk of zoonotic infectious diseases in relation to rodents

On the other hand, within the past few years, the number of "new" human diseases associated with pet or wild small-mammal reservoirs has increased dramatically, stimulating renewed interest in reservoir ecology research.

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