Ebolavirus and Marburgvirus Infections

Ebola and Marburg Virus Disease, Ebola and Marburg Hemorrhagic Fever, African Hemorrhagic Fever

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Importance

Ebolaviruses and marburgviruses are incompletely understood pathogens that cause severe, often fatal, illnesses in humans and non-human primates. These diseases have been known as Ebola and Marburg hemorrhagic fevers, respectively, after the most dramatic symptoms in severe cases. The names "Ebola virus disease" or Marburg virus disease" are now preferred by the World Health Organization (WHO) and some other groups.

Most species of ebolaviruses and the only known species of marburgvirus occur in Africa. Current evidence suggests that the reservoir hosts are probably bats, while other animals and people are incidental hosts. Humans seem to become infected with marburgviruses in caves or mines harboring bats, while ebolavirus infections tend to be associated with handling tissues from infected nonhuman primates and other species. Once a virus has entered human populations, it can spread from person to person. Some epidemics have affected hundreds of people, particularly when nosocomial spread occurs from inadequate medical supplies or barrier nursing procedures, or when outbreaks are not recognized for long periods. Although the mortality rate varies, the most pathogenic viruses may kill up to 90% of those who become infected. Treatment options are limited, and usually consist of supportive care alone. Epizootics in gorillas and chimpanzees are equally serious, and may threaten the survival of these species in the wild. Other wild mammals including duikers also seem to be killed during outbreaks.

One species, *Reston ebolavirus*, occurs in the Philippines. This virus does not seem to affect humans, although some people may seroconvert. However, it can cause fatal illness in nonhuman primates. Between 1989 and 1996, *Reston ebolavirus* was isolated repeatedly at primate quarantine facilities in the U.S. and Italy; in all but one instance, infected monkeys had been imported from a single facility in the Philippines. The source of the virus was never found, but infected monkeys do not seem to have been exported since this facility was closed in 1997. In 2008, however, *Reston ebolavirus* was discovered in pigs during an unusually severe outbreak of porcine reproductive and respiratory syndrome (PRRS) in the Philippines. Recently, this virus was also found in pigs with PRRS in China. Based on experimental studies, *Reston ebolavirus* alone does not seem to cause any illness in pigs, although its effect during co-infection with other pathogens has not yet been evaluated. Accumulating evidence suggests that ebolaviruses or their relatives may also occur in other locations, although the clinical significance of these viruses for humans and domesticated animals is uncertain.

Etiology

Ebola and Marburg hemorrhagic fever are caused by members of the genera *Ebolavirus* and *Marburgvirus,* respectively, in the family Filoviridae. The names of these viruses have undergone several taxonomic changes since they were first discovered, including new changes officially accepted in 2013. Currently, the genus *Ebolavirus* contains five recognized viral species: *Zaire ebolavirus*, *Sudan ebolavirus*, *Taï Forest ebolavirus* (formerly *Cote d'Ivoire ebolavirus*), *Reston ebolavirus* and *Bundibugyo ebolavirus*. The common name for the single virus in each of these species is Ebola virus (formerly Zaire ebolavirus), Sudan virus (formerly Sudan ebolavirus), Tai Forest virus (formerly Cote d'Ivoire ebolavirus), Reston virus (formerly Reston ebolavirus) and Bundibugyo virus. *Marburgvirus* contains a single species, *Marburg marburgvirus* (formerly *Lake Victoria marburgvirus*), and two individual viruses, Marburg virus and Ravn virus, within this species.

A third genus, *Cuevavirus*, (species *Lloviu cuevavirus;* Lloviu virus) has been proposed for a filovirus found during an outbreak of viral pneumonia among Schreiber's bats (*Miniopterus schreibersii*) in Europe. Very little is known about Lloviu virus. To date, it has not been isolated in culture, or found in other species.

Species Affected

Bats are thought to be the reservoir hosts for filoviruses, and appear to carry these viruses asymptomatically. Antibodies to ebolaviruses and/or viral RNA have been

found in a number of bat species in Africa, with a high seroprevalence in several species of fruit bat. All studies to date have examined bats for *Zaire ebolavirus* or *Reston ebolavirus*, although the other ebolaviruses are probably also maintained in these animals. Outside Africa, antibodies to *Reston ebolavirus* were found in a species of fruit bat (*Rousettus amplexicaudatus*) in the Philippines. The cave-dwelling Egyptian fruit bat (*Rousettus aegyptiacus*) seems to be the primary host for *Marburg marburgvirus,* although evidence of infection has been found in other fruit bats and insectivorous bats. *Marburg marburgvirus* is the only filovirus, to date, that has actually been isolated from the tissues of bats in the wild.

Other reservoir or amplifying hosts may also exist. In 1998, *Zaire ebolavirus* RNA was found in six mice (*Mus setulosus* and *Praomys* sp) and a shrew (S*ylvisorex ollula),* and these species were proposed as possible reservoir hosts. However, the results have not been confirmed by other groups, and virus isolation was unsuccessful. Recent experiments suggest that pigs may be able to transmit some ebolaviruses, including *Reston ebolavirus* and *Zaire ebolavirus*.

The African filoviruses (all filoviruses except *Reston ebolavirus*) cause severe illness in nonhuman primates and some other animals. While there is no formal evidence for a causative role in some species, ebolavirus outbreaks have been linked to reports of dead and dying gorillas (*Gorilla gorilla*), chimpanzees (*Pan troglodytes*), mandrills (*Mandrillus* sp.), guenon (*Cercopithecus* sp.) and other nonhuman primates, as well as duikers (a species of forest antelope, *Cephalophus dorsalis*), bush pigs (red river hog, *Potamochoerus porcus*) and other animals. Attempts to isolate ebolaviruses or detect viral RNA were successful in chimpanzees, gorillas and duikers. Antibodies to these viruses have been reported in nonhuman primates including mandrills, drills (*Mandrillus* sp.), baboons (*Papio* sp.), colobus monkeys (*Colobus badius*), guenon, chimpanzees and gorillas. There have been no reports of illnesses or unusual deaths among domesticated animals during ebolavirus outbreaks in Africa. One study detected antibodies in dogs, but did not find virological evidence of infection. Viruses were not found during limited sampling of live cattle, sheep, goats and pigs during outbreaks and serological studies have not yet been performed in these animals. Species that can be infected experimentally include a number of nonhuman primates, pigs and guinea pigs. Other laboratory rodents are also used as models for human disease, but they are not normally susceptible to wild type viruses except by parenteral inoculation and when very young (i.e., suckling mice less than 8 days of age).

Other than bats, *Reston ebolavirus* has been found only in nonhuman primates (e.g., cynomolgus macaques, *Macaca fascicularis*), which become ill, and domesticated pigs. Whether *Reston ebolavirus* can be maintained in swine populations is not known. *Marburg marburgvirus* affects non-human primates. Antibodies to filoviruses were recently found in Bornean orangutans (*Pongo pygmaeus*) in Indonesia.

Zoonotic Potential

Zaire ebolavirus, Sudan ebolavirus, Bundibugyo ebolavirus and *Tai Forest ebolavirus* can cause severe illness in humans, although Tai Forest virus infections have rarely been documented. *Reston ebolavirus* does not seem to be pathogenic for humans, but people may seroconvert after exposure to infected nonhuman primates or pigs.

Geographic Distribution

Zaire ebolavirus, Sudan ebolavirus, Tai Forest ebolavirus and Bundibugyo ebolavirus

Zaire ebolavirus, *Sudan ebolavirus*, *Tai Forest ebolavirus* and *Bundibugyo ebolavirus* are endemic in parts of Africa south of the Sahara desert. Human illnesses caused by these viruses have been reported mainly in central and western Africa, and have typically been associated with rain forests. While outbreaks have been documented in a limited number of countries, serological surveys in bats and other animals suggest that some viruses may be more widespread.

Marburg marburgvirus

Marburg marburgvirus has been found in bats, nonhuman primates and/or humans from eastern Africa to the far western edge of the Congo. The human illness seems to be most prevalent in eastern Africa, although one outbreak was reported from Angola. A case reported from South Africa may have been acquired in Zimbabwe. Imported human cases have been seen sporadically in other areas, including Europe and North America. In recent decades, they have mainly been reported among travelers returning from Africa, but a large Marburg hemorrhagic fever outbreak occurred in Germany and Yugoslavia in 1967, among laboratory workers who had been exposed to tissues from imported green (vervet) monkeys (*Cercopithecus aethiops*).

Reston ebolavirus

Reston ebolavirus occurs in the Philippines. This or other filoviruses might also exist in other locations. In 2014, *Reston ebolavirus* was found in pigs during a PRRS outbreak in China. Antibodies to filoviruses have been detected in several species of fruit bats in China and Bangladesh, and 18% of healthy Bornean orangutans (*Pongo pygmaeus*) in rehabilitation facilities were seropositive on Kalimantan Island, Indonesia. Outbreaks among imported, nonhuman primates in the United States and Italy were eradicated.

Transmission

How filoviruses are transmitted between bats, or transmitted from bats to other animals, is still uncertain.

Although these viruses can be found in bat tissues and blood, they typically seem to be absent from secretions or excretions such as oral fluids, urine and feces (although virus was found in the feces of one experimentally infected bat), and attempts to inoculate bats by exposing respiratory and oral mucus membranes to virus were unsuccessful. It is possible that virus shedding in secretions and excretions occurs intermittently, at very low levels and/or under certain physiological conditions. There is some evidence that transmission might occur when bats give birth. Seasonal changes in the prevalence of *Marburg marburgvirus* RNA were reported in older juvenile Egyptian fruit bats, with peaks during the twice-yearly birthing seasons. These peaks seem to coincide with a higher risk of human infection. Pregnant fruit bats are also more likely to be seropositive than nonpregnant females. .

Filoviruses emerge periodically in nonhuman primates or people after infection from an outside source. Most *Marburg marburgvirus* infections in humans have been associated with transmission within caves, probably from infected bats, although some people were infected by exposure to nonhuman primate tissues in the laboratory. Some ebolaviruses might also be acquired directly from bats; however, humans often become ill after handling the carcasses of animals found in the forest, especially nonhuman primates and duikers. Blood, secretions and excretions, and tissues from these animals may contain infectious virus. Filoviruses have been reported to survive for some time in blood and tissues at room temperature, and can be transmitted on fomites, particularly those contaminated by blood. In incidental hosts, filoviruses are thought to enter the body mainly through mucous membranes and broken skin. Arthropod-borne transmission is theoretically possible, but most authors suggest it is unlikely.

Once ebolaviruses or marburgviruses have infected humans, they can spread from person to person. Blood can contain large amounts of virus, contaminating the environment if patients hemorrhage. These viruses are also found in many secretions and excretions that are not visibly contaminated with blood, including saliva, tears, breast milk, semen and feces. Urine may be a source of virus, but *Zaire ebolavirus* was absent from patients' urine during one outbreak. Aerosol transmission has been reported in some experimentally infected nonhuman primates, although virus does not seem to spread readily between cages in other studies. While people might theoretically become infected by this route, aerosols do not seem to be important during human outbreaks. Filoviruses disappear from blood and most tissues after the acute stage of the disease. They may, however, persist for a time in some "immune privileged" body sites, such as the testes and possibly the anterior chamber of the eye. In one patient, *Marburg marburgvirus* was apparently transmitted sexually, 13 weeks after the onset of disease. *Zaire ebolavirus* was isolated from the semen of a convalescent patient up to 82 days after the onset of clinical signs, and detected by RT-PCR for as long as 91 days. This virus was also recovered from the breast milk of a convalescing patient, 15 days after the onset of disease, and transmission to a nursing child may be possible. How efficiently filoviruses can spread by casual contact during the early stages of the illness is still uncertain, but transmission was not reported in some cases, and isolation of infected individuals has been sufficient to stop outbreaks in Africa.

The extent of transmission between nonhuman primates during outbreaks in the wild is controversial; however, current evidence suggests that these viruses are not spread efficiently, and nonhuman primates are unlikely to act as maintenance hosts. Virus spread is likely to depend on the extent of interactions between members of the population, as well as the infectivity of body fluids and carcasses. Most other species (e.g., duikers) have not been examined, but the role of domesticated pigs is under investigation. Piglets inoculated with *Zaire ebolavirus* shed this virus in nasal and oral fluids, and could infect piglets in close contact. Viral RNA was also found in rectal samples and blood. Piglets transmitted this virus to cynomolgus macaques housed in the same room, most likely by droplets and/or aerosols. Some, but not all, piglets inoculated with *Reston ebolavirus* also shed this virus in nasopharyngeal secretions, urine and/or rectal swabs. *Reston ebolavirus* had disappeared from blood and tissues by one month after infection. Whether sustained transmission of ebolaviruses can occur in swine populations has not yet been determined.

Disinfection

Ebolaviruses and marburgviruses are both reported to be susceptible to sodium hypochlorite, glutaraldehyde, β-propiolactone, 3% acetic acid (pH 2.5), formaldehyde and paraformaldehyde. Recommended dilutions of sodium hypochlorite may vary with the use. Calcium hypochlorite, peracetic acid, methyl alcohol, ether, sodium deoxycholate and some other agents have also been tested against ebolaviruses, and found to be effective. In addition, filoviruses can be inactivated by ultraviolet light, gamma irradiation, heating to 60°C (140°F) for 30-60 minutes or boiling for 5 minutes.

Infections in Animals

Incubation Period

Experimental inoculation of nonhuman primates with filoviruses often results in clinical signs after 3-5 days, although the incubation period was reported to be as long as 16 days in some animals. Pigs developed a fever 4 days after inoculation with *Zaire ebolavirus*.

Clinical Signs

Nonhuman primates are severely affected by filoviruses. Wild chimpanzees and gorillas are often found dead. Clinical signs observed in dying wild animals (of various species) during ebolavirus outbreaks have included

vomiting, diarrhea, hair loss and emaciation, as well as bleeding from the nostrils. Whether all of these signs are associated with filovirus infections or some were caused by other diseases is uncertain. During the 1989 *Reston ebolavirus* outbreak in Virginia, the clinical signs in cynomolgus monkeys included anorexia, swollen eyelids, increased lacrimation, nasal discharge, coughing and splenomegaly. Fever, subcutaneous hemorrhages, epistaxis and/or bloody diarrhea were less common. The most common clinical signs at the exporting facility were respiratory signs and diarrhea, while hemorrhages occurred but were rare (1% of animals). Nonhuman primates that are experimentally infected with filoviruses may develop fever, anorexia, vomiting, diarrhea, dyspnea, splenomegaly and weight loss. A skin rash is common, although it can be absent in some species, or in animals inoculated by certain routes. Hemorrhagic signs may include petechiae, bleeding into the gastrointestinal tract, or bleeding from puncture wounds and mucous membranes. Shock and hypothermia are soon followed by death. African species of ebolaviruses are usually more pathogenic than *Reston ebolavirus*: the clinical signs are more severe, hemorrhages are more common and the mortality rate is higher.

Piglets (approximately 5-6 weeks of age) inoculated with *Zaire ebolavirus* developed a fever and respiratory signs, which progressed to dyspnea, anorexia and lethargy, while less severe signs occurred in slightly younger piglets inoculated with the same virus. Guinea pigs infected with unpassaged filoviruses from primates may have a fever and weight loss, but recover. In this species, severe illness is only seen in animals infected with serially passaged virus adapted to guinea pigs. No clinical signs have been reported in infected wild bats, and experimentally infected bats remain asymptomatic.

Reston ebolavirus does not seem to causes any illness in experimentally inoculated pigs. However, this virus has been detected in pigs with porcine reproductive and respiratory syndrome in both the Philippines and China, and whether it can exacerbate other illnesses or predispose animals to other infections is unknown. The PRRS outbreak in the Philippines was unusually severe, but consistent with other outbreaks caused by atypical PRRS viruses. These pigs were also infected with porcine circovirus type 2.

Post Mortem Lesions

Petechiae, ecchymoses and frank hemorrhages may be present at necropsy. Hemorrhages can occur in any organ, but they are particularly common in the gastrointestinal tract, kidneys, and pleural, pericardial and peritoneal spaces. The liver and spleen may be swollen and friable, and the liver may be severely reticulated and discolored. Other potential lesions include interstitial pneumonia, nephritis and a maculopapular rash, as well as necrosis of the liver, lymphoid tissue, adrenal cortex or pulmonary epithelium.

The gross lesions in young pigs experimentally infected with *Zaire ebolavirus* were pulmonary consolidation and enlargement of the lung-associated lymph nodes, which were sometimes mildly hemorrhagic. The right atrium was hemorrhagic in some animals, although the cause of this lesion was uncertain. Mild lung and lymph node lesions were reported in some asymptomatic piglets infected with *Reston ebolavirus,* but it was not certain if they could be attributed to this virus.

Diagnostic Tests

Filovirus infections can be diagnosed by detecting antigens with an antigen-capture ELISA or immunostaining, and by detecting viral RNA with RT-PCR. Ebolaviruses and marburgviruses can be isolated in many cell lines, including Vero or Vero E6 cells (viruses from pigs may not show cytopathic effect in Vero cell lines until the 2nd or 3rd passage). Electron microscopy can identify virus particles, which have a distinctive, filamentous pleomorphic, appearance, in tissues. In primates, filoviruses occur in high concentrations in the liver, spleen, lungs, lymph nodes and skin. Liver, spleen, muscle and skin have been taken from wild animal carcasses in good condition for surveillance by RT-PCR. This test can sometimes detect ebolavirus RNA in the bones of decomposed carcasses. Virus isolation is more difficult: unpublished data suggests that carcasses decomposing in the African forests may contain infectious virus for only 3 to 4 days after death. In bats, filoviruses have been found in tissues such as the liver and spleen, and sometimes in the blood.

Serological tests include indirect immunofluorescence (IFA) and ELISAs, but neutralization tests are unreliable for filoviruses. Cross-reactions can occur. Immunoblotting may be used in research.

Treatment

Because most filovirus infections are serious and often fatal in both humans and nonhuman primates, infected animals are usually euthanized.

Control

Disease reporting

Animals that may be infected with ebolaviruses or *Marburg marburgvirus* must be reported immediately, to protect humans who may be exposed and aid in controlling the outbreak.

Prevention

Quarantine of nonhuman primates during importation protects humans and healthy nonhuman primates from exposure to filoviruses. To prevent the exportation of *Reston ebolavirus*, the government of the Philippines has banned wild-caught monkeys from export and established a quarantine period for captive-bred primates. During outbreaks, suspects and exposed animals should be isolated, and euthanized after confirmation of the disease. Strict

infection control procedures are necessary to prevent virus transmission on fomites. Prevention of human exposure during diagnosis and eradication activities is vital, as humans are severely affected by most filoviruses.

Measures to prevent infection of swine with *Reston ebolavirus* in endemic areas have not yet been established, but normal biosecurity measures should be helpful. Pigs should not be allowed to contact bats or nonhuman primates.

Morbidity and Mortality

In Africa, high mortality rates have been reported in gorilla, chimpanzee and duiker populations during some human ebolavirus epidemics. There have also been reports of other dead and dying primates, as well as bush pigs and possibly other species. Outbreaks in wild animals can occur suddenly, and may cause widespread mortality on one area while having little or no impact on other regions. The effect on local populations can be severe. Gorilla and duiker numbers fell an estimated 50% in one preserve, while chimpanzee populations decreased by 88% during another outbreak. One study estimated 90-95% mortality (5000 animals) in a population of gorillas. Experimental inoculation of gorillas or chimpanzees is not done, but mortality can be very high in other nonhuman primates inoculated with African filoviruses. Infections are almost always fatal in macaques inoculated with *Zaire ebolavirus*, although animals inoculated with *Sudan ebolavirus* may survive. Antibodies have also been reported in some wild primate populations, suggesting that some animals can recover or are resistant to disease. In one survey, none of 145 captive-born mandrills and chimpanzees had antibodies to ebolaviruses, but 13% of wild-born chimpanzees, 3%of mandrills, 7% of gorillas, 4% of baboons, and 1% of guenon were seropositive.

Reston ebolavirus also has a high case fatality rate in susceptible captive primates. During the first outbreak to be recognized, 82% of the cynomolgus monkeys died at a U.S. quarantine facility. (A complication is that these monkeys were also infected with simian hemorrhagic fever virus, which is pathogenic for this species.) Experimental infection of cynomolgus monkeys resulted in a case fatality rate greater than 80%. The mortality rate was 14% at the exporting facility where these monkeys originated, while 2% average mortality was reported at similar facilities in the Philippines. Viral antigens were detected in 32% of dead or moribund monkeys and 4% of healthy monkeys at this facility. The source of the infection was not found, but imported primates from the Philippines were virus-free after the infected export facility was closed in 1997. However, *Reston ebolavirus* was found in domesticated pigs in the Philippines in 2008, during an investigation of a PRRS outbreak. Seroprevalence to *Reston ebolavirus* was high (70%) among pigs on affected farms, but no antibodies were found in pigs from an area unaffected by illness. High morbidity and mortality rates were reported in the sick pigs infected with both viruses, but pigs inoculated with *Reston ebolavirus* alone remained asymptomatic. In pigs, *Zaire ebolavirus* infections have currently been described only in experimentally infected animals less than 2 months of age. The illness seems to be more severe in older piglets than one-month-old animals, which all survived in one experiment.

Infections in Humans

Incubation Period

The precise incubation period for filovirus infections is difficult to determine, as the time of exposure is uncertain or not described in most cases. Some estimates indicate a potential range of 2 to 21 days, with symptoms usually appearing in 4 to 10 days. The initial signs occurred after 3 to 13 days in a limited number of cases where the time of exposure was known. Estimates of the mean incubation period during outbreaks have ranged from 6 to 13 days, and sometimes differ even for the same outbreak.

Clinical Signs

Marburg marburgvirus, Zaire ebolavirus, *Sudan ebolavirus* and *Bundibugyo ebolavirus* appear to cause similar diseases, although the severity of the illness and most prevalent syndromes might differ with the virus. Only one infection with *Tai Forest ebolavirus* has been published, but it was described as severe and hemorrhagic, and resembled other ebolavirus infections. Published information for clinical signs during outbreaks is limited; however, the initial symptoms have been described as nonspecific and flu-like, with a high fever, chills, headache, severe malaise and muscle aches or generalized pain, followed by abdominal pain, nausea, vomiting and diarrhea. A nonpruritic, erythematous, maculopapular rash, which may develop fine scaling, can appear on the face, torso and extremities. Dysphagia, pharyngitis, and conjunctivitis or conjunctival congestion are reported to be common. One clinical summary described a grayish exudate in the pharynx, sometimes with tapioca-like whitish-clear granules on the soft palate. Other mucosal lesions, such as glossitis, gingivitis, and cold-sore like lesions, have been mentioned. Debilitation is often rapid, and generalized pain may be seen. Pregnant women may abort. Common changes in laboratory parameters include leukopenia (at the early stage) and thrombocytopenia, as well as elevated liver enzymes. Some patients are reported to experience a brief remission before deteriorating, while some may recover without developing more severe signs.

After a few days, patients can develop other symptoms including neurological signs, dyspnea, and signs of increased vascular permeability, especially conjunctival injection and edema. Mild to severe bleeding tendencies may also be seen. In mild cases, this can be limited to bruising, bleeding of the gums, epistaxis, petechiae and/or mild oozing from venipuncture sites. In severe cases, patients have hemorrhages from the gastrointestinal tract or other sites. Massive bleeding can be seen in fatal cases.

Other serious signs include metabolic disturbances, severe dehydration, diffuse coagulopathy, shock and multi-organ failure. Although many patients die, some begin to recover after a week or two. During convalescence, which can be slow, reported complications have included joint pain, uveitis, deafness, orchitis, recurrent hepatitis, transverse myelitis, pericarditis and mental dysfunction (e.g., psychosis). Secondary infections can also occur at this stage, and skin in the area of the rash often sloughs. It should be noted that descriptions of the syndromes caused by filoviruses are generally limited to severe cases seen in hospitals, and milder cases might not have been observed.

Unlike other filoviruses, *Reston ebolavirus* does not seem to be pathogenic for humans. Asymptomatic seroconversion can be seen.

Diagnostic Tests

Ebola or Marburg hemorrhagic fever can be diagnosed by detecting antigens with an antigen-capture ELISA or immunostaining, and by detecting viral RNA by RT-PCR. Reverse transcription loop–mediated isothermal amplification methods have been described. Virus isolation can also be used (though available in limited locations) and electron microscopy may be helpful. In humans, filoviruses are most reliably detected in the blood (including serum) during the acute-stage of the disease, but they may also be found in oral fluids and in some cases in urine, breast milk, semen, anterior eye fluid and other body fluids, and in many tissues including the skin. Skin biopsies may be collected at post-mortem. Serological assays include ELISA tests and IFA, but neutralization tests are unreliable. Because the consequences of misdiagnosis (including false positive diagnosis) are severe, multiple techniques are used to confirm the infection whenever possible.

Treatment

Standard treatment currently consists of supportive therapy, including maintenance of blood volume and electrolyte balance, as well as analgesics and standard nursing care.

No specific treatment has been demonstrated yet to be safe and effective in humans; however, experimental drugs, vaccines and monoclonal antibodies to filoviruses have been tested in animals, with varying degrees of success in nonhuman primates. These experimental treatments are diverse, and may be aimed at inhibiting virus replication and/or entry into cells, treating clotting abnormalities or sepsis, or boosting immune responses. Most experimental treatments have been tested very early in the incubation period, but some were promising when started up to 2 days after exposure, or even after early clinical signs (e.g., mild elevation in temperature) developed. A few drugs have advanced to human phase I clinical trials, which are the initial tests to determine whether agents appear to be safe for human use.

Control

Disease reporting

International health regulations require that nations report acute hemorrhagic fever syndromes immediately to WHO, without waiting for the causative agent to be identified. Suspected human cases of Ebola or Marburg hemorrhagic fever should be reported immediately to the nation's public health service, to prevent transmission and aid in case management and diagnosis. In the U.S., cases are reported to public health departments and to CDC's Special Pathogens Branch.

Prevention

In Africa, ebolavirus infections are often linked to exposure to wild animal tissues during butchering. Because the full host range may not be known, all sick and dead wild animals should be avoided (including for use as food). To prevent infection from animals that might be infected but have not yet developed obvious clinical signs, good personal hygiene should be used when handling and preparing meat, and the meat should be thoroughly cooked. Surveillance for deaths and illness in wild animals may provide an early warning to prevent human epidemics, but such deaths have not been seen in all human outbreaks.

Marburg marburgvirus infections have been linked to exposure to caves, mines and cave-dwelling bats, but the means of transmission from bats to humans is still unknown. If contact is unavoidable (e.g., occupational exposure), personal protective equipment and good hygiene should be used. Some caves have been closed after human cases were recognized.

Human epidemics can be stopped by isolating patients in facilities with barrier nursing procedures and strict infection control measures. Healthcare workers should use the personal protective equipment currently recommended by experts (e.g., gloves, gowns, masks, eye protection and other equipment) to prevent exposure to blood and body fluids. Burial practices should avoid all contact with the body or fomites. During convalescence, the possibility of exposure during breastfeeding or sexual intercourse should be considered. Ebolaviruses have been found in milk 15 days after the onset of illness (although the maximum period of shedding is unknown), and in semen for much longer. Sexual abstinence has been recommended for at least three months after recovery.

Reston ebolavirus is not known to affect humans. As a precaution, tissues from infected animals should not be eaten or handled. Good hygiene and appropriate personal protective equipment should be used if these animals or their tissues must be handled.

Morbidity and Mortality

Illnesses caused by filoviruses have occurred as isolated cases, small clusters of cases, or large outbreaks which may affect hundreds of people. Some outbreaks seem

to originate with a single person, while multiple transmission events have been reported in others. High risk activities include butchering wild animals and visiting caves and mines. Outbreaks can be propagated by transmission to family members and other close contacts through nosocomial transmission, unsafe self-treatment at home, funeral practices and other routes. Healthcare workers are at high risk, as hospital supplies are limited in some areas where filoviral diseases occur, and barrier nursing practices may be inadequate. Other factors that help propagate the disease include poor availability of healthcare, reluctance to see a medical practitioner, and difficulty in distinguishing some cases from other serious illnesses, particularly in the early stages. As a result, some outbreaks have been identified months after they began.

Outbreaks of Ebola hemorrhagic fever are reported periodically in Africa, typically during the rainy season. The number of reported outbreaks has increased, due either to a higher incidence or better recognition of the disease. Marburg hemorrhagic fever was only recently recognized as a serious and recurring problem in humans. This disease was initially recognized in 1967, during an outbreak in laboratory workers exposed to infected primate tissues. Only 6 cases were described during the following 3 decades, 3 cases in travelers to Africa and three in their contacts. In 1998, however, this virus caused an epidemic affecting hundreds of people in the Democratic Republic of the Congo (DRC). This outbreak was associated with a mine where infected bats were later discovered. Several different viral strains were isolated during the epidemic, suggesting that the virus had been introduced repeatedly into the population via infected miners. This outbreak also uncovered a pattern of hemorrhagic disease in the mine dating to 1987 or earlier, and one survivor of an earlier outbreak was found to have antibodies to this virus. In 2004-2005, another large outbreak was reported in Angola, where *Marburg marburgvirus* was not thought to exist. Unlike the previous outbreak, it seems to have originated with a single person, and was propagated by person-to-person transmission. Several additional cases have been reported since that time, in miners or travelers who visited caves.

Case fatality rates are usually high for African filoviruses, and the prognosis is poor in patients who become severely ill. *Zaire ebolavirus* is thought to be the most pathogenic virus, with case fatality rates from outbreaks in Africa ranging from 44% to 88%.;*Sudan ebolavirus* appears to be less virulent, with a case fatality rate estimated to be 41-65%, (or 26-54%, depending on the cases included). However, higher mortality rates have been reported in small numbers of individuals who were not treated. The case fatality rate was reported to be 36% in the only known outbreak caused by *Bundibugyo ebolavirus,* and varies widely in Marburg hemorrhagic fever. It was 22-23% during the 1967 laboratory outbreak caused by *Marburg marburgvirus* in Europe, and 50% in the 6 cases reported between 1967 and 1994. However, case fatality rate may have been as high as 83% (56% in laboratory-confirmed cases) during the outbreak in DRC, and it was reported to be 88% in Angola. It is not known whether higher mortality rates are associated with more virulent filoviruses (or strains of these viruses), higher doses of virus, concurrent malnutrition and disease, or the availability and quality of healthcare.

Whether African filoviruses can cause mild or asymptomatic infections is still uncertain. The possibility of such infections is suggested by reports of antibodies and cell-mediated immune responses to filoviruses in people who have no history of Ebola or Marburg hemorrhagic disease. Seroprevalence rates tend to be higher in groups that have more contact with wild animals or live in rural forest ecosystems. However, illnesses without hemorrhages might have been misdiagnosed as other diseases such as malaria, which can also be severe. Cross-reactivity with other viruses may also be a problem in serological tests. In particular, there may be undiscovered filoviruses in Africa (and other locations) that are less pathogenic or nonpathogenic in humans.

Seroconversion to *Reston virus* does not seem to be common. In the Philippines, seroprevalence rates were 1% or less in people who had been exposed to either nonhuman primates or infected pigs. All of the primate-exposed positive samples came from people associated with the single export facility known to have housed infected animals.

Internet Resources

Centers for Disease Control and Prevention (CDC). Ebola Hemorrhagic Fever
http://www.cdc.gov/vhf/ebola/

CDC. Marburg Hemorrhagic Fever
http://www.cdc.gov/vhf/marburg/

Public Health Agency of Canada. Pathogen Safety Data Sheets
http://www.phac-aspc.gc.ca/lab-bio/res/psds-ftss/index-eng.php

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