Ebolavirus and Marburgvirus Infections

Ebola and Marburg Virus Disease, Ebola and Marburg Disease, Ebola and Marburg Hemorrhagic Fever, Filovirus Disease, African Hemorrhagic Fever, Cercopithecus-associated Hemorrhagic Fever (Marburg)

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Importance

Ebolaviruses and marburgviruses (collectively, filoviruses) are zoonotic viruses that cause systemic illnesses with a high proportion of severe cases in humans. The case fatality rate in people is often around 30-60% or higher in Africa, and has sometimes reached 90% where medical care is inadequate. Treatment has historically been limited to supportive care, though new options such as monoclonal antibodies are promising. However, cost and other factors still limit their availability. Most filoviruses are endemic to Africa, where they are thought to be maintained in bats but can infect other animals, resulting in multiple opportunities for human exposure. Once a virus has entered humans, it can spread from person to person. Some larger epidemics have affected hundreds to thousands of people, particularly where medical supplies or barrier nursing procedures are inadequate, or when outbreaks are not recognized for long periods. A particularly large and prolonged outbreak occurred in 2013-2016, when an Ebola virus become established in impoverished, densely populated urban areas of Africa. It resulted in more than 25,000 cases and 11,000 deaths, as well as a few imported cases on other continents. Epizootics in gorillas and chimpanzees are also serious and may kill large numbers of animals.

An ebolavirus found in the Philippines, Reston virus, can affect nonhuman primates, though it is not known to cause any illness in humans. In 2008, Reston virus was found in pigs during severe outbreaks of porcine reproductive and respiratory syndrome (PRRS) in both the Philippines and China. The significance of Reston virus infections in pigs is still under investigation, but it seems to be capable of causing respiratory disease under some conditions.

Etiology

Ebola and Marburg virus disease, also known as Ebola and Marburg hemorrhagic fever, are caused by members of the genera *Ebolavirus* and *Marburgvirus*, respectively, in the family Filoviridae.

The genus *Ebolavirus* currently contains six recognized viral species: *Zaire ebolavirus*, *Sudan ebolavirus*, *Taï Forest ebolavirus* (formerly *Cote d'Ivoire ebolavirus*), *Reston ebolavirus*, *Bundibugyo ebolavirus* and *Bombali ebolavirus*. The common name for the single virus in each of these species is, respectively, Ebola virus (formerly Zaire ebolavirus), Sudan virus (formerly Sudan ebolavirus), Tai Forest virus (formerly Cote d'Ivoire ebolavirus), Reston virus (formerly Reston ebolavirus), Bundibugyo virus and Bombali virus. Collectively, all of the viruses in this genus are referred to as ebolaviruses, a term that should not be confused with the single virus called Ebola virus. 'African ebolaviruses' includes all of these viruses except Reston virus, which is found in Asia. Because Bombali virus has been seen only in bats to date, references to African ebolaviruses in this factsheet generally also exclude Bombali virus. The genus *Marburgvirus* contains a single species, *Marburg marburgvirus* (formerly *Lake Victoria marburgvirus*), with two individual viruses, Marburg virus and Ravn virus. Relatively little is known about Ravn virus, which has been reported only three times in humans, Tai Forest virus, which was confirmed in a single human case, and Bombali virus.

Two other filoviruses are known to infect bats, but have not been found in any other species. Lloviu virus, which belongs to the species *Lloviu cuevavirus* and genus *Cuevavirus*, was found during an outbreak of viral pneumonia among Schreiber's bats (*Miniopterus schreibersii*) in Europe. It is not certain whether Lloviu virus was responsible for this outbreak or an incidental finding. Měnglà virus, the only known representative of the genus *Dianlovirus*, was detected in a fruit bat in China. Two other filovirus genera, *Striavirus* and *Thamnovirus*, contain viruses that only seem to infect fish.

Species Affected

Reservoir hosts

Bats, which appear to be infected subclinically with marburgviruses and ebolaviruses, are thought to be the reservoir hosts for all of these viruses. Virus

isolation has been demonstrated only for Marburg virus, and evidence of infection with ebolaviruses in bats, to date, is based solely on the detection of nucleic acids and antibodies.

The cave-dwelling Egyptian fruit bat (*Rousettus aegyptiacus*) seems to be the primary host for marburgviruses and is known to host both Marburg and Ravn virus. There is also evidence of marburgvirus infection in other fruit bats and insectivorous bats. Antibodies to African ebolaviruses and/or viral RNA have been found in several bat species, though laboratory experiments suggest that Egyptian fruit bats are not suitable hosts. Antibodies to Reston virus were found in several bat species in the Philippines, including the fruit bat *Rousettus amplexicaudatus*, and nucleic acids were detected by PCR in cave-dwelling *Miniopterus schreibersii*.

Some researchers have speculated that other wildlife (e.g., rodents, nonhuman primates) or pigs might also play some role in maintaining ebolaviruses. To date, all wildlife species examined in Africa seem to be incidental hosts, and recent serological surveys also found no evidence to support a significant role for pigs in this location. However, pigs are known to be significant hosts for Reston virus in the Philippines, though whether they could maintain this virus long-term is unclear.

Incidental hosts

Nonhuman primates are susceptible to infection with Ebola virus, Sudan virus, Bundibugyo virus, Tai Forest virus, Reston virus and both marburgviruses. Experimental susceptibility to a particular virus can differ between species. In Africa, 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 primates, as well as duikers (*Cephalophus dorsalis*), bush pigs (*Potamochoerus porcus*), brush-tailed porcupines (*Atherurus africanus*) and other animals. While there is no formal evidence for a causative role in some of these species, ebolaviruses and/ or their DNA were detected in the carcasses of chimpanzees, gorillas and duikers. Reston virus infections have been seen in pigs, and experimental infections with Ebola virus can be established in pigs and ferrets. Ferrets have also been experimentally infected with Sudan, Bundibugyo, Tai Forest and Reston viruses, but they do not seem to be susceptible to marburgviruses.

There is little definitive information about other species. In 1998, Ebola virus RNA was found in six mice (*Mus setulosus* and *Praomys* sp.) and a shrew (*Sylvisorex ollul*a) in Africa, and these animals were proposed as possible reservoir hosts. However, virus isolation was unsuccessful and the results have not been confirmed by other groups. Laboratory rodents have limited susceptibility to filoviruses: immunocompetent animals inoculated with unaltered viruses develop few or no clinical signs, though some viruses can be artificially adapted to replicate at high levels in rodents as models for human disease.

With the possible exception of pigs, there have been no reports of illnesses or unusual deaths among domestic animals during ebolavirus outbreaks in Africa. Older serological studies sometimes reported antibodies to these viruses in guinea pigs, some livestock, and even chickens in Africa, but they used a serological test (IFA) that is no longer considered to be reliable. Recent studies with more specific tests found that a few pigs were seropositive; however, the patterns of reactivity suggested that most infections might have been caused by other unknown filoviruses. Some healthy dogs in Africa were also found to be seropositive, though the specificity of the tests used in these studies has been questioned. Two pet dogs exposed to ebolavirus patients in Italy and the U.S. did not get infected.

Ebolaviruses were not detected during very limited virus sampling of live cattle, sheep, goats and pigs during early outbreaks or, more recently, by PCR in pigs or dogs. Some animal species (e.g., sheep and goats) were historically described as “completely insensitive” when inoculated with large amounts of live ebolaviruses for the production of hyperimmune serum in Russian studies, but whether this indicates asymptomatic infection or complete absence of virus replication seems to be uncertain. Recent *in vitro* studies found that ebolaviruses were able to replicate in cultured cells from two different species of snakes. Whether this suggest that some reptiles might be susceptible to ebolaviruses is unclear. Marburgviruses did not replicate in the same snake cells.

Zoonotic potential

Ebola virus, Sudan virus, Bundibugyo virus, Tai Forest virus, Marburg virus and Ravn virus can all affect humans. Reston virus does not seem to cause any symptoms in people, though they may seroconvert.

Geographic Distribution

Filoviruses that cause illnesses in people (Ebola virus, Sudan virus, Tai Forest virus, Bundibugyo virus, Marburg virus and Ravn virus) seem to be limited to parts of subSaharan Africa. Human infections with ebolaviruses have been reported mainly in central and western Africa, but serological surveys, as well as the distribution of bat species known to be infected, suggest that some viruses may be more widespread. Marburgviruses have been found in bats, nonhuman primates and/or humans from eastern Africa to the far western edge of the Congo, though they mainly seem to cause human illnesses in eastern Africa.

Reston virus is endemic in the Philippines, but was detected in pigs during a PRRS outbreak in China in 2008. Serological studies have found evidence of filovirus infections in bats in China, Bangladesh and Singapore, and Mengla virus was discovered recently in Chinese bats. A virus might also be endemic in Indonesia, where 18% of healthy Bornean orangutans (*Pongo pygmaeus*) in rehabilitation facilities on Kalimantan Island were seropositive. Lloviu virus is the only filovirus currently known to exist in Europe.

Transmission

Bats are reported to shed marburgviruses in oral secretions and, less frequently, in urine, feces and vaginal secretions. Although some studies were unable to detect these viruses in experimentally infected bats, others were able to isolate live viruses and/or viral RNA for up to 5-19 days when they are first infected. Bats in direct contact or in cages below infected animals seem to become infected by the oral route. Ebolaviruses might be transmitted similarly, though this is not certain yet.

In incidental hosts, filoviruses are thought to enter the body mainly through mucous membranes and broken skin. People mostly seem to become infected with marburgviruses in caves, probably from infected bats, or after exposure to infected captive nonhuman primates or their tissues. Periods when bats give birth appear to coincide with a higher risk of infection. Some ebolaviruses might also be transmitted directly to people from bats; however, most index cases are either from an unknown source or associated with handling the carcasses of infected incidental hosts, such as nonhuman primates and duikers.

Incidental hosts can readily spread filoviruses. Humans and other primates can shed these viruses in most secretions and excretions including saliva, ocular secretions, urine, feces, breast milk, vaginal mucus and semen, while pigs were found to shed Ebola virus and Reston virus at least in nasal and oral fluids and feces. Virus shedding increases as the clinical signs become more severe, and large amounts of virus occur in blood, which can contaminate the environment if patients hemorrhage. Early in the illness, most person-to-person transmission seems to occur during close contact, and the risk of transmission through casual contact at this time is thought to be low. However, breast milk and semen may contain enough virus to infect a nursing infant or sexual partner even in people who are not seriously ill. Filoviruses can also cross the placenta. The possibility of aerosol and/or respiratory droplet transmission was suggested in some experimentally infected nonhuman primates, but alternative explanations were possible. Respiratory transmission does not seem to be a significant source of person-to-person spread.

Virus shedding in most body fluids ends with recovery, but viruses may persist in milk and semen for some time during and after convalescence. Semen, in particular, can occasionally contain filoviruses for up to a year or more. Studies on milk have, to date, found live virus for up to a few weeks into convalescence, and viral nucleic acids for as long as 16 months after recovery in one exceptional case. However, the latter study used a highly sensitive PCR test, live virus was not found and the nursing infant did not become infected. Filoviruses can also persist in the anterior chamber of the eye, but this does not seem to result in virus shedding in ocular secretions.

Filoviruses can be transmitted on fomites, particularly those contaminated by blood. At 21ºC (70°F), most studies of dried blood recovered viable Ebola virus for only a few days, though one found it for as long as 7-10 days. Ebola virus was also detected for up to 2 weeks in liquid blood at this temperature, and up to 32 days in blood within a syringe needle. Live virus was recovered for a few days to a week from the carcasses of experimentally infected nonhuman primates at 27ºC (81°F). Longer survival times have been seen at lower temperatures, e.g., 4°C (39°F). Arthropod-borne transmission via mechanical vectors is theoretically possible but unlikely to be significant.

Disinfection

Various ebolaviruses and/or marburgviruses are reported to be inactivated by sodium or calcium hypochlorite, phenolic disinfectants, glutaraldehyde, β-propiolactone, 3% acetic acid (pH 2.5), peracetic acid, alcohols (e.g., methyl alcohol, 70% ethanol), iodides (e.g., povidone iodine), lipid solvents, some but not all detergents, formaldehyde and paraformaldehyde. Some studies have suggested that certain viruses may require longer disinfectant contact times than others. Physical methods of inactivation include exposure to ultraviolet light or gamma irradiation, heating to 60°C (140°F) for 30-60 minutes or boiling for 5 minutes.

Infections in Animals

Incubation Period

The incubation period is often around 3-5 days, but can be as long as 16 days, in experimentally infected nonhuman primates. Pigs inoculated with Ebola virus or Reston virus developed clinical signs after 3-4 days.

Clinical Signs

No clinical signs have been reported in wild bats infected with ebolaviruses or marburgviruses. Experimentally infected bats are also asymptomatic, though there may be mild microscopic inflammatory hepatic lesions and mild elevations in some liver enzymes.

Information about naturally infected incidental hosts is limited. Wild chimpanzees and gorillas infected with African ebolaviruses are often found dead. Clinical signs reported in dead and dying nonhuman primates, duikers and other animals during ebolavirus outbreaks in Africa included vomiting, diarrhea, hair loss, emaciation and bleeding from the nostrils. However, it is not certain that all of these deaths were caused by ebolaviruses. Fever, anorexia, vomiting, diarrhea, dyspnea, splenomegaly, weight loss and, in some species, a maculopapular skin rash are common signs in experimentally infected nonhuman primates. There may also be hemorrhagic signs, such as petechiae, bleeding into the gastrointestinal tract, or bleeding from puncture wounds and mucous membranes. Shock and hypothermia are soon followed by death. The specific signs may vary with the virus and species of primate, and mild illnesses and asymptomatic infections are also possible, especially in animals inoculated orally or via the conjunctiva.

Captive cynomolgus monkeys infected with Reston virus during an outbreak in Virginia mainly had nonspecific signs (e.g., anorexia, less often fever), swollen eyelids, increased lacrimation, nasal discharge, coughing and splenomegaly. Hemorrhagic signs including subcutaneous hemorrhages, epistaxis and/or bloody diarrhea were less common. These animals were also infected with simian hemorrhagic fever virus, and the contributions of each virus to the signs were uncertain. Respiratory signs and diarrhea were the most common signs at one infected exporting facility in the Philippines, though these signs were also seen in some uninfected animals. Hemorrhages were rare, but sudden death was reported in some outbreaks. Experimentally infected nonhuman primates have illnesses that resemble those caused by African ebolaviruses but are generally less severe and less likely to include hemorrhages.

Pigs in the Philippines and China were found to be infected with Reston virus during severe outbreaks of PRRS, though coinfection with PRRS virus and, in some cases, porcine circovirus type 2 made the contribution of Reston virus to the illness uncertain. Two studies of experimentally infected young pigs reported discordant results. One, which used a higher viral dose, found that the animals remained asymptomatic. In the other study, pigs developed severe respiratory disease from acute interstitial pneumonia. The initial signs were nonspecific (e.g. anorexia, somnolence), but progressed to productive cough and/or serous nasal discharge and, in many cases, dyspnea and evidence of cyanosis, especially on the snout. Survivors recovered completely. Young pigs experimentally infected with Ebola virus also had fever, anorexia, lethargy and respiratory signs, which progressed to dyspnea.

The clinical signs in ferrets administered high doses of Ebola, Sudan, Bundibugyo or Reston virus included nonspecific signs (e.g., depression, hunched posture, rapid weight loss), diarrhea, dehydration, nasal and ocular discharge, labored breathing and multiorgan failure. Some studies also reported hemorrhages, particularly cutaneous petechiae and ecchymoses and/or blood in the stool. Ferrets inoculated with Tai Forest virus had no fever or other overt signs of illness, though they lost weight, and Ravn virus and Marburg virus caused no clinical signs. Infections in contact animals suggest that the severity of the illness in naturally infected ferrets is probably more variable: while some animals that contracted Ebola virus from the inoculated ferrets died, others seroconverted without becoming ill. Some other species such as guinea pigs may have a fever and weight loss after inoculation with unpassaged filoviruses from primates, but recover.

Post Mortem Lesions

Hemorrhages, often in the form of petechiae and ecchymoses, may be found on various internal organs, skin and mucous membranes of filovirus-infected nonhuman primates. The liver, spleen, lymph nodes, adrenal glands and some other organs may be enlarged and/or congested and friable. The liver may be severely reticulated and discolored. Some species may also have a maculopapular rash. Similar lesions (e.g., petechial skin rashes and other hemorrhagic signs, reticulated pallor of the liver, mottled splenomegaly), as well as pulmonary lesions (necrotizing pneumonia, bronchiolitis, and perivasculitis) have been reported in experimentally infected ferrets.

Pigs co-infected with Reston virus and PRRS virus had necropsy lesions consistent with PRRS. Lung lesions associated with interstitial pneumonia, including pulmonary consolidation and enlargement of the lung-associated lymph nodes, were found in young pigs experimentally infected with Ebola virus and some pigs inoculated with Reston virus. The right atrium was hemorrhagic in some Ebola virus-infected pigs, although the cause of this lesion was uncertain. Asymptomatic pigs infected with Reston virus in another study had mild lung and lymph node lesions which were not definitively attributed to this virus.

Infected bats have no gross lesions.

Diagnostic Tests

Frequently used assays for virus detection in animals include antigen-capture ELISA or immunostaining for viral antigens, and RT-PCR. Virus isolation is less common, due to the need for high biosafety level (e.g. BSL 4) facilities. If virus isolation is warranted, it can be done in many cell lines, though Vero cells are often used. Viruses from pigs may not show cytopathic effect until the 2nd or 3rd passage. Recovered viruses can be identified by RT-PCR or immunofluorescence. Electron microscopy, which reveals virus particles with a distinctive filamentous, pleomorphic appearance in cultures or tissue samples, may also be helpful.

Filoviruses can be found in the blood and most secretions and excretions of live animals, and in various tissues after death. 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. If these tissues are unavailable or unsuitable, RT-PCR can sometimes detect ebolavirus RNA in the bones of decomposed carcasses. Virus isolation from carcasses is more difficult than the detection of viral RNA; it seems to be possible for only a few days and possibly up to a week at room temperature or warmer. Filoviruses and their nucleic acids can be difficult to find in bats, but may be present in tissues such as the liver and spleen, blood, and some secretions and excretions, particularly oral fluid.

Serological tests, usually ELISAs and immunoblotting, are mainly used in research. At least one ELISA has been developed for pigs. Indirect immunofluorescence (IFA) was also used at one time, but it was found to be prone to nonspecific reactions. One group has developed a microtiter immunostained plaque reduction neutralization test (miPRNT) for pigs. Cross-reactivity can be an issue in serological tests, mainly between the different species of ebolaviruses.

Treatment

Animals infected with African filoviruses are usually euthanized to keep these viruses from spreading to humans. Reston virus-infected animals are also euthanized in most cases.

Control

Disease reporting

Animals that may be infected with ebolaviruses or marburgviruses must be reported immediately to a country's authorities.

Prevention

Infected or exposed nonhuman primates are usually isolated then euthanized after confirmation of the disease. Strict infection control procedures are necessary during this time to prevent virus transmission on fomites, and humans must be protected from exposure. To prevent the exportation of Reston virus, the government of the Philippines has banned wild-caught monkeys from export and established a quarantine period for captive-bred primates. Specific measures to prevent pigs from becoming infected with Reston virus in endemic areas have not been established, but normal biosecurity measures should be helpful. As much as possible, pigs should be restricted from contact with bats or nonhuman primates in these regions.

Very little is known at present about the susceptibility of other species, and the disposition of exposed pets is unclear. In western countries, one dog that belonged to an infected person was euthanized, while another was quarantined at an isolation facility and monitored similarly to exposed humans. Neither animal was found to be infected.

Morbidity and Mortality

African filoviruses

Ebolaviruses appear to differ in their virulence in nonhuman primates, based on studies in experimentally infected animals. Ebola virus seems to cause the most severe signs. High mortality rates in susceptible wildlife sometimes accompany human ebolavirus epidemics. These outbreaks can occur suddenly, and may cause widespread mortality in 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; chimpanzee populations decreased by 88% during another outbreak; and one study estimated 90-95% mortality (5000 animals) in a population of gorillas. However, exposure does not appear to be universally fatal: serology in African primate populations, as well as some studies in primates inoculated by oral or conjunctival exposure, suggest that mild or asymptomatic infections are possible.

The effects of African filoviruses on domestic animals, if any, are currently unclear. There has been some speculation that pigs might be involved in amplifying or maintaining ebolaviruses in Africa, based on their susceptibility to experimental infection and a few anecdotal reports of pig deaths that occurred around the time of human outbreaks. However, recent serological studies, which found antibodies in < 1% of 400 pigs in Sierra Leone and 4-6% of pigs in Guinea, West Africa, do not seem to support this hypothesis. The patterns of serological reactivity in many pigs did not appear to be consistent with the viruses causing human outbreaks, and most of the seropositive animals in the study from Guinea were born after the human epidemic. Experimental Ebola virus infections were more severe in 5-6 week-old piglets than one-month-old animals, which all survived.

Reston virus

Reston virus infections in captive nonhuman primates were all associated with animals imported from the Philippines. Until recently, all outbreaks were traced to a particular quarantine facility in the Philippines, which was closed in 1997. However, the virus was found at another quarantine facility in 2015, after 6 cynomolgus macaques died unexpectedly. An investigation found that 6% of all nonhuman primates at this facility were seropositive and measles virus was also circulating. The mortality rate in experimentally infected nonhuman primates varies, but it can be greater than 80% in experimentally infected cynomolgus macaques.

Reston virus co-infected pigs were detected during severe outbreaks of PRRS in the Philippines and China in 2008-2009. The contribution of Reston virus to these outbreaks was uncertain, as the illness was comparable to outbreaks caused by other atypical PRRS viruses, and one study found no overt clinical signs in pigs inoculated with Reston virus. However, a more recent study suggests that this virus may sometimes cause clinical signs in some pigs and/or potentiate other viruses. There was no apparent effect of age on disease severity in this study. Once Reston virus infects pigs, it seems to spread readily: seroprevalence was approximately 70% among pigs on affected farms in the Philippines.

Infections in Humans

Incubation Period

Estimates for the incubation period in filovirus infections indicate a potential range of 2 to 21 days, with most cases probably appearing within about 5-11 days.

Clinical Signs

African ebolaviruses and marburgviruses appear to cause similar symptoms. The initial symptoms are usually nonspecific and flu-like. While the presenting signs can vary, many patients initially have a high fever, chills, headache, severe malaise and muscle aches or generalized pain, followed by abdominal pain, nausea, vomiting and diarrhea. Hiccups often accompany the gastrointestinal signs. A nonpruritic, erythematous, maculopapular rash, which may develop fine scaling or become confluent, can appear on the face, torso and extremities. Pharyngitis, dysphagia, cough

and conjunctivitis or conjunctival congestion are also 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 also been mentioned. Debilitation is often rapid after the initial stage. Some patients are reported to experience a brief remission before deteriorating, while some may recover without developing more severe signs.

After a few days, some patients may develop neurological signs, dyspnea, and/or signs of increased vascular permeability, including conjunctival injection and edema. Thrombocytopenia is common, and mild to severe bleeding tendencies may be seen, though measures to prevent disseminated intravascular coagulation (DIC) have reduced their frequency in treated patients. In mild cases, hemorrhagic signs can be limited to bruising, bleeding of the gums, epistaxis, petechiae and/or mild oozing from venipuncture sites. While frank hemorrhaging is reported to be uncommon, it can occur, especially from the gastrointestinal tract or after a birth or C-section. Other serious signs include metabolic disturbances, severe dehydration, diffuse coagulopathy, shock and multi-organ failure. Increased gastrointestinal permeability may result in secondary infections. Pregnant women usually abort or give birth either to a stillborn infant or one who dies soon after birth.

Although many patients die, some begin to recover after a week or two. Convalescence may be slow and can include complications such as joint pain, unilateral or bilateral uveitis and other ocular signs, deafness, orchitis, recurrent hepatitis, transverse myelitis, pericarditis and neurological signs (e.g., seizures, headache, memory loss, confusion, other mental status changes). Secondary infections can also occur at this stage, and skin in the area of the rash often sloughs. Rare recrudescent infections have been reported, including one characterized by encephalopathy.

Milder cases are poorly characterized. One adult infected with Marburg virus had nonspecific symptoms and slight signs of purpura, and an infant developed fever, diarrhea, vomiting and splenomegaly. Neither patient was reported to be seriously ill. Common clinical signs noted in some mildly affected, seropositive contacts of ebolavirus patients included headache, fever and fatigue, while a minority also had gastrointestinal signs, muscle or joint pain and/or bleeding. However, a definitive link between the symptoms and ebolavirus infection could not be determined in these cases, as the diagnosis was retrospective.

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

Diagnostic Tests

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 other body fluids such as urine, breast milk and semen. These viruses are widespread in tissues, including the skin, in acute disease. During convalescence, they are known to persist only in aqueous humor, semen and milk, though nucleic acids were also found in open ulcers associated with hospitalization (e.g., pressure sores, wounds) for a short period after viremia ended. Virus shedding in semen may be intermittent.

Antigen-capture ELISAs, rapid antigen tests such as lateral flow assays, and RT-PCR are used most often for diagnosis in humans. The specificity of these tests varies. Some antigen tests developed for Ebola virus cannot detect other ebolavirus species (e.g., Sudan virus), and some PCR tests can distinguish individual viruses, while others can only identify them as ebolaviruses or marburgviruses. Rapid antigen screening tests can be confirmed by RT-PCR; however, false negatives are possible with the latter test during the first 3 days of the illness, and it may need to be repeated. Rapid antigen tests, using oral fluids or oropharyngeal swabs, are also useful for postmortem diagnosis, though other samples (e.g., skin biopsies) may also be collected. Immunohistochemistry is rarely used in humans for diagnosis, though it may be employed in research. Virus isolation has limited availability, but can be used if warranted, and electron microscopy might be helpful in rare circumstances.

Serology is minimally useful in clinical cases, due to variability in the development of antibody responses and the possibility of pre-existing antibodies in endemic regions. However, it can be employed in retrospective diagnosis or research. ELISAs and immunoblotting are the most commonly used tests, while IFA is thought to be prone to nonspecific reactivity. Virus neutralization has been considered unreliable, as neutralizing antibodies were not always found in infected people; however, some recent reports described finding neutralizing antibodies in a high proportion of ebolavirus survivors.

Treatment

Standard treatment consists of supportive therapy, including maintenance of blood volume and electrolyte balance. Experimental single or multiple monoclonal antibody cocktails appear to reduce mortality in patients infected with Ebola virus, and similar products are in development for Sudan virus and Marburg virus. Antivirals, such as favipiravir, have also been tried in some patients. Convalescent plasma was used occasionally in the past, though its efficacy was uncertain, and some researchers reported that it did not seem to be effective in recent Ebola virus outbreaks.

Uveitis in survivors is usually treated with corticosteroids. Whether antivirals would also be helpful is unknown. Favipiravir was administered in at least one case where Ebola virus was isolated from aqueous humor and the eye was not responding well to steroids.

Prevention

In Africa, ebolavirus infections are often linked to exposure to wild animal tissues (‘bushmeat’) during butchering. Because the full host range may not be known,

contact with all sick wildlife and their carcasses should be avoided. Good personal hygiene should be used when handling and preparing any meat (including that of domestic animals), as some animals may have few clinical signs in the early stages, and meat should be thoroughly cooked. Bushmeat bans have been tried in some areas, but such bans may be ignored in areas with high rates of poverty. They have also had some unintended consequences, including the proliferation of underground bushmeat sales that complicate disease surveillance and mitigation. Surveillance for deaths and illness in wild animals might provide an early warning to prevent human epidemics, and at least one formal wildlife mortality surveillance program has been established. However, wildlife deaths are not seen in all human outbreaks.

Marburgvirus infections have mainly been linked to exposure to caves or mines with cave-dwelling bats. If contact with bats or their caves is unavoidable (e.g., occupational exposure), personal protective equipment (PPE) and good hygiene should be used. Some caves have been closed to human entry after human cases were recognized. Control measures directed at bats are unlikely to be successful and may even be counterproductive: after one attempt to control Marburg virus by exterminating the resident bats, the bats that repopulated the cave had a higher rate of infection.

Human epidemics have been successfully stopped by tracing infected individuals and isolating patients in facilities with barrier nursing procedures and strict infection control measures. Recommendations for PPE during potential exposure to blood or body fluids are available from sources such as the WHO and Médecins Sans Frontières/ Doctors without Borders. Burial practices should avoid all contact with the body or fomites. Recently developed experimental or conditionally approved Ebola virus vaccines have been given to people at high risk of exposure, such as healthcare workers. Ring or limited prophylactic vaccination of the public has also helped reduce transmission in some outbreaks. Ebola virus vaccines were variably cross-protective against other ebolaviruses in nonhuman primate studies, but they do not seem to provide any protection against marburgviruses.

Because filoviruses can be transmitted in semen for some time after recovery, the WHO recommends sexual abstinence or the use of condoms for at least 6 months, or until two consecutive tests, at least a week apart, find no viral RNA in semen. A few men can shed virus n semen even after this time. Breast-feeding should be avoided during the acute stage of the illness, and the WHO suggests that recovered women continue to avoid breast-feeding until two negative RT-PCR tests in consecutive breast milk samples, taken at least 24 hours apart. In situations where there is no good alternative to breast-feeding, pasteurization of breast milk might be an alternative. The possibility of virus persistence in the eye should also be considered with invasive procedures such as cataract surgery. How long filoviruses might persist in this location is uncertain, but ocular fluid samples tested 1.5-3 years after recovery had no evidence of virus.

Although Reston virus is not known to affect humans, care should be taken to avoid direct contact with infected animals or their tissues, and appropriate PPE should be used if such contact is unavoidable.

Morbidity and Mortality

Most cases of ebolavirus disease have been caused by Ebola virus or Sudan virus, with a smaller number from Bundibugyo virus. Tai Forest virus caused a serious illness in a veterinarian who was investigating outbreaks among wild chimpanzees in Africa, and may be either rare or underdiagnosed. As of 2020, Marburg virus is known to have caused nearly 500 human illnesses, but Ravn virus was detected in only three. Whether this difference reflects relative virus prevalence, exposure or human susceptibility is unclear. Reston virus does not seem to cause disease in humans, but 1-4% of those who had been exposed to either captive nonhuman primates or infected pigs in the Philippines were seropositive.

Illnesses caused by filoviruses may appear as isolated cases, small clusters, or large outbreaks affecting hundreds to thousands of people. Once a filovirus infects a person, it tends to be propagated by transmission to family members and other close contacts, including through nosocomial transmission or funeral practices that involve direct contact with the body. The 2013-2016 Ebola virus outbreak in West Africa, which spread widely in impoverished, densely populated urban areas, was particularly large, with at least 11,000 deaths and approximately 28,600 suspected, probable or laboratory confirmed cases. Some outbreaks seem to originate with a single person, while multiple transmission events have been reported in others.

The reported case fatality rate in filovirus outbreaks ranges from around 20% to nearly 90%, with one source estimating an overall rate of 44% for all viruses, as of 2020. It can be influenced by comorbidities (e.g., malaria, malnutrition), the quality of healthcare and other factors. At one time, pregnant women were also thought to have more severe illnesses, but findings from recent outbreaks cast doubt on this hypothesis. The case fatality rate was initially 74% in the 2013-2016 West African Ebola virus outbreak, but eventually fell to 31-37%. This decrease has been attributed to improved treatment and supportive care, as well as better recognition of milder cases. During the same outbreak, the case fatality rate was 19% for imported cases in U.S. and European hospitals, where advanced medical care and investigational drugs were consistently available and the patients were less likely to have comorbidities such as malaria. Similarly, it was 22-23% in laboratory workers exposed to Marburg virus-infected primates and tissues in Europe in the 1960s, but > 80% during some Marburg virus outbreaks in Africa.

Investigations of filovirus outbreaks have confirmed a few milder clinical cases and asymptomatic infections by RT-PCR or virus isolation, but the frequency of such cases

is still unclear. Antibodies to ebolaviruses were found in < 5% of asymptomatic contacts of clinical cases during the 2013-2016 Ebola virus outbreaks, and in 8-12% of contacts who recently had mild illnesses. Ebolavirus seroprevalence in the general population of Africa ranges from < 2% to 9% in rural regions, and can be as high as 19% in localized populations with high exposure to wildlife, while reports in African healthcare workers vary from 2% to 41%. Studies of marburgviruses have typically found antibodies to these viruses in < 5% of either the general population or higher risk groups (e.g., miners), though there are a few reports of seroprevalence as high as 16%. While cross-reactivity to unknown filoviruses might account for some seropositive individuals, these studies suggest that the currently known African filoviruses can cause mild as well as serious illnesses.

Internet Resources

Centers for Disease Control and Prevention (CDC). Ebola Hemorrhagic Fever

CDC. Marburg Hemorrhagic Fever

European Centre for Disease Prevention and Control (ECDC). Ebola virus disease

Médecins Sans Frontières(MSF) Ebola Project - Personal Protective Equipment, PPE

Public Health Agency of Canada. Pathogen Safety Data Sheets

Wisconsin Primate Research Center. Primate Info Net

World Health Organization (WHO). Ebola virus disease

WHO. Marburg virus disease

WHO. Personal Protective Equipment for Use in a Filovirus Disease Outbreak: Rapid Advice Guideline

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*Link defunct

