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Phillip B. Iverson  
Iowa State University

Loren A. Will  
Iowa State University

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Ebola Hemorrhagic Fever

Phillip B. Iverson, DVM
Loren A. Will, DVM, MPH

History and Introduction

In 1976, epidemics of severe hemorrhagic fever occurred simultaneously in both Zaire and Sudan. Of 550 cases reported, fatalities reached 88% in Zaire and 53% in Sudan, resulting in a total of 430 deaths. Ebola virus, named after a small river in northwestern Zaire, was isolated from both epidemics. It was discovered during this outbreak that the spread of the epidemic was dependent on close contact with clinical cases and that it was stifled when basic quarantine procedures were instituted.

Another fatality occurred in 1977 due to Ebola in a different area of Zaire. While investigating this death, it was discovered that there were probably two previous fatal cases along with a nonfatal case. An missionary physician, Dr. Cairns, contracted the disease in 1972 while conducting an autopsy on a patient thought to have died of yellow fever. In 1979, the original outbreak site in Sudan generated a new episode of Ebola hemorrhagic fever. This resulted in 34 cases with 22 fatalities. Each of these outbreaks was similar in that the index case died before the disease could be recognized. Investigators were brought in to discover the source of the initial infections, but their efforts were fruitless.

No further cases of Ebola hemorrhagic fever were reported until 1989. Similar hemorrhagic fever virus and a new strain of Ebola virus were isolated concurrently from a group of cynomolgus monkeys housed in a quarantine facility in Reston, VA. The Ebola virus spread slowly within quarantine rooms, with death occurring within 2 to 7 days following the onset of clinical signs. Whereas animal handlers were shown to seroconvert, none showed any signs of disease. These events demonstrated that it was a less virulent strain of Ebola than those of Africa for humans. Valuable information concerning the clinical signs and pathology in monkeys was accumulated; however, the source was traced only as far as an exporter in the Philippines.

Ebola hemorrhagic fever reappeared in 1995 within the region of Bandundu, Zaire. Retrospective studies have shown that the first identified case had an onset of illness on January 6, 1995, and the last case was recognized on June 29, 1995. During that time period, a total of 315 cases were reported and 244 ended in fatalities. The 77% death loss is consistent with previous African outbreaks. Field teams captured more than 3,000 birds and mammals and several thousand possible insect vectors. Unfortunately, the source has not yet been identified.

Most recently, Ebola-Reston has resurfaced within the United States at a monkey containment facility in Texas. Although no humans became ill, these continued outbreaks are examples of the susceptibility of the U.S. to Ebola. Documentation of the Texas outbreak is presently being published. If future epidemics of Ebola hemorrhagic fever are to be eliminated, methods of diagnosis need to be improved and implementation of control programs must be increased.

The purpose of this article is to summarize the virology, pathology, clinical manifestations, and epidemiology of Ebola virus and to discuss methods of containing future outbreaks of Ebola hemorrhagic fever.

Virology

Ebola virus is a bacilliform rod that contains a negative-sense RNA genome. It is mor-
Marburg virus pictured between 2 human liver cells at 75,000X magnification.

phologically similar to, yet antigenically dis-

tinct from, the other member of the
Filoviridae family, the Marburg virus. Dis-
covered in 1967, Marburg virus behaves
similarly to Ebola virus because it also af-

ects primates, causing hemorrhagic fever.
Both viruses were originally classified as
members of the Rhabdoviridae family, but
subsequent studies proved them to be dis-
tinct.8

Ebola has three subtypes (Zaire, Sudan,
and Reston) which have common as well as
unique epitopes.9 History has shown that
the individual subtypes have resulted in in-
fecions of varying severity. The infectivity
of Ebola virus is stable at room temperature
(20°C) but is largely destroyed in 30 min-
utes at 60°C. The virus can also be inacti-
vated by ultraviolet and gamma radiation,
lipid solvents, B-propiolactone, and commer-
cial hypochlorite and phenolic disinfectants.
Due to its aerosol infectivity, high mortality
rate, potential for person-to-person trans-
mission, and the absence of any known pre-
vention or treatment, Ebola virus is classi-

cified as a biosafety level 4 pathogen by the
World Health Organization. Maximum con-
tainment facilities are required for all labo-
atory work.10

Pathogenesis and Pathology

Transmission of Ebola virus has been shown
to occur through direct contact with infected
blood, secretions, organs, or semen. Al-
though there has not been documentation to
show aerosol transmission between humans,
this was the primary mode of spread between
the cynomolgus monkeys in Reston, VA.5
Subsequent to transmission, the virus un-
dergoes an incubation period of 2 to 21 days
(4-10 days average). Afterward, abrupt ill-
ness begins.15

The full pathogenesis of this disease is
still not understood; however, once infection
is established, the progression of disease is
striking. With the Zaire subtype,
intracytoplasmic vesiculation and mitochon-
drial swelling are followed by breakdown of
cellular organelles. Along with the cyto-
pathic changes come large proliferations of
virions. The cytopathic effects of both the
Sudan and Reston subtypes are usually less
severe due to the slower rate of infection.11

Studies on monkeys have shown that the
virus may replicate in organ parenchymal
cells, macrophages, or endothelial cells. Dis-
seminated intravascular coagulation (DIC)
frequently occurs, but in spite of that, it is
not clear whether it is an active cause of the
disease process or merely a result of organ
necrosis and an inability by the liver to pro-
duce sufficient clotting factors.12 Shock is
often seen in filovirus-infected patients and
is presumably due to substances such as tu-
mor necrosis factor (TNF-alpha) which may
increase vascular permeability.13

Monkeys, guinea pigs, suckling mice,
and hamsters have all been experimentally
infected with Ebola virus. In monkeys,
Ebola-Zaire is highly virulent with an incu-
bation period of 4 to 16 days, leading to
death. The target organs are the liver,
spleen, lymph nodes, and lungs, all of which

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undergo extensive necrosis.² Interestingly, Ebola-Sudan is sometimes self-limiting in monkeys, and Ebola-Reston ordinarily is even less pathogenic.¹ Nevertheless, the Reston subgroup can kill. Death due to Ebola-Reston has a consistent finding of marked splenomegaly, often 3 to 4 times the normal size.⁵

The most prominent lesion found in humans is focal necrosis of the liver parenchyma. Gross pathologic changes due to Zaire and Sudan subtypes include hemorrhagic diathesis into skin, mucous membranes, visceral organs, and the lumen of the stomach and intestine. Swelling of the spleen, lymph nodes, kidneys, and brain are other consistent findings.¹⁴

**Clinical Manifestations**

The first clinical sign noted in the Reston monkeys was an abrupt onset of anorexia in animals that otherwise appeared normal. A decrease in defecation followed, and some monkeys had puffy eyelids, lacrimation, nasal exudate, and coughing. Upon palpation, splenomegaly was apparent. These animals generally experienced death within 2 to 7 days after the onset of clinical signs.⁶

Humans experience sudden fever with other nonspecific signs of headache, malaise, and myalgia. Other early signs include bradycardia and conjunctivitis. Within 2 to 3 days, nausea, vomiting, and diarrhea appear with thrombocytopenia and leukopenia. Hemorrhages in the gastrointestinal tract lead to hematemesis and melena. A consistent finding around day 5 is a macropapular rash over the trunk. This is notable since it is not seen in other viral hemorrhagic fevers, with the exception of dengue and lassa. Death due to shock usually occurs 6 to 9 days following the onset of clinical disease.¹⁶ The similarity of these signs to other African fevers negates the possibility of a diagnosis by clinical observations alone, which may account for the failure to recognize Ebola virus until the early 1970’s.

**Epidemiology**

The epidemiology of Ebola virus is mysterious. Present knowledge is based primarily on the major outbreaks in Sudan and Zaire in 1976 and the recent outbreak in Zaire in 1995. All of the index cases of these outbreaks have died before investigations commenced, hence they all acquired the disease by unknown means. The discovery of Ebola virus in monkeys imported into the U.S. from the Philippines led many to believe that monkeys were the natural reservoir. The lack of evidence for monkey die-offs or for latent viral infection in non-human primates raises questions as to the validity of that theory.¹⁷ Zoonosis from other mammals is a possibility. Ebola shares many characteristics with Lassa Fever, which is maintained by chronic infection of rodents in Africa. In addition, antibodies to Ebola virus were found in guinea pigs retrieved by Dr. Cairns in 1981.³ While rodents may not be the true reservoir, this may be an indication that the virus is present in plant material they ingested, or was transferred by the bite of an arthropod. If the reservoir is a mammal, the virus’ immunosuppressive characteristics, lack of immune recognition of the virus, and decreased cytopathogenicity after isolation in mammalian cell cultures suggest that Ebola’s existence in nature may involve persistent infection of a mammalian host.¹⁴

No matter the source, the progression of Ebola hemorrhagic fever epidemics has been perpetuated by person-to-person contact. During the latter stages of the illness, which is characterized by vomiting, diarrhea, and often hemorrhage, the risk for transmission is at its peak. Infection has not been reported in persons whose contact with an infected person solely occurred during the incubation period. In the 1976 Zaire epidemic, considerable transmission was traced to contaminated syringes and needles at a hospital. Secondary transmission from patients cared for in their homes was only 4 to 11%. Considering that simple patient isolation procedures interrupt virus spread, it is most likely that Ebola virus is spread by blood and body fluids but not aerosol droplets.¹⁸ In contrast, the spread of disease among monkeys in the Reston, VA facility was airborne.⁵ So far this has not applied to humans. The 1995 epidemic in Zaire produced results similar to previous African outbreaks. After the initial outbreak, the next wave of cases was generated among friends and family of those first infected at the Kikwit hospitals. Likewise, the second and third generation of infections were generated from other friends.
or relatives of the first generation of cases. The limited secondary attack rate suggests that transmission is not efficient.

**Control and Treatment**

The elimination of all future cases of Ebola hemorrhagic fever is impossible without better knowledge concerning the natural history of the disease. Until efforts are successful in locating the natural reservoir, no progress can be made in eradicating the virus from the environment. Humans will continue to come into contact with the source, and sporadic cases will be unavoidable. Vaccines may be the only tool which can prevent further cases without knowledge of the source. Safe effective vaccines would be helpful in preventing chance infections and invaluable for health professionals dealing with infected patients.

At the moment, the primary weapons against epidemics are educating the public about Ebola virus and training health care workers to follow the guidelines for managing patients with suspected hemorrhagic fever. It has been shown in the past that the primary focus for virus spread has been the area where patient care has been given (i.e., hospitals and homes). Likewise, it has been shown that quarantine procedures are very effective in eliminating transfer of the disease. Strict barrier nursing techniques should be practiced. Particular emphasis should be given to high-risk nursing procedures such as placing intravenous lines and handling of body fluids. Hospital staff should all be equipped with gowns, gloves, and masks. Anyone coming into close physical contact with an infected individual without protection should be considered exposed and put under surveillance.

While use of less-than-sterile technique may be common in African hospitals, the main problem has been associated with difficulties in diagnosis of the disease. By the time management procedures have been implemented, the Ebola virus has already spread to those associated with the case. Development of an easy and accurate method of detection is essential to early diagnosis and prevention of spread. Clinical diagnostics are helpful but not conclusive. Virus isolation is potentially useful but very expensive. Visualization by electron microscope is time consuming. At this time, serologic diagnosis appears to be the key to identifying Ebola virus infection.

The most widely used assay for antibodies to filoviruses is indirect fluorescent antibody (IFA). Although this technology has been useful, its results have occasionally been misleading. It has led to misdiagnosis of diseases thought to be due to filoviruses and has shown a high prevalence of antibodies to Ebola virus in the absence of any recognized disease.

A newly developed direct immunoglobulin (IgG) enzyme-linked immunosorbent assay (ELISA) using infected Vero cells adsorbed to plastic plates may be the final solution, as it is both more sensitive and specific than IFA. ELISA apparently has correctly confirmed all known positive tested sera and has given negative results to sera highly unlikely to have been exposed to Ebola virus. In both regards the IFA has given contrary results. In addition, an antigen capture ELISA has been developed that is inexpensive and will detect low concentrations of virus antigen. This may be useful in the search for reservoir hosts, as well as screening animals entering into the U.S.

Treatment of Ebola hemorrhagic fever has been highly ineffective. One patient with a laboratory-acquired Ebola virus infection survived after being treated with 450 ml of plasma from convalescent patients and 6 million units of leukocyte interferon daily for 14 days. Unfortunately, trials with these treatments in monkeys showed poor results. Due to complications, supportive therapy is extremely difficult. There are problems with secondary bacterial infection and acid-base and electrolyte management. Other complications, such as hypoxia, shock, and blood loss must be managed. Intravenous heparin therapy may be beneficial before hemorrhage has begun. After the onset of hemorrhage, platelets and clotting factors should be given. As the case fatality rates indicate, therapy is often in vain.

**Conclusion**

Like most diseases, prevention is the best medicine. Obviously, research needs to continue to ascertain the constitution of Ebola virus and the consequence of infection in mammals. Nevertheless, if epidemic preven-
tion is the primary focus, efforts need to be concentrated toward implementing containment guidelines in the face of an outbreak in a timely fashion, and discovering the reservoir of Ebola virus. The solutions to accomplishing these goals are educating the public in regard to the signs of Ebola hemorrhagic fever and developing a practical and effective method of identifying infected persons and carriers of the virus.

**Editor's Note**

A recent report in *Science News* (vol. 150, Nov. 9, 1996, p. 294) stated that Robert Swanepoel and colleagues have demonstrated that bats are capable of carrying Ebola after experimental inoculation without becoming ill. It is possible that the bat may later be shown to serve as a natural reservoir in the wild.

**References**


